Guideline Resource Unit
guru@ahs.ca

Alberta Bone Marrow and Blood Cell Transplant Program:

Standard Practice Manual

Alberta Health Services
Cancer Care Alberta

Table of Contents

Indications

Acute Myeloid Leukemia (AML)
Acute Lymphoblastic Leukemia (ALL)
Myelodysplastic Syndromes (MDS)
Chronic Myelogenous (CML)
Bcr-Abl-Negative Myeloproliferative Neoplasms (MPN)
Chronic Lymphocytic Leukemia (CLL)
Lymphoma
Myeloma, Amyloidosis
Severe Aplastic Anemia (SAA)
Hemoglobinopathies
Multiple Sclerosis (MS)
Systemic Sclerosis (SSc)
Germ Cell Tumours (GCT)

Complications

Graft-vs-Host Disease (GVHD)
CMV, VZV, HSV, HHV6
EBV/Posttransplant Lymphoproliferative Disorder (PTLD)
Pneumocystis and Bacterial Prophylaxis
Fungal Prophylaxis
Graft Failure, Poor Graft Function, Chimerism
Donor Lymphocyte Infusion (DLI), 2nd HCT for Relapse
Neutropenic Fever
Central Venous Catheter (CVC) Complications
Hepatic Complications and Viral Hepatitis
Cytokine Release Syndrome (CRS) and Neurotoxicity (ICANS)
Cytopenia, Transfusions

Other Topics

Conditioning for HCT
Patient Eligibility
Donor Selection
Stem Cell Mobilization
Vaccination
Cord Blood Transplantation (CBT)
ABO-Incompatible Graft
Long-Term Follow-Up
Nutritional Support
Microbially-Contaminated or Non-Conforming Cellular Therapy Products

Appendices

- Follow-up Test Guidelines
  - Post Autologous Transplant
  - Post Allogeneic Transplant
  - Post CAR T-cell Transplant
- Additional Information
  - Copyright
  - Conflict of Interest
  - Glossary of Abbreviations
  - Revision History

Indications

Acute Myeloid Leukemia (AML)

Presented by: Lynn Savoie

Summary

- Disease risk stratification will be based on the cytogenetic and molecular features of the tumour cells, response to first induction, presence of secondary or therapy related disease, white blood cell (WBC) at diagnosis and measurable residual disease.
- Patients with favourable cytogenetics and no unfavourable molecular changes show good response to chemo-immunotherapy and in the majority of cases will enter a second remission if relapse occurs. Patients with t(8;21) or inv(16)/t(16;16) without evidence of MRD should undergo allogeneic stem cell transplant in CR2.
- Patients with a normal karyotype who are FLT3 ITD negative and either NPM1 mutation positive or CEBPα biallelic mutation positive are expected to have a favourable outcome to chemo-immunotherapy and should be offered an allogeneic stem cell transplant in CR2.
- Patients in the intermediate cytogenetic risk group may be offered a transplant from a matched sibling or a matched unrelated donor in CR1. This includes patients with a normal karyotype as well as non-informative cytogenetic changes. Patients with t(8;21) or inv(16)/t(16;16) and a KIT mutation appear to fall into this risk group. Patients with FLT3 ITD at low allelic ratio and with FLT3 TKD mutation also appear to fall into this risk group.
- Patients with high-risk features will likely not be salvageable at relapse and should be offered transplant in first complete remission. This includes high-risk cytogenetics, those with a normal karyotype who are FLT3 ITD positive, various molecular findings on NGS, those requiring more than one chemotherapy cycle to achieve a complete remission, as well as those with secondary or therapy related disease or measurable residual disease after two cycles of chemotherapy.
- Patients who relapse after conventional chemotherapy should undergo stem cell transplantation in CR2.
- It is preferable for patients to be in complete remission (defined as fewer than 5% blasts and no active extra-medullary disease) at the time of transplantation. Patients with untreated or refractory CNS disease or with circulating blasts are not eligible for transplantation.
- Patients should receive at least one cycle of post-remission therapy prior to transplantation if transplantation cannot occur within 4 weeks of the complete remission being achieved.

Background

Risk stratification in AML has traditionally relied on patient and disease characteristics at diagnosis (chiefly: age, cytogenetics, white blood cell count at diagnosis and the presence of an antecedent hematological disorder or therapy related disease) and on the response to induction chemotherapy. While patients in favourable risk categories may enjoy long-term disease-free survival, AML may be virtually incurable with conventional treatment in patients with high-risk features and those with poor response to chemotherapy. Recently, the interaction of molecular abnormalities with cytogenetic risk

groups has been defined. Risk-adapted therapy attempts to avoid exposing favourable-risk patients to the morbidity and mortality risks of stem cell transplant while directing high-risk patients to up-front transplant in order to minimize relapse risk early in the course of therapy. Measurable residual disease (MRD) after induction and/or consolidation chemotherapy is also becoming more reliably prognostic.

Prognosis

Cytogenetic Risk Groups

Table 1. Southwest Oncology Group (SWOG) and Medical Research Council (MRC) criteria for favourable, intermediate, unfavourable and unknown cytogenetic risk groups.

Classification	SWOG Criteria	MRC Criteria (as for SWOG, except):
Favourable	t(15; 17) – with any other abnormality inv(16)/t(16; 16)/del(16q) – with any other abnormality t(8; 21) – without del(9q) or complex karyotype	t(8; 21) – with any other abnormality
Intermediate	+8, -Y, +6, del(12p) normal karyotype	abnormal 11q23 del(9q),del(7q) – without other abnormalities Complex karyotypes (≥ 3 abnormalities, but <5) All abnormalities of unknown prognostic significance
Unfavourable	-5/del(5q), -7/del(7q), t(8; 21) with del(9q) or complex karyotype inv(3q), abn11q23, 20q, 21q,del9q, t(6; 9) t(9; 22), abn17p, Complex karyotypes (≥3 abnormalities)	Complex karyotypes (≥5 abnormalities)
Unknown	All other clonal chromosomal aberrations with fewer than 3 abnormalities	

Table 2. Results with conventional chemotherapy.

Results with Conventional Chemotherapy			
	Favourable Cytogenetics	**Intermediate Cytogenetics**	**Unfavourable Cytogenetics**
CR	80-90%	~70%	30-50%
DFS	70-85%	40-55%	10-20%

Abbreviations: CR = complete remission; DFS = disease-free survival.

Table 3. Relapse rates associated with post-remission therapies.

Relapse Rates with post-remission therapies			
Study	**Allogeneic Transplant**	**Autologous Transplant**	**Chemotherapy**
GIMEMA 1995	24%	40%	57%
GOELAM 1997	28%	45%	55%
MRC 1998	19%	35%	53%
ECOG/SWOG 1998	29%	48%	61%

Data for children excluded. In the MRC study, BMT was compared with an observation arm after 4 cycles of chemotherapy, rather than a direct comparison with high dose chemotherapy as in the other studies.

Molecular Risk Groups

Patients with normal cytogenetics make up the largest group of patients with AML, yet they show significant variability in outcomes with standard treatment. The likely explanation for this finding is the influence of molecular abnormalities that go undetected by standard cytogenetics. Among these abnormalities, mutations of *NPM-1* and bZIP in-frame mutated CEBPA are associated with significantly better overall survival (OS) compared to patients with the wild-type loci. Internal tandem duplications (ITD) to FLT-3 confer inferior OS on patients who harbour these mutations. Next-generation sequencing is now done routinely in transplant eligible patients and allows for the detection of many other known mutations of potential clinical significance.

AML with myelodysplasia-related gene mutations is now categorized in the adverse-risk group. These mutations, typically associated with AML following an antecedent hematologic disease, are also prevalent in de novo AML and indicate adverse risk even in the absence of myelodysplasia-related cytogenetic abnormalities[6,26,42,44,45]. These include mutations in the RUNX1, ASXL1, *BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2* genes. Additional disease-defining recurring cytogenetic abnormalities are included in the adverse-risk group, including t(3q26.2;v) involving the *MECOM* gene[31,73], or t(8;16)(p11.2;p13.3) associated with *KAT6A::CREBBP* gene fusion[46].

The presence of a pathogenic *TP53* mutation (at a variant allele fraction of at least 10%, with or without loss of the wild-type *TP53* allele) defines the new entity AML with mutated *TP53*. This subtype of AML is associated with a very poor prognosis and the utility of a stem cell transplant may be debated.

Combined Cytogenetic and Molecular Risk Groups

Table 4 outlines the risk groups according to the most recent European LeukemiaNet (ELN) classification.

Table 4. ELN risk classification 2022

Risk category†	Genetic abnormality
Favourable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB*::*MYH11* • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*, • Cytogenetic and/or molecular abnormalities not classified as favourable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* • Mutated *TP53*

Conventional induction chemotherapy for patients with non-promyelocytic AML consists of combination chemotherapy with an anthracycline and Cytarabine. In patients with a FLT3 mutation a FLT3 inhibitor is added. Patients with good risk cytogenetics and NPM1 mutations as well as certain patients with intermediate risk cytogenetics are offered gemtuzumab ozogamicin along with their chemotherapy. In the setting of therapy-related or antecedent hematologic malignancy patients, CPX-351 is substituted. Patients with acute promyelocytic leukemia are offered induction with Arsenic trioxide and ATRA.

Minimal Residual Disease

Despite the above clinical and genetic risk factors present at diagnosis, the outcome of individual patients is still highly variable indicating other factors are at play. The detection of measurable residual disease at various time points during therapy likely reflects these yet unexplained factors. Several studies have indicated that undetectable or low MRD values at any time point distinguish patients with more favourable outcomes in terms of relapse-free survival (RFS) and OS than those with higher values including pre-transplantation. Post two cycles of intensive chemotherapy may be the most informative. How to use this information is currently being investigated with active intervention clinical trials.

Table 5 adds measurable residual disease after 2 cycles of chemotherapy (e.g., 1 induction and 1 consolidation) and other prognostic factors to the cytogenetic and molecular risk stratification to further help with decision on allogeneic stem cell transplantation in first complete remission.

Table 5. Cytogenetic and molecular risk stratification including minimal residual disease and other Prognostic factors. (From Cornelissen et al: Blood 2016)[58]

AML risk group‡	AML risk assessment criteria at diagnosis	MRD after cycle 2	Risk of relapse following consolidation approach		Prognostic scores for RM that indicate alloHSCT as preferred consolidation		
			Chemotherapy or autoHSCT (%)	AlloHSCT (%)	EBMT score	HCT-CI score	NRM risk (%)
Good	-t(8;21) or AML1-ETO, WBC< 20 -inv16/t (16;16) or CBFB-MYH11 -CEBPA-biallelic mutant-positive -t(8;21) or AML1-ETO plus WBC>20 or mutant KIT	Positive or negative	35-40	15-20	NA(≤1)	NA (<1)	10-15
Intermediate	-CN-X-Y, WBC <100, CRe -t(8;21) or AML1-ETO plus WBC >20 or mutant KIT	Negative	50-55	20-25	≤2	≤2	<20-25
Poor	-CN –X-Y, WBC<100, CRe	Positive	70-80	30-40	≤3-4	≤3-4	<30
	-t(8;21) or AML1-ETO, WBC>20 and/or mutant KIT	Positive					
	-CN-X-Y, WBC<100, n CRe	Negative					
	-CN-X-Y, WBC>100	Negative					
	-CA, but non-CBF, MK-negative, no abn3q26						
Very Poor	-CN -X –Y, WBC>100	Positive	>90	40-50	≤5	≤5	<40
	-CA, but non-CBF, MK-negative, no abn3q26, EV1-negative	Positive					
	-MK-positive	Positive or negative					
	-abn3q26 -Non-CBF, EVI1-positive -Non-CBF with mutant p53, or -mutant RUNX1, or mutant ASXL1 -or biallelic FLT3-ITD with -FLT3-ITD:FLT3 WT ratio of >0.6						

Abbreviations: CA = cytogenetic abnormalities; CBF = core binding factor; CN = cytogenetically normal; CRe = early complete remission; EBMT = European Group for Blood and Marrow Transplantation; HCT-CI= hematopoietic cell transplantation comorbidity index; ITD = internal tandem duplication; MK = monosomal karyotype; NA = not applicable; NRM = non-relapse mortality; –X –Y = deleted X or Y chromosome.

Treatment

If CR has been achieved further therapy is necessary for potential cure. The nature of consolidation therapy must be individualized for each patient based on a risk analysis of the risk of relapse of the AML versus the risk of the proposed consolidation therapy. This will depend on prognostic features of the leukemia, response to therapy, performance status and type of hematopoietic stem cell donor available. High dose Ara-c (HiDAC) is the mainstay of consolidation chemotherapy as there has been shown to be a dose intensity effect to cytarabine suggesting that HiDAC is necessary in induction or consolidation. Additional agents such as FLT3 inhibitors or gemtuzumab ozogamicin are added as indicated and CPX-351 can replace HiDAC in the appropriate patients. Generally, at least one cycle is administered in all patients if only to allow for planning of an allogeneic stem cell transplant although the absolute need for this is controversial. Autologous stem cell transplantation shows some superiority in event-free survival over chemotherapy alone for consolidation, however, is not routinely recommended unless a donor is not available.

- **Favourable risk patients:** In patients with AML with t(8;21), inv 16, isolated NPM1 mutation or bZIP in-frame mutated CEBPA data suggests that provided there are no additional risk factors multiple cycles of HiDAC provide higher overall survival than lower doses of cytarabine or stem cell transplant. Our recommendation is 2-4 cycles of HiDAC post induction chemotherapy accompanied by gemtuzumab ozogamicin for the first two cycles.

- **Intermediate risk patients:** HiDAC has been shown to be preferable to lower dose cytarabine in this cytogenetic group as well but its superiority over stem cell transplantation has not been established. It is generally recognized that an allogeneic stem cell transplant provides a decreased relapse rate at a cost of increased treatment related mortality when compared to consolidation chemotherapy or autologous transplantation. The transplant related mortality gap between match related and unrelated donors has been shown to be significantly reduced in recent years. A suitable hematopoietic stem cell donor should be sought, and myeloablative stem cell transplantation should proceed as soon as possible, ideally after one cycle of HiDAC based on a risk/benefit analysis.

- **High risk patients:** All efforts should be undertaken to find a suitable donor for eligible high-risk patients. During that time the patient should receive ongoing cycles of HiDAC chemotherapy up to a total of 4 cycles or CPX-351 up to 2 cycles. The patient should proceed to allogeneic stem cell transplantation as soon as a donor is identified.

References

1. Bishop J. The treatment of adult acute myeloid leukemia. Semin Oncol 2007;24(1):466-75.
2. Gorin M. Autologous stem cell transplantation in acute myeloid leukemia. Blood 1998;92(4):1073-90.
3. Burnett A, Goldstone A, Stevens R, Hann IM, Rees JK, Gray RG, et al. Randomised addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. Lancet 1998 Mar;351(9104):700-8.
4. Cassileth P, Harrington D, Appelbaum F, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Engl J Med 1998 Dec;339(23):1649-56.
5. Linker C, Ries C, Damon L, Sayre P, Navarro W, Rugo HS, et al. Autologous stem cell transplantation for acute myeloid leukemia in first remission. Biol Blood Marrow Transplant 2000;6(1):50-7.
6. Burnett A, Kell J, Rowntree C. Role of allogeneic and autologous hematopoietic stem cell transplantation in acute myeloid leukemia. Int J Hematol 2000;72(3):280-4.
7. Ogawa H, Ikegame K, Kawakami M, Takahashi S, Sakamaki H, Karasuno T, et al. Impact of cytogenetics on outcome of stem cell transplantation for acute myeloid leukemia in first complete remission: a large-scale retrospective analysis of data from the Japan Society for Hematopoietic Transplantation. Int J Hematol 2004 Jun;79(5):494-500.
8. Slovak M, Kopecky K, Cassileth P, Harrington DH, Theil KS, Mohamed A, et al. Karyotypic analysis predicts outcome of preremission and postremission in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group study. Blood 2000 Dec;96(13): 4075-83.
9. Jourdan E, Reiffers J, Stoppa A, Sotto JJ, Attal M, Bouabdallaha R, et al. Outcome of adult patients with acute myeloid leukemia who failed to achieve complete remission after one course of induction chemotherapy: a report from the BGMT Study Group. Leuk Lymphoma 2001 Jun;42(1-2):57-65.
10. Appelbaum F. Who should be transplanted for leukemia? Leukemia 2001;15(4):680-2.
11. Robak T, Wrzesien-Kus A. The search for optimal treatment in relapsed and refractory acute myeloid leukemia. Leuk Lymphoma 2002;43(2):281-91.
12. Burnett A, Wheatley K, Goldstone A, Stevens RF, Hann IM, Rees JH, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukemia at differing risks of relapse: results of the UK MRC AML 10 trial. Br J Haematol 2002 Aug;118(2):385-400.
13. Byrd J, Mrozek K, Dodge R, Carroll AJ, Edwards CG, Arthur DC, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood 2002 Dec;100(13):4325-36.
14. Lowenberg B, Griffin JD, Tallman M. Acute myeloid leukemia and acute promyelocytic leukemia. Hematology Am Soc Hematol Educ Program 2003:82-101.
15. Levi I, Grotto I, Yerushalmi R, Ben-Bassat I, Shpilberg O. Meta-analysis of autologous bone marrow transplantation versus chemotherapy in adult patients with acute myeloid leukemia in first remission. Leuk Res 2004 June;28(6):606-12.
16. Yanada M, Matsuo K, Emi N. Efficacy of allogeneic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a meta-analysis. Cancer 2005;103(8):1652-8.
17. Stone R, O'Donnell M, Sekeres M. Acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 2004:98-117.
18. Bienz M, Ludwig M, Leibundgut E, Mueller BU, Ratschiller D, Solenthaler M, et al. Risk assessment in patients with acute myeloid leukemia and a normal karyotype. Clin Cancer Res 2005 Feb;11(4):1416-24.
19. Breems D, Van Putten W, Huijgens P. Prognostic index for relapsed patients with acute myeloid leukemia in first relapse, J Clin Oncol 2005;23(9):1969-78.
20. Morzek K, Marrcucci G, Paschka P, Whitman SP, Bloomfield CD. Clinical relevance of mutations and gene-expression changes in adult acute myeloid leukemia with normal cytogenetics: are we ready for a prognostically prioritized molecular classification? Blood 2007 Jan;109(2):431-48.
21. Paschka P, Marcucci G, Ruppert A, Mrózek K, Chen H, Kittles RA, et al. Adverse prognostic significance of kit mutations is adult acute myeloid leukemia with inv (16) and t(8:21): a Cancer and Leukemia Group B Study. J Clin Oncol 2006 Aug;24(24):3904-11.
22. Weick JK, Kopecky KJ, Appelbaum FR, Head DR, Kingsbury LL, Balcerzak SP, et al. A randomized investigation of high dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: A Southwest Oncology Group study. Blood 1996;88(8):2841-51.

23. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. N Eng J Med 1994;331(14):896-903.
24. Zittoun RA, Mandelli F, Willemze R, de Witte T, Labar B, Resegotti L, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. N Eng J Med 1995;332(4):217-23.
25. Harousseau JL, Cahn JY, Pignon B, Witz F, Milpied N, Delain M, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. Blood 1997;90(8):2978-86.
26. Burnett AK, Goldstone AH, Stevens RM, Hann IA, Rees JKH, Gray RG, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. Lancet 1998;351(9104):700-8.
27. Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogenic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Eng J Med 1998;339(23):1649-56.
28. Bloomfield CD, Lawrence D, Byrd JC, Carroll A, Pettenati MJ, Tantavahi R, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. Cancer Res 1998;58(18):4173-9.
29. Byrd JC, Dodge RK, Carroll A, Baer MR, Edwards C, Stamberg J, et al. Patients with t (8:21) (q22:q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered. J Clin Oncol 1999;17(12):3767-75.
30. Palmieri S, Sebastio L, Mele G, Annunziata M, Annunziata S, Copia C, et al. High dose cytarabine as consolidation treatment for patients with acute myeloid leukemia with t (8;21). Leuk Res 2002;26(6):539-43.
31. Byrd JC, Ruppert AS, Mrózek K, Carroll AJ, Edwards CG, Arthur DC, et al. Repetitive cycles of high-dose cytarabine benefit patients with acute myeloid leukemia and inv (16) (p13q22) or t (16:16) (p13; q22): results from CALGB 8461. J Clin Oncol 2004; 22(6): 1087-94.
32. Schlenk RF, Pasquini MC, Pérez WS, Zhang MJ, Krauter J, Antin JH, et al. HLA-identical sibling allogeneic transplants versus chemotherapy in acute myelogenous leukemia with t (8;21) in first complete remission: collaborative study between the German AML Intergroup and CIBMTR. Biol Blood Marrow Transplant 2008;14(2):187-96.
33. Farag SS, Ruppert AS, Mrózek K, Bloomfield CD. Outcome of induction and postremission therapy in younger adults with acute myeloid leukemia with normal karyotype: a Cancer and Leukemia Group B study. J Clin Oncol 2005;23(3):482-93.
34. Cassileth PA, Lynch E, Hines JD, Oken MM, Mazza JJ, Bennett JM, et al. Varying intensity of postremission therapy in acute myeloid leukemia. Blood 1992; 79(8):1924-30.
35. Visani G, Olivieri A, Malagola M, Brunori M, Piccaluga PP, Capelli D, et al. Consolidation therapy for acute myeloid leukemia: a systematic analysis according to evidence based medicine. Leuk Lymph 2006;47(6):1091-1102.
36. Sierra J, Martino R, Sanchez B, Pinana JL, Valcarcel D, Brunet S. Hematopoietic transplantation from adult unrelated donors as treatment for acute myeloid leukemia. Bone Marrow Transplant 2008;41(5):425-37.
37. Moore J, Nivison-Smith I, Goh K, Dodds A. Equivalent survival for sibling and unrelated donor allogeneic stem cell transplantation for acute myelogenous leukemia. Biol Blood Marrow Transplant 2007;13(5):601-7.
38. Abu-Duhier FM, Goodeve AC, Wilson GA, Gari MA, Peake IR, Rees DC, et al. FLT3 internal tandem duplication mutations in adult acute myeloid leukemia defines a high-risk group. Br J Haematol 2000;111(1):190-5.
39. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council of AML 10 and 12 trials. Blood 2001;98(6):1752-9.
40. Thiede C, Steudel C, Mohr B, Schaich M, Schakel U, Platzbecker U, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood 2002;99(12):4326-35.
41. Schnittger S, Schoch C, Dugas M, Kern W, Staib P, Wuchter C, et al. Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. Blood 2002;100(1):59-66.
42. Fröhling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood 2002;100(13): 4372-80.

43. Beran M, Luthra R, Kantarjian H, Estey E. FLT3 mutation and response to intensive chemotherapy in young adult and elderly patients with normal karyotype. Leuk Res 2004;28(6):547-50.
44. Schnittger S, Schoch C, Kern W, Mecucci C, Tschulik C, Martelli MF, et al. Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. Blood 2005;106(12):3733-9.
45. Döhner K, Schlenk RF, Habdank M, Scholl C, Rucker FG, Corbacioglu A, et al. Mutant nucleophosmin (NMP1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interactions with other gene mutations. Blood 2005;106(12):3740-6.
46. Döhner K, Wie AH, Appelbaum FR, Cradduock C, DiNardo CD et al. Diagnosis and managment of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 2022: 140912):1345-1377
47. Verhaak RG, Goudswaard CS, van Putten W, Bijl MA, Sanders MA, Hugens W, et al. Mutations in nucleophosmin (NMP1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. Blood 2005;106(12):3747-54.
48. Thiede C, Koch S, Creutzig E, Steudel C, Illmer T, Schaich M, et al. Prevalence and prognostic impact of NPM1 mutations in 1485 patients with AML. Blood 2006;107(10):4011-20.
49. Falini B, Nicoletti I, Martelli MF, Mecucci C. Acute myeloid leukemia carrying cytoplasmic/mutated nucleoplasmin (NPMc+ AML): biologic and clinical correlates. Blood 2007;109(3):874-85.
50. Schlenk RF, Döhner K, Krauter J, Frohling S, Corbacioglu A, Bullinger L, et al. Mutations and treatment outcomes in cytogenetically normal acute myeloid leukemia. New Eng J Med 2008;358(18):1909-18.
51. Schnittger S, Kohl TM, Haferlach T, Kern W, Hiddemann W, Spiekermann K, et al. KIT-D816 mutations in AML1-ETO-positive AML are associated with impaired event-free and overall survival. Blood 2006;107(5):191-9.
52. Cairoli R, Beghini A, Grillo G, et al. Prognostic impact of c-KIT mutation in core binding factor leukemias. An Italian retrospective study. Blood 2006;107(9):3463-8.
53. Paschka P, Marcucci G, Ruppert AS, Mrozek K, Chen H, Kittles RA, et al. Adverse prognostic significance of KIT mutations is adult acute myeloid leukemia with inv (16) and t (8:21): a Cancer and Leukemia Group B Study. J Clin Oncol 2006;24(24):3904-11.
54. Ossenkoppele GJ, Schuurhuis GJ. MRD in AML: is it time to change the definition of remission. Best Pract Res Clin Haematol 2014; 27)3-4):265-271.
55. Terwijn M, Putten WL, Keider A, van der Velden VHJ, Brooimans RA, Pabst T, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. J Clin Oncol. 2013;31(31):3889-3897.
56. Walter RB, Buckley SA, Pagel JM, Wood BL, Storer BE, Sandmaier BM, et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. Blood. 2013;122(10):1813-1821.
57. Walter RB, Gooley TA, Wood BL, Milano F, Fang M, Sorror ML, et al. Impact of pretransplantation minimal residual disease, as detected by multiparametric flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. J Clin Oncol 2011; 29(9);1190-1197.
58. Buckley SA, Appelbaum FR, Walter RB. Prognostic and therapeutic implications of minimal residual disease at the time of transplantation in acute leukemia. Bone Marrow Transplant 2013;48(5):630-641.
59. Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. Blood 2016;127(1):62-70.

Acute Lymphoblastic Leukemia (ALL)

Presented by: Lynn Savoie

Summary

- The search for a donor should be undertaken for all patients, including those with standard risk disease until it has been proven that they can tolerate the intensification portion of the chemotherapy protocol.
- Transplantation in first complete remission will be offered to patients who meet other eligibility criteria and who have any one of the following:
    - A high white blood cell count at diagnosis (pre-B cell phenotype > 30, pre-T cell phenotype > 100).
    - Failure to enter complete measurable residual disease negative remission within 28 days of starting induction chemotherapy.
    - Complex (>5 abnormalities), low hypodiploid (30-39 chromosomes) or near triploid (66-79 chromosomes) karyotypes.
    - t(8;14), KMT2A gene rearrangements or IKZF1 mutations.
    - Philadelphia-like disease.
    - Intolerance of post-induction chemotherapy such that less than 80% of scheduled chemotherapy is likely to be delivered.
- Transplantation in first complete remission should be considered in patients with Philadelphia chromosome positivity who do not achieve early MRD clearance or who are unable to tolerate planned chemotherapy
- Patients without documented CNS disease should receive at least four doses of intrathecal chemotherapy for CNS prophylaxis prior to transplant.
- Patients should be in remission (defined as fewer than 5% blasts in a normocellular bone marrow and no active extramedullary disease or circulating blasts) at the time of transplantation.
- BCR-ABL will be monitored post-transplant and TKI therapy re-instituted upon any evidence of molecular positivity. TKI prophylaxis should be considered for those with high-risk disease at the time of transplant (see below for details).
- Stem cell transplantation should be offered to all transplant-eligible patients with recurrent ALL, a suitable donor and meeting general eligibility criteria (including remission status) for transplantation.
- CAR-T therapy with Tisagenlecleucel may be offered in the setting of relapsed or refractory disease.

Background

The age-adjusted incidence rate of ALL in the US is 1.6 per 100,000 individuals per year, with approximately 6070 new cases and 1430 deaths estimated in 2013[1,2]. The median age at diagnosis is

14 years; 60% of patients are diagnosed at younger than 20 years, whereas 24% are diagnosed at 45 years or older[2]. The potential years of life lost due to leukemia in Canada has been reported to be 37,000[3]. The large number of years lost for a relatively uncommon diagnosis reflects the occurrence of leukemia among very young individuals and the high mortality these patients experience.

Chemotherapy

With current treatment regimens, the cure rate among children with ALL is approximately 80-90%[4]. The long-term prognosis for adults with ALL treated with conventional chemotherapy regimens, however, remain poor, with cure rates of only 30 to 40%[5-12]. This reflects the greater tendency for older individuals to have adverse chromosomal markers (notably t (9; 22)) and other unfavorable prognostic indicators (high white blood cell (WBC) count, longer time to complete response). Multidrug chemotherapy regimens have been the standard approach to treatment of adults with ALL. Such regimens generally consist of 4- or 5-drug induction protocols followed by intensive re-induction, consolidation or intensification to address residual disease. These regimens also feature CNS prophylaxis in the form of whole brain radiotherapy or intrathecal chemotherapy and prolonged antimetabolite-based maintenance, as has been used successfully in management of pediatric cases.

In recent years, a growing body of data has shown that, at least for late adolescents and young adults (defined variably up to 40 years of age), treatment with pediatric-based protocols produces superior outcomes to the regimens standardly used in adults[14-17]. Canadian data has shown that a pediatric approach can safely be extended to adults up to the age of 60 with only minor modifications[18]. This protocol is heavily dependent on L-Asparaginase in intensification and has been shown to have the best outcomes if 80% of L-Asparaginase doses can be delivered; this has been shown to be possible in 80% of patients. Meaningful comparisons of this strategy with early transplantation have yet to be published.

Many novel therapies are being studied in the management of ALL and may affect the need for or the outcome of stem cell transplantation in the future. These include Blinatumomab[19], Inotuzumab[20], the addition of Rituximab to chemotherapy[21] and CAR-T cell therapy[22].

CNS prophylaxis in the form of, intrathecal chemotherapy and/or high dose systemic chemotherapy has been shown to be necessary throughout chemotherapy and prior to stem cell transplantation.

Risk Stratification in ALL

Risk stratification in adult ALL has been based on disease (molecular findings, cytogenetics, WBC at diagnosis, response to treatment) and patient (chiefly age) factors. Leukemic blasts with T-cell or mature B-cell immunophenotype or the presence of a mediastinal mass are associated with overall improved survival. Blasts bearing the Philadelphia chromosome or t(4; 11), older patient age, high WBC or poor response to chemotherapy (> 4 weeks to complete response) portend a poor outcome

with standard treatment. It is likely that co-expression of myeloid markers and extensive lymphadenopathy will have a similar impact on survival.

Working together, the British Medical Research Council and the Eastern Cooperative Oncology Group were able to analyze the influence of cytogenetics on outcome of 1522 adults with ALL. This collaborative effort found that patients with t (9; 22), t (4; 11), t (8; 14), low hypodiploidy (30-39 chromosomes, usually with deletion 3 and 7) and near triploidy (66-79 chromosomes) had especially poor prognoses (5-year EFS 13 – 24%), while those with high hyperdiploidy (51-65 chromosomes) and tetraploidy (84-100 chromosomes) enjoyed relatively favourable outcomes (5-year EFS 46 – 50%)[23].

Within the last decade, a new moleculary defined entity, Philadelphia-like or BCR/ABL like ALL has been described. This subtype is associated with adverse clinical features, persistence of minimal residual disease, and a poor prognosis. While it lacks the BCR/ABL fusion it is characterized by a diverse spectrum of kinase fusions and cytokine receptor gene rearrangements that may be similarly amenable to molecularly targeted therapies[24].

The use of minimal residual disease (MRD) has been well-established in children with ALL. Studies in adults have also shown the strong correlation between MRD and risks for relapse, and the prognostic significance of MRD measurements during and after initial induction therapy. How to ultimately use MRD in deciding on the need for hematopoietic stem cell transplantation has not yet been fully established but is likely to play a role, particularly when tested after induction[25-32].

Hematopoietic Stem Cell Transplant (HSCT)

Transplantation in First Complete Remission

At any stage of disease, allogeneic bone marrow transplantation (BMT) results in lower relapse risk than standard chemotherapy. Many investigators have been unable to demonstrate an improvement in overall survival using this strategy as a result of high treatment-related mortality in this modality. Investigators at Princess Margaret Hospital reported their experience with a policy of allogeneic HSCT for all patients with ALL younger than 55 who had a related donor. Patients with Philadelphia-chromosome positive ALL were offered transplantation from a matched, unrelated donor if one was available. This strategy resulted in 3-year EFS of 40% for patients with donors and 39% for patients without. This strategy of universal allogeneic stem cell transplantation in ALL failed to improve outcome of patients with Philadelphia-negative ALL, while outcome was equivalent among patients with Philadelphia-positive disease.

In other cases the difference between allogeneic blood cell transplantation (BCT) and conventional chemotherapy has been more pronounced. The French LALA ’87 trial demonstrated improved overall survival among high-risk patients undergoing alloHSCT in CR1 (10-year OS 44%), compared with those who received chemotherapy or autologous BCT (10-year OS 11%). A similar impact on survival

among standard-risk patients was not seen (OS 49% versus 43%). The UK ALL XII study was of similar design to the LALA '87 trial, demonstrating superior 5-year EFS for alloHSCT in CR1 (54%) versus chemotherapy or autoHSCT (34%). Again, the greatest improvement in outcome was seen among high-risk patients (5-year EFS 44% versus 26%) while modest gains were demonstrated in patients with standard-risk disease (66% versus 45%).

Despite the above data, it remains unclear whether adult patients treated with paediatric protocols would gain a benefit from SCT. In their study of a 156 BCR-ABL negative patients treated with the DFCI protocol the 5 year OS amongst patients receiving an allogeneic SCT was 44% while for those not undergoing a SCT the survival was 74% with the difference possibly related to transplant related mortality. Seftel and colleagues compared 422 Ph-ve ALL patients aged 18-50 years with 108 patients receiving DFCI chemotherapy[35]. Expectedly, treatment related mortality was higher in those receiving a SCT (37% vs. 6%). At 4 years, the incidence of relapse was similar for those receiving SCT and chemotherapy (24% vs. 23%), however, both DFS and OS were improved for those receiving chemotherapy alone (40% vs. 71% for DFS and 45% vs. 73% for OS).

Transplantation in first complete remission will be offered to patients who meet other eligibility criteria and who have any one of the following:

- A high white blood cell count at diagnosis (pre-B cell phenotype > 30, pre-T cell phenotype > 100).
- Failure to enter complete measurable residual disease negative remission within 28 days of starting induction chemotherapy.
- Complex (>5 abnormalities), low hypodiploid (30-39 chromosomes) or near triploid (66-79 chromosomes) karyotypes.
- Philadelphia chromosome (or BCR-Abl), t(8;14), KMT2A gene rearrangements or IKZF1 mutations.
- Philadelphia-like disease.
- Intolerance of post-induction chemotherapy such that less than 80% of scheduled chemotherapy is likely to be delivered.

Philadelphia-positive Acute Lymphoblastic Leukemia

Twenty to forty percent of transplant-eligible adults with ALL will be found to have the Philadelphia chromosome as a sole or contributing cytogenetic abnormality. Patients with this abnormality tend to have other adverse prognostic features and have the lowest CR rate (< 65%) and shortest remission durations (median remission duration ~ 9 months) with conventional therapy. Overall survival is between 0 – 16%. In single-institution, non-randomized studies, leukemia-free survival after allogeneic BCT for Philadelphia-positive ALL is 30-40%.

The addition of imatinib to standard chemotherapy is feasible and safe and has been shown to improve remission rates and duration in this disease. This has allowed for more eligible patients to proceed to allogeneic stem cell transplantation.[36-41]. The use of second-generation TKIs is also being studied and dasatinib may prove to be of even more value given its inhibition of SRC and better CNS penetration. Finally, there is accumulating data that the more potent Ponatinib may result in even more profound responses and possibly eradicate the need for stem cell transplantation.[42-43]. Although allogeneic HSCT remains the standard post-remission approach for many patients with BCR-ABL positive ALL, patients who achieve early MRD negativity by PCR (e.g. after induction with the Chalandon protocol) may be continued on post-induction chemotherapy + TKI without a transplant; these patients should continue with indefinite TKI and regular PCR monitoring. However, all patients with persistent molecular positivity should be referred for allogeneic HSCT if otherwise eligible. Consideration should be given to switching to a more potent TKI such as dasatinib or ponatinib in these MRD+ patients prior to transplant. Furthermore, patients with subsequent recurrence of MRD detectable disease by PCR should also be referred for transplant.[44-49]

BCR/ABL monitoring should be done every 3 months for the first year post transplant then with every visit. If there is re-appearance of a TKI transcript, treatment with a TKI should be reinitiated. The choice of TKI would depend on responses pre transplant and comorbidities. There is no data to suggest duration of TKI therapy in this setting but it would be at least for many years after return to negativity or possibly indefinitely.

TKI maintenance may have a potential role in reducing the risk of relapse following HSCT. However, pre-emptive therapy has also led to favorable long-term outcomes[50-52]. A meta-analysis of the use of TKI's post-transplant showed that use of TKIs (all generations) after allo-HSCT for patients in CR1 improved OS when given as a prophylactic or pre-emptive regimen. Limited data suggest that second-generation TKIs (ie, dasatinib) have a better OS, especially in patients with MRD-positive status[53]. Consideration should be given to the use of TKI's post transplantation for those with high-risk disease such as BCR/ABL MRD positivity or in second complete remission at the time of transplantation.

Transplantation beyond First Complete Remission

The outcome for patients with ALL who fail to achieve a remission or who relapse remains poor, and such patients are generally offered alloHSCT from a matched or mismatched sibling, a volunteer unrelated donor or with umbilical cord blood stem cells. Long-term prognosis depends on time from remission to relapse, with shorter remissions being associated with worse prognosis. Allogeneic sibling HSCT in second CR results in 15-35% LFS, while for patients with refractory relapse, LFS between 8 – 33% have been reported. It is generally recommended that patients complete a course of CNS prophylaxis between relapse and transplantation.

CAR-T Therapy

Tisagenlecleucel is indicated in Canada for the treatment of relapsed or refractory acute lymphoblastic leukemia in patients under the age of 26. This indication is based partly on the results of a single-cohort, multi-center phase II trial (ELIANA) conducted by Maude et al[54]. In this study, children and young adults with relapsed or refractory CD19+ B-cell ALL received a single infusion of tisagenlecleucel after lymphodepleting chemotherapy. The primary end point, the overall remission rate at 3 months, was 82%, with all responding patients negative for MRD by flow cytometry. Event-free and overall survival were 50% and 76% at one year. Cytokine release syndrome occurred in 77% of patients, with tocilizumab required in 48%. Neurological events occurred in 40%. There were significant improvements in patient-reported outcomes (PedsQL and EQ-5D) three months after treatment[55]. Real world evidence in 255 patients with relapsed or refractory ALL further supports the use of tisagenlecleucel in this context. In this report twelve-month EFS and OS were 52.4% and 77.2%[56].

Brexucabtagene autoleucel has been approved by the FDA for use in adults with relapsed or refractory ALL based on the ZUMA-3 phase II study. This showed that in patients aged 28-52 with a median followup of 16.4 months, 39 patients had complete remission or complete remission with incomplete haematological recovery, with 31 (56%) patients reaching complete remission. Median duration of remission was 12·8 months, median relapse-free survival was 11·6 months and median overall survival was 18·2 months. Among responders, the median overall survival was not reached, and 38 (97%) patients had MRD negativity[57].

As yet there is no data to guide the sequencing of CAR-T cell therapy and transplantation in this setting.

References

1. National Cancer Institute. SEER Fact Sheet: Acute lymphoblastic leukemia. Bethesda: 2012. Available at: http://seer.cancer.gov/statfacts/html/alyl.html
2. Sigel R, Naishaham D, Jemal A. Cancer statistics, 2013, CA Cancer J Clin 2013.
3. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2014. Toronto, ON: Canadian Cancer Society; 2014.
4. Pui CH, Yang JJ, Hunger SP et a;. Childhood acute lymphoblastic leukemia: progress through collaboration. J Clin Oncol 2015: 33; 2938-2948
5. Annino L, Vegan ML, Camera A et al. Treatment of adult acute lymphoblastic leukemia: long-term follow-up of the GIMEMa ALL 0288 randomized study. Blood 2002; 99:863-71.
6. Bassan R, Hoelzer D, Modern therapy of acute lymphoblastic leukemia. J Clin Oncol 2011: 29; 532-43.
7. Kantarjian H, Thomas D, O'Brien S et al. Long term follou-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD) , a dose-intensive regimen in adult acute lymphoblastic leukemia. Cancer 2004; 101:2788-2801.
8. Larson RA, Dodge RK Burns CP et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 1995; 85:2025-37.
9. Linker C, Damon L, Ries C, Navarro W Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin ONcol 2002; 20:2464-71.
10. Rowe JM, Buck G, Burnett AK et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients form the international ALL trial: MRC UKALL XII/ECOG E 2993. Blood 2005; 106:3760-7.
11. Takeuchi J, Kyo T, Naito K et al, Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. Leukemia 2002; 16: 1259-66
12. Thomas X, Boiron J-M, Huguet F et al, Outcomes of treatment of adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial J Clin Oncol 2004; 22:4075086.
13. Stock W, La M Sanford B et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated n cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood 2008: 112:1646-54
14. de Bont JM, Holt Bvd, Dekker AW et al, Significant differences in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. Leukemia 2004;18:2032-5.
15. Hallbook H, Gustafsson G, Smedmyer B et al, Treatment outcome in young adults and children > 10 years of age with acute lymphoblastic leukemia in Sweden: a comparison between a pediatric protocol and an adult protocol. Cancer 2006;107:1551-61.
16. Ramanujachar R, Richards S, Hann I et al. Adolescents with acute lymphoblastic leukemia: outcome on UK national paediatric (ALO97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer 2007;48:254-61.
17. Stock W, Luger SM, Advani AS et al. A pediatric regimen for older adolscents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood 2019; 133: 1548-1559
18. Storring JM, Minden MD, Kao S et al, Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. Br J of Haem 2009;146:76-85.
19. Gokbuget. N, Dombret H, Bonifacio M et al, Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018; 131:1522-1531.
20. Kantarjian HM, DeAngelo DJ, Stelljes M et al, Inotuzumab ozogamicne versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer 2019; 125:2474-2487.
21. Maury S, Chevret S, Thomas X et al, Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. N Engl J Med 2016: 375:1044-53.
22. Maude SL, Laetsch TW Buechner J et al, Tisagenleleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia, N Engl J Med 2018; 378:439-448.
23. Moorman AV, Harrison CJ, Buck GA et ak, Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): Analysis of cytogenetic data from patients treated on the Medical Research Counceil (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood 2007; 109:3189-97.
24. Khan M, Siddiqi R, Tran TH, Philadelphia chromosome-like acutel lymphoblastic leukemia: A review of the genetic basis, clinical features, and therapeutic options Semin Hematol 2018: 55:235-241.

25. Mortuza FY, Papioannou M, Moreira IM et al, Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukemia J Clin Oncol 2002;20:1094-1104.
26. Bruggemann M, Raff T, Flohr T et al, Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood 2006;107:1116-23.
27. Holowiecki J, Krawczyk-Kulis M, Giebel S et al, Status of minimal residual disease after induction predicts outcome in both standard and high-risk Ph-negative adult acute lymphoblastic leukemia. The Polish Adult Leukemia Group ALL 4-2002 MRD Study. Br J Haem 2008;142:227-37.
28. Patel B, Rai L, Buck, et al, Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALLXII/ECOG2993. Br J Haem 2010:148:80-9.
29. Vidriales MB, Perez JJ, Lopez-Berges MC et al, Minimal residual disease in adolescent (older than 14 years) and adult acute lymphoblastic leukemias: early immunophenotypic evaluation has high clinical value. Blood 2003; 101:4695-4700.
30. Bassan R, Spinelli O, Oldani E, Intermesoli T, Tosi M, Peruta B, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood*. Apr 30 2009;113(18):4153-62.
31. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood*. Aug 30 2012;120(9):1868-76.
32. Ribera JM, Oriol A, Morgades M, Montesinos P, Sarrà J, González-Campos J, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. *J Clin Oncol*. May 20 2014;32(15):1595-604.
33. Thiebaut A, Vernant JP, Degos L, Huguet FR, Reiffers J, Sebban C, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation. A follow-up report of the French protocol LALA 87. *Hematol Oncol Clin North Am*. Dec 2000;14(6):1353-66, \
34. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. Feb 15 2008;111(4):1827-33.
35. Seftel MD, Neuberg D, Zhang MJ, Wang HL, Ballen KK, Bergeron J, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. *Am J Hematol* 2016;9193):322-329.
36. de Labarthe A, Rousselot P, Huguet-Rigal F et al, imatinib in combination with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of of the GRAAPH-2003 study Blood 2007;109:1408-13.
37. Thomas DA, Faderl S, Cortes J et al. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia with hyper-CVAD and imatinib mesylate. Blood 2004;103:4396-4407.
38. Wassmann B, Pfeifer h, Goekbuget N et al, Alternating versus concurrent schedules of imatinib and chemotherapy for newly diagnosed BCR-ABL –positive acute lymphoblastic leukemia. Blood 2006;108:1469-77.
39. Yanada M, Takeuchi J, Sugiura I et al High complete remission rate and promising outcomes by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group J Clin Oncol 2006;24:460-6.
40. Towatari M, Yanada M, Usui N et al. Combination of intensive chemotherapy and imatinib can rapidly induce high-quality complete remissions for a majority of patients with newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia. Blood 2004;104:3507-12.
41. Bassan R, Rossi G, Pogliani EM et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. J Clin Oncol 2010;28:3644-52.
42. Jabbour E, Short N, Ravandi F et al. Combination of hyper-CVAD with Ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre phase 2 study. The Lancet Haematology 2018; 5(12): E618-627.
43. Short N, Jabbour E, Sasaki K et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia Blood 2016, 128 (4): 504-507

44. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman AV, Durrant IJ, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood. May 7 2009;113(19):4489-96
45. Thyagu S, Minden MD, Gupta V, Yee KW, Schimmer AD, Schuh AC, et al. Treatment of Philadelphia chromosomepositive acute lymphoblastic leukaemia with imatinib combined with a paediatric-based protocol. Br J Haematol. Aug 2012;158(4):506-14.
46. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. Jun 11 2015;125(24):3711-9.
47. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia. Jul 2014;28(7):1467-71
48. .Ravandi F, Jorgensen JL, Thomas DA, O'Brien S, Garris R, Faderl S, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood. Aug 15 2013;122(7):1214-21.
49. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Kim DH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. Aug 6 2015;126(6):746-56.
50. Carpenter PA, Snyder DS, Floweres ME et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. Blood 2007;109:2791-3.
51. Chen H, Liu KY, Xu LP et al, Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. J Hematol Oncol 2012;5:29.
52. Pfiifer H, Wassmann B, Bethge W et al. Randomized comparison of prophylactic and minimal residual disease-triggered after allogeneic stem cell transplantation for BCR-ABL positive acute lymphoblastic leukemia. Leukemia 2013;27(6):1254-62.
53. Maude SL, Laetch TW, Buechner J et al, Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia NEJM 2018; 378(5): 439-48
54. Warraich Z, Tenneti P, Thai T et al. Relape Prevention with Tyrosoine Kinase Inhibitors after Allogeneic Transplantation for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Systematic Review Biol Blood Marrow Tranplant 2020; 26(3); e55-e64.
55. Laetsch TW, Myers GD, Baruchel A et al. Patient-reported quality of life after tisagenlecleucle infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leuekmia: a global, single-arm. Phase 2 trial. Lancet Oncol. 2019; 20(12): 1710-18).
56. Pasquini MC, Hu Z-H, Curran K et al. Real-world evidence od tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv 2020; 4(21): 5414-24
57. Sha BD, Ghobaid A, Oluwole O et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukemia: phase 2 results of the single-arm, open labe, multicenter ZUMA-3 study. Lancet 2021 398(10299):491-502.

Myelodysplastic Syndromes (MDS)

Presented by: Michelle Geddes

Summary

- All patients should have risk stratification including calculation of the Revised International Prognostic Scoring System (R-IPSS) at diagnosis.
- Patients with high (>4.5 to 6 points) or very high (>6 points) R-IPSS should be offered HCT if they are transplant-eligible.
- Patients with intermediate (>3 to 4.5 points) R-IPSS with symptomatic cytopenias or evidence of disease progression, who are transplant-eligible, can be considered for allogeneic HCT; with consideration of patient values and discussion around risks of transplant compared to the underlying disease.
- Sibling typing should be initiated at the earliest opportunity for all transplant-eligible patients.
- Disease control as a bridge to transplant with induction chemotherapy (consider if blasts >10% and no TP53 mutation and/or adverse cytogenetic profile) or hypomethylating agents such as azacitidine should be considered for patients with higher risk disease or elevated blast counts at presentation. The optimal therapy in this setting is not clear.
- Consider minimizing iron overload pretransplant to minimize the adverse effects of iron overload on treatment-related mortality.
- Myeloablative conditioning is preferred over non-myeloblative conditioning in patients who are fit to improve patient outcomes. Our standard conditioning is myeloablative busulfan + fludarabine + 4Gy TBI (see Conditioning chapter).
- Patients under the age of 40 or with an appropriate family history should be screened for congenital causes of MDS (i.e. Fanconi, dyskeratosis congenita). Appropriate consideration of hereditary syndromes should be made during donor search and planning of conditioning.
- In very high-risk patients, i.e., complex karyotype and p53 mutation, alternatives to transplant should be considered.

Background

Myelodysplastic syndromes are a heterogeneous group of related clonal stem cell disorders featuring dysplastic changes in one or more bone marrow cell lines, ineffective hematopoiesis, bone marrow failure, and often clonal evolution and/or transformation to acute leukemia. It is a disorder of the elderly, with a median age of 65-70 years at diagnosis. Allogeneic stem cell transplantation remains the only curative option; however the majority of patients are not eligible for transplantation due to age and/or comorbidity. For those who are eligible, the variable natural history of the disease and relative toxicity of transplant are important factors in the decision between supportive care, hypomethylating agents, lenalidomide, medical therapy including growth factors and allogeneic transplantation, and clinical trials.

Etiology

A history and physical exam should investigate for potential etiology of MDS:

- Ionizing radiation
- Cytotoxic agents (i.e., alkylating agents, topoisomerase inhibitors)
- Occupational or environmental carcinogens (i.e., viruses, benzenes, heavy metals)
- Inherited disorders (i.e., Fanconi anemia) especially in consideration of related donors
- Antecedent hematologic disorders (i.e. paroxysmal nocturnal hemoglobinuria, aplastic anemia).

Cytogenetic abnormalities are found in 40-70% of *de novo* MDS, and 95% of therapy-related MDS.

Table 1. World Health Organization (WHO) Classification (2016 revision)[1]

WHO Classification	Dysplastic lineages	Cytopenias[1]	% BM Ringed sideroblasts	BM and PB blasts	Karyotype
MDS with single lineage dysplasia	1	1 or 2	<15%/<5%[2]	BM <5%, PB <1%, no Auer rods	Any except del(5q)
MDS with multilineage dysplasia	2 or 3	1-3	<15%/<5%[2]	BM <5%, PB <1%, no Auer rods	Any except del(5q)
MDS with ringed sideroblasts Single lineage dysplasia Multilineage dysplasia	 1 2 or 3	 1 or 2	 ≥15%/≥5%[2]	 BM <5%, PB <1%, no Auer rods	 Any except del(5q)
MDS with isolated del5q	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) ±1 additional (not -7or del(7q))
MDS with excess blasts MDS-EB-1 MDS-EB-2	 0-3 0-3	 1-3 1-3	 None or any	 BM 5-9% or PB 2-4%, no Auer BM 10-19% or PB 5-19% or Auer rods	 Any Any
MDS, unclassifiable With 1% PB blasts With 1 lineage dysplasia & pancytopenia Defining cytogenetic abnormality	 1-3 1 0	 1-3 3 1-3	 None or any None or any <15%	 BM<5%, PB1% BM<5%, PB<1% BM<5%, PB<1%	 Any Any MDS-defining

Table 2. Revised IPSS (R-IPSS) for MDS[2]

Prognostic Variable	Score						
	0	0.5	1	1.5	2	3	4
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/μL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/μL)	≥0.8	<0.8					

**Cytogenetic definitions:*
Very good: -Y, del(11q)
Good: Normal, del(5q), del(12p), del(20q), double including del(5q)
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities
Very poor: Complex: >3 abnormalities.

Table 3. Survival based on total score from the R-IPSS

Risk Group	IPSS-R score	Median overall survival (years)	Median time to 25% AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3	5.3	10.8
Intermediate	>3 to 4.5	3	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

Automatic IPSS-R Calculator can be accessed at: https://www.mds-foundation.org/ipss-r-calculator/
For these and other online calculators also see http://www.mdsclearpath.org

Incorporation of molecular data into the Revised IPSS score has been found to improve prognostication in MDS. Independent significant prognostic factors for survival include age, R-IPSS, EZH2, SF3B1 and TP53[3]. A linear predictive model was built which resulted in four prognostic groups (low, intermediate-1, intermediate-2 and high) with a median overall survival of 37.4, 23.2, 19.9 and 12.2 months, respectively, (P<0.001).

Intensity of Treatment in Allogeneic Stem Cell Transplantation for MDS

Reduced intensity conditioning therapy is known to have a higher relapse rate in MDS but lower treatment-related mortality. In a retrospective study of 836 patients with MDS transplanted with an HLA matched sibling, the 3-year relapse rate was higher in patients given reduced intensity conditioning (HR 1.6, p=0.001) but a corresponding decrease in 3-year non-relapse mortality (NRM) resulted in similar progression-free survival (PFS, 33% vs. 39%) and overall survival (OS) rates (41% vs. 45%).[4] The role of treatment intensity was evaluated in a randomized multicenter phase III clinical trial comparing reduced intensity conditioning (RIC) including FluBu2 (2 days busulfan) to

myeloablative conditioning regimens including our current conditioning fludarabine and busulfan without TBI.[5] The study was stopped early due to increased relapse rates with RIC 48% vs 13.5%) with a nonsignificant reduction in OS at 18 months (68% vs 78% for RIC and MAC, respectively) and a lower relapse-free survival with RIC (47% vs 68%). Notably, TRM was lower at 4.4% with RIC vs 15.8% with MAC. Outcomes with FLUBUP/TBI remain to be determined but compare favorably with these series. Local outcomes comparing the use of TBI in patients with MDS from 1999-2010 suggest improved 2-year DFS in patients given FLUBUP/TBI compared to FLUBUP alone (2-year DFS 67% vs. 41%) although with small numbers the difference is not statistically significant. The decision has been made to incorporate TBI in the transplant regimen of patients with MDS.

Outcomes with Allogeneic Transplantation

An *EBMT review of 1333 patients age >50 with high risk MDS or secondary AML* who received allogeneic sibling (61%) or unrelated donor (39%) hematopoietic stem cell transplant with a myeloablative (38%) or reduced intensity conditioning (62%) regimen.[6] Of the 1333 patients, 449 (34%) were >60y of age. *Four-year OS was 31%.* Factors associated with higher risk of relapse include use of RIC (HR 1.44, P<0.01) and advanced disease stage at transplantation (HR, 1.51; P<0.01). Factors associated with increased non-relapse mortality include advanced disease stage at transplantation (HR, 1.43; 95% CI, 1.13 to 1.79; P = 0.01), use of an unrelated donor (P = 0.03), and RIC (HR, 0.79; 95% CI, 0.65 to 0.97; P =0 .03). *The major factor associated with 4-year OS was disease stage at transplantation* (HR, 1.55; P<0.01) and challenges remain in with both higher relapse rates posttransplant and higher treatment-related mortality with MDS compared to de novo AML.

A single-centre study at the University of Wisconsin describes the importance of pre-transplant disease burden (as reflected by the proportion of bone marrow blasts at transplant). Patients entering transplant with < 5% blasts had a lower probability of relapse at 1-year than those entering transplant with 5-20% blasts (18% (8-28%) vs. 35% (16-54%), p=0.07).[7] The use of chemotherapy to achieve fewer than 5% blasts did not adversely affect the outcome of transplant in this cohort. The use of myeloablative conditioning was unable to overcome the adverse effect of high disease burden (>5% blasts): relapse rates were similar for patients with >5% blasts, regardless of whether myeloablative or non-myeloablative conditioning was used (28% (CI 8-48%) vs. 50% (CI 18-82%), p=0.33).

As NGS studies become available and more information is available about disease prognostication with transplant. A Japanese study of 797 patients with MDS showed that in patients with cytogenetics and NGS testing, cox regression analysis showed approximately 70% of the hazard ratio of transplant was related to clinical factors ie performance status, comorbidities, transfusion history and 30% contributed by adverse genetic risk.[8] An especially high risk category of patients with both mutation TP53 and complex karyotype did very poorly with transplant with a median survival of 4.8 months; 38% died before day 100 and >80% within 2 years of transplant, largely due to early relapse in 60% of patients. A retrospective review of 1514 patients with MDS undergoing stem cell

transplantation showed shorter survival and time to relapse in patients with TP53 mutations, and shorter survival in patients with JAK2 and RAS mutations.[9]

Comparison of HCT vs non-HCT. A landmark decision analysis by the CIBMTR compared outcomes in newly diagnosed MDS between three treatment strategies: transplantation at diagnosis, transplantation at leukemic progression, and transplantation at an interval from diagnosis but before leukemic progression.[10] Low and intermediate-1 IPSS groups maximized survival with delayed transplantation, especially in patients <40y old, and outcomes were better with transplantation prior to leukemic transformation. Patients in Int-2 and high risk IPSS groups maximized survival with transplantation at diagnosis. An updated cohort study with Markov decision analysis in 2013 using older patients (age 60-70y) stratified by IPSS and reduced intensity conditioning transplant vs nontransplant strategies (basic supportive care, ESAs if anemia, hypomethylating agents for Int-2 and high risk disease) showed improved life expectancy with RIC transplant for int-2 and high risk MDS, and longer life expectancy with non-RIC treatments for low and int-1 disease.[11]

Bridge to HCT. The use of azacitidine provides further options for care and potentially for bridge to transplantation and cytoreduction. Several case series using azacitidine as bridge to transplantation shows this treatment is feasible; effect on transplant outcomes is being determined.[12-14] An EBMT retrospective review of 209 patients with higher risk MDS showed that outcomes at 3 years were not significantly different between patients treated with hypomethylating agents or chemotherapy prior to HCT with respect to OS (42% versus 35%), RFS (29% versus 31%), cumulative incidence of relapse (45% versus 40%), and NRM (26% versus 28%), despite younger age and a higher proportion of patients with primary refractory disease in the hypomethylating group arm.[15] In patients with very high blast counts >10% and a planned rapid progression to transplant, chemotherapy can provide a faster response and is more likely to result in a CR to help bridge to transplant, but has more toxicities. For patients with monosomy 7, del 7q, ≥3 chromosomal abnormalities, or mutation of *TP53,* hypomethylating agents are recommended over intensive chemotherapy or supportive care due to poor response rates to intensive chemotherapy in MDS patients with these features. For patients with high-risk disease, treatment is recommended as a bridge to curative therapy during transplant workup.

References

1. Swerdlow S, Campo E, Harris N, Jaffe, E, Pileri S, Stein H, Thiele J, Arber D, Jasserjian R, Le Beau M, Orazi A, Siebert R Editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer; 2017.
2. Haase D et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012 (120): 2454-2465.
3. Nazha A, Narkhede M, Radivoyevitch T, Seastone DJ, Patel BJ, Gerds AT, Mukherjee S, Kalaycio M, Advani A, Przychodzen B, Carraway HE, Maciejewski JP, Sekeres MA. Incorporation of molecular data into the Revised International Prognostic Scoring System in treated patients with myelodysplastic syndromes. Leukemia. 2016 Nov;30(11):2214-2220. doi: 10.1038/leu.2016.138. Epub 2016 May 20.

4. Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood 2006 Aug;108(3):836-46.
5. Scott B, Pasquini M, Logan B, Wu J, Devine S, et al. Myeloablative vs reduced-intensity hematopoietic cell transplant for acute myeloid leukemia and myelodysplastic syndromes. Journal of Clinical Oncology 2017; 25(11): 1195.
6. Lim Z, Brand R, Martino R, van Biezen A, Finke J, Bacigalupo A, et al. Allogeneic hematopoietic stem cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. Journal of Clinical Oncology 2010;28(3):405-11.
7. Warlick ED, Cioc A, DeFor T, Dolan M, Weisdorf D. Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant disease burden. Biol Blood Marrow Transplant 2009 Jan;15(1):30-8.
8. Yoshizato T, Nannya Y, Atsuta Y, Shiozawa Y, Iijima-Yamashita Y, Yoshida K, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood. 2017;129(17):2347
9. Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, Grauman PV, Hu ZH, Spellman SR, Lee SJ, Verneris MR, Hsu K, Fleischhauer K, Cutler C, Antin JH, Neuberg D, Ebert BL. Prognostic mutations in Myelodysplastic Syndrom after Stem Cell Transplantation. NEJM. 2017;376(6):536.
10. Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Perez WS, Anasetti C, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood 2004 Jul; 104(2):579-85.
11. Koreth J, Pidala J, Perez WS, Deeg HJ, Garcia-Manero G, Malcovati L, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. Journal of Clinical Oncology 2013 31(21):2662-70
12. Damaj G, Duhamel A, Robin M, Beguin Y, Michallet M, Mohty M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. Journal of Clinical Ocology 2012 30(36):4533-40.
13. Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplant therapy with azacitidine vs induction therapy and posttransplantation outcome with MDS. Biol Blood Marrow Transplant. 2012; 18(8):1211-8
14. Voso MT, Leone G, Piciocchi A, Fianchi L, Santarone S, Candoni A, et al. Feasibility of allogeneic stem cell transplantation after azacitidine bridge in higher risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study. Annals of Oncology 2017; 28(7): 1547-1553.
15. Biol Blood Marrow Transplant. 2016 Sep;22(9):1615-1620. Comparison of intensive chemotherapy and hypomethylating agents before allogeneic stem cell transplantation for advanced myelodysplastic syndromes: a study of the myelodysplastic syndromes subcommittee of the chronic malignancies working party of the European society for blood and marrow transplant research. Biology of Blood and Marrow Transplant 2016 ;22(9):1615-20.

Chronic Myelogenous Leukemia

Presented by: Lynn Savoie

Summary

Chronic Phase

First line Therapy:

- First line therapy is with a tyrosine kinase inhibitor (TKI) (imatinib, dasatinib or nilotinib)
- Molecular monitoring with quantitative PCR (polymerase chain reaction) every 3 months
    - Cytogenetics and mutation analysis as per the chronic myeloid leukemia (CML) treatment guidelines
    - Assess milestones as per provincial CML treatment guidelines

Subsequent Therapy:

- Adjust TKI therapy as per CML treatment guidelines for patients showing resistance or intolerance to first-line therapy, options include imatinib, dasatinib, nilotinib, bosutinib, ponatinib or asciminib
- In patients on a second generation TKI showing warning signs, who experience a suboptimal response or failure and are otherwise transplant eligible, perform human leukocyte antigen (HLA) typing of patient and siblings followed by a search for a volunteer unrelated donor (VUD) if no suitable family member is identified
- Transplantation should be undertaken for eligible patients who fail to meet the provincial treatment guideline milestones for response to two second generation TKIs, ponatinb and/or asciminib
- Transplantation should be undertaken in eligible patients who are unable to tolerate tyrosine kinase inhibitors such that compliance becomes an issue
- Patients found to carry the T315I mutation should receive ponatinib or asciminib during the donor search and workup periods

Blast Phase

- HLA type patients and siblings and proceed with VUD or alternate donor search if no family match identified
- Attempt to induce CP2 prior to allogeneic stem cell transplantation with chemotherapy and TKIs
- Transplantation is contraindicated in blast phase

Monitoring for Relapsed/Refractory CML Post Transplantation

- Quantitative peripheral blood PCR for brc/abl transcript every 3 months for 2 years then every 6 months to 5 years and then yearly to coincide with scheduled follow up appointments

Treatment of Relapsed Disease Posttransplant
Molecular Relapse or Relapse in Chronic Phase:

- Minimize immunosuppression
- Initiate therapy with at least a second generation TKI, preferably one not used pre-transplant, if a positive nested PCR is detected at ≥6 months post-transplant or if the BCR/ABL ratio is rising prior to that
- If no response toTKI a mutation analysis should be sent prior to proceeding to escalating doses of TKI

Blast Phase Relapse:

- Minimize immunosuppression
- Perform mutation analysis
- Re-induce chronic phase prior to a second transplant in eligible patient– overall prognosis poor; palliation is a reasonable choice

Background

Chronic myelogenous leukemia makes up 14% of new leukemias, with a median age of 67 years. It is associated with the Philadelphia chromosome t(9;22) and p190, p210 or p230 bcr/abl fusion proteins. The Philadelphia chromosome is found in multiple cell lineages including granulocyte, erythroid, megakaryocyte, and B lymphocyte lineages. Progression of disease is often associated with cytogenetic evolution with common additional abnormalities including +Ph, +8, i(17q) and +19.

Natural History of CML

The natural history of CML involves a chronic phase, and blast phase. Prior to tyrosine kinase inhibitor (TKI) therapy, without stem cell transplantation progression to blast phase occurred on average 3-5 years after diagnosis. in the pre-imatinib era, with sudden onset of blast crisis pre-imatinib in 0.4% of patients in the first year, 1.8% in the second year, and 2.6% in the third year[1]. In the tyrosine kinase era life expectancy approximates normal[2].

Accelerated Phase: World Health Organization (WHO) Classification[3]

- Blasts 10-19% in peripheral blood or bone marrow
- Peripheral blood basophils ≥ 20%
- Persistent platelets < 100/nl unrelated to therapy or > 1000/nl unresponsive to therapy
- Increasing spleen size and/or white blood cell count unresponsive to therapy
- Clonal cytogenetic evolution

Blast Phase: WHO Classification[3]

- Blasts ≥ 20% in peripheral blood or bone marrow
- Extramedullary blast proliferation
- Large foci or clusters of blasts in bone marrow biopsy

Treatment

Front Line Treatment

Treatment with a TKI as first-line treatment for all newly diagnosed CP-CML patients is recommended. Currently in Alberta therapy is begun with imatinib, dasatinib or nilotinib. The choice of TKI should be guided by an individual patient's comorbidities. Patients having achieved their therapeutic milestones with and tolerant of a TKI should continue on it.

Peripheral blood Q-RT-PCR should be performed every 3 months. If a molecular response greater than 4.7-log reduction (MMR) is reached and stable for 2 years, the frequency of Q-RT-PCR may be decreased to every 4-6 months. The recommended definition of first-line optimal treatment response to tyrosine kinase inhibitors (TKIs) in accordance with European Leukemia Net guidelines[4], are defined as:

- BRC-ABL1 ≤10% (at least a 1-log reduction)
- BRC-ABL1 <1% (2-log reduction) and or Ph+ 0 at 6 months
- BRC-ABL1 ≤0.1%(≥3-log reduction) at 12 months, and thereafter

A second-generation TKI (nilotinib, dasatinib or bosutinib) is recommended for patients with imatinib resistance/ intolerance, or who fail to achieve any of the treatment milestones while on imatinib. The choice of a second-generation TKI should be guided by an individual patient's comorbidities. The presence of specific mutations will override other considerations when determining the optimal agent to employ. Asciminib, an allosteric inhibitor of the myristoyl site of the BCR-ABL protein, is available in the third line for patients who have failed or are resistant to at least 2 prior traditional TKI's. The third-generation drug, Ponatinib, is also available for patients in whom other TKI therapy is not appropriate, including CML that is T315I mutation positive or when there is resistance or intolerance to all other TKI therapy.

Human leukocyte antigen (HLA) typing of the patient and siblings is recommended when a patient presents in AP or BC or when there is suboptimal response, loss of a previously obtained response or significant intolerance.

Syngeneic Transplantation for CML

Although not commonly used, syngeneic transplantation provides evidence that graft-versus-leukemia effect is useful but not necessary for the cure of CML with high dose chemotherapy. A 1982 series of 22 patients, including 12 in chronic phase, resulted in 7 of 12 patients alive at 20-26 years[5]. Syngeneic transplants remain a viable option for a small number of patients, especially without other

donor options. Registry analysis shows a much higher relapse rate of 40% compared to 7% in allogeneic transplantation thought secondary to lack of graft versus leukemia effect. Supporting the importance of this effect is the higher relapse rate in T-cell depleted transplants and effectiveness of donor lymphocyte infusion (DLI). However, toxicities due to GVHD in syngeneic transplants are minimal.

Allogeneic Transplantation for CML

Allogeneic transplantation is a potentially curative modality for CML associated with increased toxicity up front compared to non-transplant therapy. An IBMTR (International Bone Marrow Transplant Registry) comparison of allogeneic stem cell transplantation with German CML Study Group trials using hydroxyurea or interferon showed that in the first 18 months the relative risk of death with transplant was 5.9, with similar mortality between the two groups between 18 and 56 months, and lower overall mortality with transplant after 56 months[6]. Seven-year survival was higher in the transplant group (58% versus 32%). Registry data reveal a 5-year survival post-transplant of 50 to 70% for matched related donor transplants and 40 to 60% for unrelated donors[7]. Advanced disease is associated with poor outcomes in allogeneic matched sibling transplantation; survival at 3 years with BuCy2 was 58% in chronic phase versus 41% in accelerated phase and 25% in blast phase, with relapse in 3%, 12%, and 27% of patients in each group[7].

The importance of obtaining a second chronic phase in patients in blast crisis pretransplant was seen in a small trial randomizing 10 patients to upfront allogeneic transplantation and 10 patients to induction chemotherapy followed by allotransplant[8]. All 10 patients transplanted in blast crisis died; 8 of 10 given induction chemotherapy achieved a second chronic phase, 7 patients were transplanted, and all of the 6 patients in the second chronic phase at the time of transplant achieved molecular remission. Median OS in this group was 23 months versus 6 months in those transplanted up front.

Data using the FLUBUP (fludarabine + busulfan) protocol in the first 21 CML patients in Calgary show a projected 3-year OS of 86% with FLUBUP/ATG (anti-thymocyte globulin), compared to a 3-year OS of 76% with the BuCy (busulfan + cyclophosphamide) protocol (p-value not significant). Transplant-related mortality at 3 years was 0% compared to 24% with BuCy (p=0.03). Further data is being accrued.

Allotransplants in the Post TKI Era

There is no evidence that transplant outcomes are worse in patients who have received prior tyrosine kinase inhibitors. An IBMTR analysis of 409 patients transplanted with prior imatinib exposure (9% imatinib intolerance, 37% imatinib failures, remainder planned transplants up front) and 900 patients without imatinib exposure revealed than in patients transplanted in first chronic phase, prior imatinib was associated with better overall survival, and no difference in transplant-related mortality, relapse, or leukemia-free survival.[9] This was confirmed in a matched pairs analysis. In patients with advanced CML, there was no difference between groups in transplant-related mortality, relapse, leukemia-free survival, and overall survival. No difference was seen in rates of acute GVHD. A single institution

study of 12 patients receiving a second generation TKI after imatinib failure showed no negative impact on transplant engraftment, relapse rate of transplant-related toxicity when compared to historical controls[10].

A report by the Swedish CML registry[11] reviewed 118 patients transplanted between 2002 and 2017. 47.4% received an allo-HSCT in first CP. TKI resistance was the most common transplant indication (62.5%). For patients diagnosed with CML in CP at <65 years of age, the cumulative probability of undergoing allo-HSCT within 5 years was 9.7%. Overall 5-year survival was 96.2%, 70.1% and 36.9% when transplanted in first CP, second or later CP, and in accelerated phase or blast crisis, respectively. Non-relapse mortality for patients transplanted in CP was 11.6%.

Timing of Transplantation

Multiple studies showed better outcomes in the pre-imatinib era if patients are transplanted in the first year after diagnosis. For example, in one study, patients transplanted within one year of diagnosis in chronic phase had a survival of 70% compared with 40% when transplanted beyond one year[12]. In the TKI era, early transplantation is no longer undertaken in patients meeting their milestones. In patients not meeting their milestones a study has shown that the degree of response immediately before transplantation was directly associated with worse outcomes for patients with only a hematological response compared with patients with a cytogenetic or molecular response advocating for the best response possible prior to transplantation[12].

Blood versus Marrow Stem Cell Source

Less relapse is seen in patients treated with peripheral blood stem cells (PCR positivity 44% with bone marrow versus 7% with peripheral blood at 4 years, p<0.009) but more chronic GVHD with peripheral blood[13]. Overall survival has been higher in peripheral blood transplants than bone marrow stem cell sources. *In vivo* T cell depletion with ATG decreases GVHD. The impact that ATG makes on altering relapse and GVHD outcomes between peripheral blood and bone marrow with the FLUBUP protocol is not fully understood.

Prognostication Pre-Allotransplant – EBMT Transplant Risk Score[14]

Table 2. European Group for Blood and Marrow Transplantation risk factor assessment

EBMT Risk Factor Assessment[4]			
Points	0	1	2
Risk Factors			
Age	<20 years	20-40 years	>40 years
Stage	1st CP	AP	BP or 2nd CP
Donor	HLA sib	MUD	
Sex Match	All others	Female to Male	
Time to Therapy	<12 months	>12 months	

Points	0	1	2	3	4	5	6	7
TRM	20	23	31	46	51	71	73	N/A
OS	72	70	62	48	40	18	22	N/A

Abbreviations: AP = accelerated phase; BP = blast phase; CP = chronic phase; EBMT = European Group for Blood and Marrow Transplantation; TRM = transplant-related mortality; MUD = matched unrelated donor

Molecular Monitoring Post HCT for CML

A retrospective review of 346 patients followed with PCR every 3 months post-transplant found that while in the first 3 months post-transplant, PCR positivity did not correlate with worse outcome. At 6 months or later, it was highly correlated with relapse (42% PCR+ relapse versus 3% PCR-, p<0.0001; 4-year OS 74% versus 93%, p=0.002)[15]. Between 6 and 12 months, the PCR+ patients had a relative risk of relapse of 26.0. However, at greater than 36 months, the short-term risk of relapse was much less; 15/59 were qualitative PCR+ but only 1 patient relapsed.

Quantitative PCR can be helpful in predicting relapse risk; at 3 to 5 months post-transplant, increasing PCR positivity is associated with increased risk of relapse. Relapse risk is 17% if PCR-, 43% if low level PCR+ (<0.02%), and 86% if PCR+ is >0.02%)[16]. In a study of 379 patients alive at 18 months, 90 had at least 1 positive test at 18 months, but only 14% relapsed (median 40,000 copies/ug) compared to 1% of PCR- patients relapsing (69 had only 1 test positive with mean 24 copies/ug)[19]. In a study of 98 patients, 69 had undetectable, decreasing, or low <50copies/ug PCR titers and only one relapsed. There was a 72% relapse rate in patients with persistent or high (>50 copies/ug) titers (p<0.00001)[17]. The correlation between blood and marrow PCR positivity is approximately 90%.

Based on this quantitative peripheral blood PCR for brc/abl transcript should be done every 3 months for 2 years then every 6 months to 5 years and then yearly to coincide with scheduled follow up appointments.

Treatment of Relapsed Disease

Treatment of Relapsed Disease Post-AlloHCT:

Imatinib is one therapy with moderate effectiveness in advanced relapsed disease post allogeneic HCT; in a review of 28 (5 chronic phase, 15 accelerated phase, 8 blast phase, 13 with previous DLI) imatinib-naïve patients who relapsed post-allotransplant, overall response to imatinib was 22/28, CCR 9/28 (35%), complete molecular response (CMR) 4/28[18]. All chronic phase patients attained CHR compared to 83% of the accelerated phase patients and 43% of the blast phase patients; one year overall survival was 74%. Five patients reactivated GVHD; three had grade III disease.

The second and third generation TKI's and asciminib have not been systemically studied post transplantation but are presumed to be equally if not more efficacious than imatinib. One study published in abstract form only supports this[20].

DLI is also effective and can induce a complete molecular response in about 70% of patients. These can be durable, with a probability of 80-90% DFS at three years and improvement of OS from 53% without DLI to 95% with DLI at three years (p=0.0001)[7,16]. There is an approximately 40% chance of GVHD greater than or equal to grade 2 and 30% chance of myelosuppression post-DLI. Responses are not generally durable in second chronic phase disease. The role of imatinib plus DLI is being investigated and a small number of patients have been reported with encouraging results[21].

A CIBMTR study retrospectively reviewed the outcomes of TKI vs. DLI vs. DLI + TKI in the setting of post-transplant relapse in the TKI era[22]. They found that patients who received a DLI alone had inferior survival compared with those who received a TKI with a DLI. Those who received a TKI alone had similar survival compared with those who received a TKI with a DLI supporting the use of a TKI alone following relapse. Therefore, initiation of TKI therapy with a second generation TKI, preferably one not used pre-transplant should be initiated if a positive PCR is detected 6 months post-transplant or if the BCR/ABL ratio is rising prior to that. If there is no response to TKI alone a mutation analysis should be sent. If there is no mutation proceed to escalating doses of TKI as per the relapse guideline section.

There is very little current data for more advanced phase relapses post-transplant. A mutation analysis should be sent. The next step is the minimization of immunosuppression as well as TKI therapy with- or without DLI should be considered in the accelerated phase potentially as a bridge to second transplant if the patient remains eligible. In the blast phase induction type chemotherapy in conjunction with TKI therapy should be undertaken prior to a second transplant if eligible. In this situation the overall prognosis is poor and palliation is a reasonable choice.

References

1. Kantarjian H, O'Brien S, Cortes J, Giles F, Thomas D, Kornblau S, et al. Sudden onset of the blastic phase of chronic myelogenous leukemia: patterns and implications. Cancer 2003 Jul;98(1):81-5.
2. Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC and Andersson TML. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. JCO 2016 Aug; 34(24):2851-2858.
3. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022 June: 36:1703-1719.
4. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020 Mar: 34 966-984
5. Fefer A, Cheever MA, Greenberg PD, Appelbaum FR, Boyd CN, Buckner CD, et al. Treatment of chronic granulocytic leukemia with chemoradiotherapy and transplantation of marrow from identical twins. N Engl J Med 1982 Jan;306(2):63-8.
6. Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H, et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. Blood 1998 Mar;91(5):1810-9.
7. Biggs JC, Szer J, Crilley P, Atkinson K, Downs K, Dodds A, et al. Treatment of chronic myeloid leukemia with allogeneic bone marrow transplantation after preparation with BuCy2. Blood 1992 Sept;80(5):1352-7.
8. Visani G, Rosti G, Bandini G, Tosi P, Isidori A, Malagola M, et al. Second chronic phase before transplantation is crucial for improving survival of blastic phase chronic myeloid leukaemia. Br J Haematol 2000 Jun;109(4):722-8.
9. Lee SJ, Kukreja M, Wang T, Giralt SA, Szer J, Arora M, et al. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. Blood 2008 Oct;112(8):3500-7.
10. Breccia M, Palandri F, Iori AP, Colaci E, Latagliata R, Castagnetti F, et al. Second-generation tyrosine kinase inhibitors before alloegeneic stem cell transplantation in patients with chronic myeloid leukemia resistant to imatinib. Leuk Res 2010 Feb;34(2):143-7.
11. Lubking A, Dreimane A, Sandin F, Isaksson C, Markevarn B, Brune M et al. Allogeneic stem cell transplantation for chronic myeloid leukemia in the TKI era: population-based data from the Swedish CML registry. BMT 2019 Nov; 54(11):1764-1774
12. De Oliveira Medeiros GR, Moreira Funke VA, Martins Lima AC, Vieira Mion AL, Menezes I et al. The Role of Molecular of Cytogenetic Response as a Favorable Prognostic Factor Before Hematopoietic Stem Cell Transplantation for Chronic Myeloid Leuekmia. Transplantation and Cellular Therapy, 2024 June 3096):e1-597
13. Kantargian H, O'Brien S, Talpaz M, Borthakur G, Ravandi F, Faderl S et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer 2007 Apr; 109(8):1556-60.
14. Gratwohl A. The EBMT risk score. BMT 2012; 47:749-756.
15. Radich JP, Gehly G, Gooley T, Bryant E, Clift RA, Collins S, et al. Polymerase chain reaction detection of the BCR-ABL fusion transcript after allogeneic marrow transplantation for chronic myeloid leukemia: results and implications in 346 patients. Blood 1995 May;85(9):2632-8.
16. Olavarria E, Kanfer E, Szydlo R, Kaeda J, Rezvani K, Cwynarski K, et al. Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplantation for chronic myeloid leukemia. Blood 2001 Mar;97(6): 1560-5.
17. Lin F, van Rhee F, Goldman JM, Cross NC. Kinetics of increasing BCR-ABL transcript numbers in chronic myeloid leukemia patients who relapse after bone marrow transplantation. Blood 1996 May;87(10):4473-8.
18. Kantarjian HM, O'Brien S, Cortes JE, Giralt SA, Rios MB, Shan J, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2002 Sept;100(5):1590-5.
19. Savani BN, Rezvani K, Mielke S, Montero A, Kurlander R, Carter CS, et al. Factors associated with early molecular remission after T cell-depleted allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2006 Feb;107(4):1688-95.
20. Chalandon Y, Iacobellie S, Hoek J, Koster L, Volin L, Finke J et al. Use of First or Second Generation TKI for CML after Allogeniec Stem Cell Transplantation: a Study by the CMWP of the EBMT. Blood 2016 Dec 128(22):4865
21. Guglielmi C, Arcese W, Dazzi F, Brand R, Bunjes D, Verdonck LF, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. Blood 2002 Jul;100(2):397-405.
22. Schmidt S, Liu Y, Hu, Z-H, Williams K, Lazarus H, Vij R et al. The Role of Donor Lymphocyte Infusion in Post-Hematopoietic Cell Transplant Relapse for Chronic Myeloid Leukemia in the Tyrosine Kinase Inhibitor Era. BBMT 2020 Jun; 26(6):1137-1143.

BCR-ABL-Negative Myeloproliferative Neoplasms

Presented by: Michelle Geddes

Summary

- Transplant eligible patients with myelofibrosis (MF) with *intermediate-2 or high-risk* disease according to the Dynamic International Prognostic Scoring System-plus (DIPPS-plus) criteria should be considered for allogeneic stem cell transplantation. This applies to both primary and post-PV/ET MF.
- Medically fit patients with *intermediate-1 risk* can be considered for transplant especially if age <65, with refractory, transfusion-dependent anemia, peripheral blood blasts >2%, or adverse cytogenetics, and should have a donor search performed.[1]
- All patients being considered for allotransplant should have mutation analysis by NGS and cytogenetics performed, if possible, to inform decision-making.
- Patients in blast phase (>20% bone marrow blasts) should be given induction chemotherapy prior to proceeding with stem cell transplantation.
- There is no convincing data to support the requirement for splenectomy or splenic radiation before transplantation. We do not recommend routine splenectomy or splenic irradiation pre-transplant.
- Our standard conditioning is myeloablative busulfan + fludarabine + 4Gy TBI (see Conditioning chapter).
- The use of JAK inhibitors pre-transplant is associated with improvement in constitutional symptoms and performance status, and decrease in spleen size, and can help improve clinical status prior to transplant. JAK inhibitors should be discontinued at the start of the conditioning for HSCT.

Background

Myeloproliferative neoplasms (MPNs) originate from acquired mutations that target the hematopoietic stem cell and induce dysregulation of kinase signaling, clonal myeloproliferation, and abnormal cytokine expression. The JAK2 V617F mutation is most frequent. Other mutations include CALR, MPL, and other mutations including some with adverse prognostic implications such as ASXL1 (38%), EZH2 (7%), IDH1/2 (45), SFSF2 (14%) and U2AF1Q157 (8%) mutations[2,3,4]. Patients with triple negative disease status for JAK2, CALR and MPL are recognized to have adverse prognosis.

The 2016 WHO MPN classification is used to diagnose MPNs into categories including polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic neutrophilic leukemia, atypical CML, myeloid/lymphoid neoplasms associated with eosinophilia and rearrangements of PDGFRA, PDGFRB, or FGFR1 or with PCM1-JAK2, and overlap syndromes including chronic myelomonocytic leukemia and myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis.[5]

Hematopoietic cell transplantation is generally considered for patients with myelofibrosis (idiopathic or post PV or ET), and overlap syndromes with poor prognosis.

Myelofibrosis

Myelofibrosis refers to the MPN classified by the WHO system as primary myelofibrosis or the phenotypically similar condition that develops in the setting of either polycythemia vera (post-PV MF) or essential thrombocythemia (post-ET MF). It is the least common of the three MPNs, with annual incidence of 0.2-1.5 cases/100 000, and carries the worst prognosis, with a median survival of around 6 years.[6] Median age at diagnosis is 65; MF is uncommon in young patients (~20% age <55). It is characterized by marrow fibrosis, myeloid proliferation and abnormal megakaryocyte morphology/clustering, splenomegaly, leukoerythroblastosis, and extramedullary hematopoiesis. Ultimately, this disease results in one of two outcomes: leukemic transformation or bone marrow failure. Currently, allogeneic stem cell transplantation is the only curative option, as all other available treatments are considered palliative.

Prognostic factors in myelofibrosis:

DIPPS can be used at any time in the disease course, and includes factors such as age >65 years, hemoglobin level <100 g/L, leukocyte count >25 x10^9/L, circulating blasts ≥1%, and presence of constitutional symptoms; this was upgraded to DIPSS-plus to incorporate three additional independent risk factors, including red cell transfusion need, platelet count <100 x10^9/L, and unfavorable karyotype (includes complex karyotype, or 1-2 abnormalities that include +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, or 11q23 rearrangement).[7,8] The eight DIPSS-plus risk factors are used to define low, intermediate-1, intermediate-2, and high risk groups, as described in the table below. A link to a D-IPSS calculator is DIPSS Prognosis in Myelofibrosis | QxMD.

Dynamic International Prognostic Scoring System - plus (DIPSS):

Risk Factors		
Age > 65 Hemoglobin < 100 gm/L Constitutional symptoms Leukocytes > 25 x 10^9 /L RBC transfusion requirement Platelets < 100 x 10^9 /L Unfavourable karyotype (complex or including -5/5q-, -7/7q-, +8, abnormal 11q23, inv(3), 12p-, i(17q)) Circulating blasts > 1%		
Prognostic Group	Number of Risk Factors	Median OS (years)
Low	0	15.4
Intermediate-1	1	6.5
Intermediate-2	2-3	2.9
High	≥ 4	1.3

MIPSS70 and MIPSS70-plus include molecular data for prognosis:[9,10]

Recently, integrated clinical, genetic and molecular models with (MIPSS70-plus v.2) or without (MIPSS-70) cytogenetics have been developed that better risk stratify patients who are transplant eligible. A link of a D-IPSS calculator is MIPSS70 score | MIPSS70-plus version 2.0 score.

MIPSS-70	MIPSS-70 Plus v.2:
Hemoglobin <100 g/L (1)	Severe anemia <800 g/L
WBC >25 x 10^9/L (2)	Moderate anemia (Hb 80-100 g/L)
Platelets <100 g/L(2)	Leukocytosis >25 x 10^9/L
Circulating blasts ≥ 2% (1)	Thrombocytopenia (<100 x 10^9/L)
Bone marrow fibrosis ≥ 2 (1)	
Constitutional symptoms (1)	Circulating blasts ≥ 2%
Absence of CALR type 1 mutation (1)	Bone marrow fibrosis grade >=2
Presence of HMR mutation* (1)	Constitutional symptoms
Presence of ≥ HMR mutations* (2)	Absence of CALR type 1/like mutation (2)
	Presence of HMR mutation[1] (1)
	Presence of ≥ 2 HMR mutations[2] (2)
	Unfavorable karyotype[3] (3)
	Very high risk karyotype
MIPSS-70 Survival:	MIPSS-70 Plus Survival:
Low (0-1): 27.7 years	Low (0-2): 20.0 years
Intermediate (2-4): 7.1 years	Intermediate (3): 6.3 years
High (≥ 5): 2.3 years	High (4-6): 3.9 years
	Very high (≥7): 1.7 years

[1]HMR: High molecular risk mutations: ASXL1, EZH2, SRSF2, IDH1/2, U2AF1.

[2] Unfavorable karyotype: any abnormal karyotype other than normal karyotype or sole abnormalities of 20 q-, 13q-, +9, chromosome 1 translocation/duplication, -Y, or sex chromosomes other than –Y.

[3]single/multiple abnormalities of -7, i(17q), inv(3)/3q21, 12p-/12p11.2, 11q-/11q23, or other autosomal trisomies not including +8, +9 (eg +21, +19); "Favorable": normal karyotype or sole abnormalities of 13q-, +9, 20q-, chromosome 1 translocation/duplication or sex chromosome abnormality including –Y; "Unfavorable": all other abnormalities

A personalized MPN prediction model was developed in an analysis of a total of 2035 patients and then validated with an external cohort. This calculator is found at https://cancer.sanger.ac.uk/mpn-multistage/ and can be used to try to individualize prognosis and inform decisions about potential transplantation.[11]

Genetics-based Prognostic Scoring System (GPSS):

Patient prognosis based on the MIPSS can be augmented by the genetics-inspired prognostic scoring system (GPSS), which incorporates high-risk karyotypes: 5q-, +8, inv(3), i(17q), -7/7q-, 11q or 12p

abnormalities, autosomal trisomies (except +9), monosomal and complex non-monosomal karyotypes. High risk GPSS was also associated with higher blast transformation rate (HR 7.4, 95% CI 2.1-26.3). In patients who had ambiguous prognosis based on differing scores by GPSS and by DIPSS-plus, those found to be higher risk on the GPSS were associated with poorer survival outcomes.[12]

Secondary Myelofibrosis:
None of the above prognostic tools were developed in patients who have secondary myelofibrosis after progression from polycythemia vera or essential thrombocytosis. In practice, the tools above are used but in a non-validated setting. There has been a model for prognosis developed in patients post-PV and post-ET: Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM), based on multivariate analysis of 685 patients with a median survival of 9.3 years. Secondary MF patients were divided into four risk categories based on: hemoglobin, circulating blasts, CALR status, platelet count and constitutional symptoms. Median survival according to risk group was: low (survival not reached), intermediate-1 (9.3 years), intermediate-2 (4.4 years), and high risk (2 years).[13] A calculator is available for the MYSEC-PM: http://www.mysec-pm.eu/

Table 5: Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM).

Secondary MF: MYSEC-PM
Risk factor (Points):
Hemoglobin <110 (2)
Circulating blasts ≥ 3% (2)
CALR UNMUTATED (2)
Platelets <150 (1)
Constitutional symptoms (1)
Median Survival: Low risk (points): NR Int-1 (points): 9.3 yrs. Int-2 (points): 4.4 yrs. High (points): 2 years

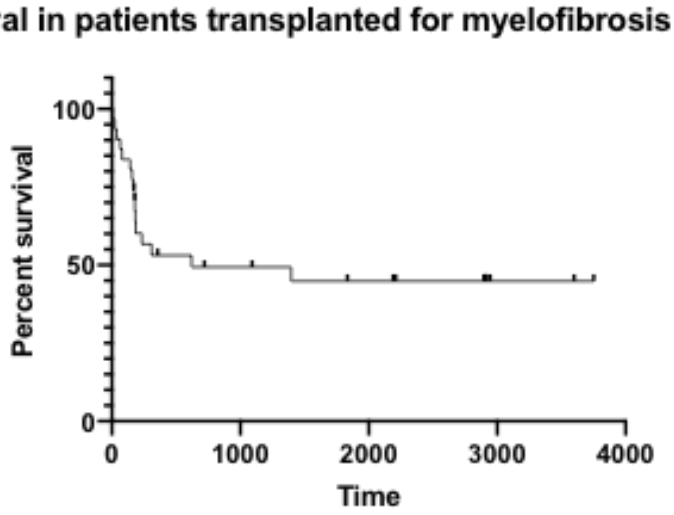
Transplantation outcomes in myelofibrosis:
Allogeneic HCT is currently the only treatment option in myelofibrosis that is capable of inducing complete hematologic, cytogenetic, and molecular remissions. However, there are associated risks of treatment-related mortality, graft failure, and disease relapse.

A multicentre analysis of 100 consecutive transplants for myelofibrosis in patients treated with JAK inhibitors found that 2-year overall survival (OS) was 61%, but 91% for those who experienced clinical improvement pretransplant on JAK inhibitors, and 32% for those with leukemic transformation on JAK inhibitor therapy.[14] Age of the patients was 32-72 years (median 59). Response to JAK

inhibitor (p=0.03), DIPSS score before starting JAK inhibitor (p=0.003), and donor type (p=0.006) were independent predictors of survival. Intensity of therapy is important in this disease and comparison of nonmyeloablative vs reduced intensity conditioning protocols showed higher levels of graft failure and poorer outcomes with nonmyeloablative regimens.[15] A retrospective analysis of 217 patients given reduced intensity conditioning regimens including Bu 3.2mg/kg vs 6.4mg/mg with fludarabine 30 g/m2 daily for 4 days showed no difference in outcomes between the two regimens.[16] Age and comorbidities affect outcomes and need to be considered as with transplants for other indications.

Comparison of HCT vs non-HCT. There are no randomized trials to compare outcomes in patients treated with JAK1/2 inhibitors vs transplantation. However, a retrospective review of 443 patients under the age of 65, not treated with JAK inhibitors, who received transplant or nontransplant (censored at time of transplant) therapy showed a survival benefit to transplant with int-2 or high risk disease, and this is used by most guidelines as indication for transplant.[17,18] The RR of mortality in patients receiving allogenic SCT vs conventional therapies was 5.6 (95% CI, 1.7-19; P = .0051) for low-risk DIPSS, 1.6 (95% CI, 0.79-3.2; P = .19) for int-1 risk, 0.55 (95% CI, 0.36-0.83; P = .005) for int-2 risk, and 0.37 (95% CI, 0.21-0.66; P = .0007) for high-risk DIPSS patients. Comparison of 5-year OS between the transplant and nontransplant cohorts showed 69% and 95% for low-risk, 52% and 77% for int-1, 50% and 41% for int-2, and 32% and 11% for high-risk patients.

Analysis of retrospective data does not provide clear support for splenectomy prior to transplantation to improve engraftment or outcomes.[19]



Kaplan Meier curve for outcomes in 31 patients transplanted for myelofibrosis in Calgary 2009-2018. Four of the 31 patients relapsed in the follow up period.

Polycythemia Vera and Essential Thrombocythemia

Hematologic transformations towards myelofibrosis and/or acute leukemia, although uncommon, represent a major cause of death in these disorders. In the case of ET, risk of myelofibrotic

transformation increases with disease duration, affecting 3-10% in the first decade after diagnosis and 6-20% in the second decade. Progression to acute leukemia occurs in a small minority of patients, with incidences of 1-2.5% in the first decade after diagnosis, and 5-8% in the second decade, and continuing to increase thereafter. Similar patterns are seen with PV, with leukemic transformation reported as high as 20%. The use of cytoreductive therapy, including alkylating agents, is known to increase the rate of leukemic transformation, and thus the true rate of transformation is unknown. Very little literature exists of transplantation for these diseases, usually in the form of case reports. Prognosis with DIPSS-plus score is not validated in this population although it is commonly used. The problems and complications associated with myelofibrotic transformation of either ET or PV are similar to de novo PMF, thus therapy of post-ET MF or post-PV MF should be approached in the same manner.

Use of JAK2 Inhibitors Prior to HSCT for Myelofibrosis

The JAK2V617F activating kinase mutation is seen in the many patients with BCR-ABL1 negative myeloproliferative patients, and Ruxolitinib, an oral JAK1/JAK2 inhibitor, is approved for the treatment of patients with symptomatic myelofibrosis, based on the data from two randomized phase 3 studies. Treatment is effective in patients without this specific mutation as other mutations in this pathway also cause symptoms. COMFORT-I and COMFORT-II compared ruxolitinib with placebo and best-available therapy (BAT), respectively, and found significant reductions in splenomegaly and improvement in constitutional symptoms.[20,21] Increased caloric intake and enhanced performance status as a result of improved constitutional symptoms and reduced splenomegaly could contribute to improved survival estimates for patients treated with ruxolitinib (71% vs. 54%, HR 0.48).[22,23] Longer follow-up will be needed.

It has been postulated that the anti-JAK2 mediated reduction in both cytokines and splenomegaly, as well as improvement in performance status, might improve outcome after allogeneic HSCT in patients with myelofibrosis. Some patients improve performance status and become transplant eligible. The down-regulation of inflammatory cytokines might have a beneficial impact on graft failure and has been seen to provide benefit in acute GVHD. The largest retrospective study examining transplant outcomes post ruxolitinib is outlined above and shows that pretransplant ruxolitinib therapy is feasible and patients responding to ruxolitinib have overall better transplant outcomes.[14]

There were concerns that abrupt discontinuation of ruxolitinib in advance of transplant may result in cytokine storm reaction and severe inflammatory response. Preliminary reports from the JAK ALLO trial[24] of ruxolitinib prior to HSCT included ten patients who discontinued ruxolitinib, 7 of whom developed life-threatening events (including cardiogenic shock, tumor lysis syndrome, severe GVHD), with two deaths within 3 weeks of drug withdrawal. This pattern has not been seen in subsequent studies; the retrospective series of 100 patients above showed two with significant adverse events after they stopped drug more than 6 days pretransplant.[14] For this reason it is recommended to continue JAK1/2 inhibitors until the day before conditioning.[18]

The average time to treatment failure with JAK 1/2 inhibitors in myelofibrosis is between two and three years. Ideally, patients should be referred for consideration of HSCT before they lose their response to these agents in order for them to undergo transplantation during a time of relatively good health. Several factors have been associated with a short (less than one year) time to treatment failure. These factors include “triple negative” myelofibrosis (negative for JAK2, MPL and CALR mutations) and ASXL-1 and EZH2 mutations, a high DIPSS-Plus score and those requiring transfusions at the time JAK 1/2 inhibitors are started. Patients with any of these risk factors should be referred at the time JAK1/2 inhibitors are started so that they can proceed to HSCT within one year or sooner. Patients with mutated CALR, 0-2 subclonal mutations without ASXL-1 or EZH2 mutations and those with mismatched donors should be followed closely and transplanted at the first sign of progression.[25]

Fedratinib, another JAK2 inhibitor selective for JAK2 relative to other kinases has now been approved by Health Canada and funding recommendations made by CADTH for treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to ruxolitinib. It is recommended for patients who are intolerant of ruxolitinib and not for patients with progressive symptoms after ruxolitinib therapy. Approval was made on the basis of the JAKARTA phase 3 randomized MF study for intermediate 2 and high risk disease with placebo and JAKARTA-2 in patients previously treated with ruxolitinib and who were refractory or intolerant. Reduction in spleen volume by 35% was seen in 30-40% of patients and there was improvement in Total Symptoms Score by ≥50% in one third of patients. Thiamine levels are required and supplementation is necessary, and monitoring for symptoms of encephalopathy is required. Other side effects include cytopenias and GI intolerance that should be proactively managed. Current data supports fedratinib’s use post ruxolitinib failure if funding is available. For patients planned for allogeneic stem cell transplant, transplant should occur earlier in the course of disease prior to multidrug resistance and before second line therapy is required for refractory disease. If fedratinib is used frontline prior to stem cell transplant, there is no evidence around management of medication prior to BMT and we would discontinue medication as per ruxolitinib protocol.

References

1. Kroger NM, Deeg JH, Olavarria E, Niederwieser D, Bacigalupo A, Barbui T, Rambaldi A, Mesa R, Tefferi A, Griesshammer M, Gupta V, Harrison C, Alchalby H, Vannuchi AM, Cervantes F, Robin M, Ditschkowski M, Fauble V, McLornan D, Ballen K, Popat UR, Passamonti F, Rondelli D, Barosi G. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. Leukemia 2015; 29(11):2126-33.
2. Vannucchi AM, Lasho TL, Guglielmelli P, Biamonte F, Pardanani A, Pereira A, Finke C, Score J, Gangat N, Mannarelli C, Kelleterline RP, Rotunno G, Knudson RA, Susini MC, Laborde RR, Spolverini A, Pancrazzi A, Pieri L,

Manfredini R, Tagliafico E, Zini R, Jones A, Zoi K, Reiter A, Duncomve A, Pietra D, Rumi E, Cervantex F, Barosi G, Cazzola M, Cross N, Tefferi A. Mutations and prognosis in primary myelofibrosis. Leukemia 2013 Sept; 27(9):1861-9)

3. Tefferi A, Lasho T, Finke C, Elala Y, Hanson C, Ketterline R, Gangat N, Pardanani A. Targeted deep sequencing in primary myelofibrosis. Blood Adv 2016;1(2):105
4. Tefferi A et al, The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients. Leukemia 2014;28(9):1804
5. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ , Le Beau MM, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood prepublished April 11, 2016.
6. Tefferi A, Guglielmelli P, Larson DR, Finke C, Wassie EA, Pieri L, Gangat N, Fjerza R, Belachew AA, Lasho TL, Ketterling RP, Hanson CA, Rambaldi A, Finazzi G, Thiele J, Barbui T, Pardanani A, Vannucchi AM. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood. 2014 Oct 16;124(16):2507-13; quiz 2615.
7. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 2009 Mar;113(13):2895-901.
8. Gangat N, Caramazza D, Valdya R, George G, Begna K, Schwager S, et al. DIPSS-Plus: a refined Dynamic International Prognostic Scoring System (DIPSS) for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol 2011 Feb;29(4):392-7.
9. Vannucchi AM, Guglielmelli P, Rotunno G, Pascutto C, Pardanani A, Ferretti V, et al. Mutation-Enhanced International Prognostic Scoring System (MIPSS) for Primary Myelofibrosis: An AGIMM & IWG-MRT Project. Blood 2014;124(21):405.
10. Tefferi A, Guglielmelli P, Larson DR, Finke C, Wassie EA, Pieri L, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood 2014 Oct 16;124(16):13; quiz 2615
11. Grinfeld J, Nangalia J, Baxter J, Wedge DC, Angelopoulos N, Cantrill R, et al. Classification and Personalized Prognosis in Myeloproliferatie Neoplasms. N Engl J Med 2018;379:1416-1430.
12. Kuykendall AT, Talati C, Padron E, Sweet K, Sallman D, List AF, et al. Am J Hematol 2019; 94(1):87-92.
13. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia 2017; 31(12):2726-2731.
14. Shanavas M, Popat U, Michaelis LC, et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis With Prior exposure to JAK1/2 Inhibitors. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22(3):432-440.
15. Slot S, Smits K, van de Donk N, Witte BI, Raymakers R, Janssen J, et al. Effect of conditioning regimens on graft failure in myelofibrosis: a retrospective analysis. Bone Marrow Transplantation (2015) 50, 1424–1431
16. Chen YB, Coughlin B, Kennedy AF, Alyea EP, Armand P, Attar EC, et al. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. Biol Blood Marrow Transplant 2013 Jun;19(6):981-7
17. Kröger N, Giorgino T, Scott BL, Ditschkowski M, Alchalby H, Cervantes F, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. Blood May 2015, 125 (21):3347-3350
18. Kröger NM, Deeg JH, Olavarria E, Niederwieser D, Bacigalupo A, Barbui T et al, Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. Leukemia (21 August 2015)
19. Li Z, Gooley T, Applebaum FR, Deeg HJ. Splenectomy and hemopoietic stem cell transplantation for myelofibrosis. Blood 2001 Apr;97(7):2180-1.
20. Versotovsek S. et al. A double-blind placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366(9):799-807.
21. Harrison C. et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366(9):787-98.
22. Cervantes F et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood 2013;122:4047-53.
23. Harrison C, Niederwieser D, Vannucchi A, Kiladijan J, Barbui T, Gisslinger B, et al. Results from a 3.5 year update of COMFORT-II, a phase 3 study comparing ruxolitinib (Rux) with best available therapy (BAT) for the treatment of myelofibrosis. EHA Annual Meeting Abstracts. 2014 June; Abstract P403.

24. Robin M, Francois S, Huynh A, Cassinat B, Bay JO, Cornillon J, et al. Ruxolitinib before allogeneic hematopoietic stem cell transplantation (HSCT) in patients with myelofibrosis: a preliminary descriptive report of the JAK ALLO study, a phase II trial sponsored by Goelams-FIM in collaboration with the Sfgmtc. Blood 2013;122(21):306.
25. Spiegel JY, McNamara C, Kennedy JA, Panzarella A, Arruda A et al. Impact of genomic alterations on outcomes in myelofibrosis patients of JAK1/2 inhibitor therapy. Blood Adv (2017); 1: 1729-38.

Additional References

Stewart WA, Pearce R, Kirkland KE, Bloor A, Thomson K, Apperley J, et al. The role of allogeneic SCT in primary myelofibrosis: a British Society for Blood and Marrow Transplantation study. Bone Marrow Transplant 2010 Nov;45(11):1587-93.

Ballen KK, Shrestha S, Sobocinski KA, Zhang MJ, Bashey A, Bolwell BJ, et al. Outcome of transplantation for myelofibrosis. Biol Blood Marrow Transplant 2010 Mar;16(3):358-67.

Deeg HJ, Gooley TA, Flowers ME, Sale GE, Slattery JT, Anasetti C, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. Blood 2003 Dec;102(12):3912-8.

Shanavas M, Messner HA, Atenafu EG, Kim DH, Krurvilla J, Lipton JH, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis using fludarabine-, intravenous busulfan- and low-dose TIB-based conditioning. Bone Marrow Transplant 2014;49:1162-9.

Chronic Lymphocytic Leukemia (CLL)

Presented by: Robert Puckrin and Mona Shafey

Summary

- Factors favoring allogeneic stem transplantation over conventional therapy include higher disease risk (high risk cytogenetics, MRD positive, short duration of response, Richter transformation) *and* low transplant risk (younger age, lack of co-morbidities, well-matched donor)
- Allogeneic stem cell transplantation may be offered to CLL patients with:
    - Relapse after at least 1 prior novel agent (BTKi and/or BCL2 inhibitor), preferably responding to a second agent as salvage treatment
    - Richter transformation responding to treatment, particularly if high-risk features such as previously treated CLL, TP53 mutated or clonally related Richter transformation, relapsed disease, or failure to achieve complete response to R-CHOP
- Autologous stem cell transplantation is not indicated to treat CLL but may be considered in selected patients with chemosensitive Richter transformation

Background

Chronic lymphocytic leukemia (CLL) represents one of the most common lymphoid malignancies of adults. With a median age at diagnosis of 70 years, many patients with this disease will die of other causes. For young patients however, this diagnosis represents a serious threat to life and aggressive management with high-dose therapy and blood stem cell transplantation (SCT) is a reasonable treatment option. This is particularly the case for patients whose CLL is associated with deletion chromosome 17p13.1 [del(17p)], which is observed in 5% of untreated CLL cases but in up to 30% of relapsed and refractory cases. CLL with del(17p) usually require therapy within 1 year of diagnosis and is now being treated with frontline BTK inhibitors such as ibrutinib. Even novel agents such as ibrutinib do not control del(17p)-associated CLL for long durations of time. A recent study by O'Brien and colleagues involving 144 patients with relapsed del(17p) CLL reported 2-year progression-free survival (PFS) rates of approximately 60% (mPFS of 30mo) and 24-month OS of 75%[1].

For a review of the diagnosis, staging, prognosis, assessments of patient fitness and response, and current treatment recommendations of the Alberta Provincial Hematology Tumour Team, please refer to the CLL Clinical Practice Guideline (LYHE-007).

Stem Cell Transplantation in CLL

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) suggests that CLL is an infrequent indication for transplant. The majority of transplants reported were allogeneic, many of which were carried out after reduced intensity or non-myeloablative conditioning.

Allogeneic Stem Cell Transplantation in CLL

Long-term survival after allogeneic SCT for CLL of the largest series of patients (n=2589), who underwent transplant between 2000 and 2010, has been reported from the European Group for Blood and Marrow Transplantation (EBMT)[2]. In this series, long-term disease control was established for patients, but with longer follow-up both event-free and overall survival decreased over time (62% at 2 years vs. 35% at 10 years for OS; 49% at 2 years vs. 28% at 10 years for EFS). The incidence of relapse was 21% at 2 years vs. 32% at 10 years, and non-relapse mortality 30% at 2 years vs. 40% at 10 years. The presence or absence of del(17p)/TP53 mutation has not been shown to impact outcome of alloSCT[3, 4]. Risk factors for relapse included active disease at time of transplant, T-cell depletion with alemtuzumab, prior autologous SCT, and use of mismatched donor, while absence of MRD at 12 months was highly prognostic for reduced relapse risk[2, 3, 4].

In regards to donor selection, the EBMT analyzed 368 chronic lymphocytic leukemia patients who underwent allogeneic hematopoietic stem cell transplantation between 1995 and 2007 [5]. There were 198 HLA-identical siblings; among unrelated transplants, 31 were well matched in high resolution ('well matched' unrelated donor, WMUD), and 139 were mismatched (MM), including 30 matched in low resolution; 266 patients (72%) received reduced-intensity conditioning and 102 (28%) received standard. There was no difference in OS at 5 years between HLA-identical siblings (55% (48-64)) and WMUD (59% (41-84)), p=0.82. In contrast, OS was significantly worse for MM (37% (29-48) p=0.005) due to a significant excess of transplant-related mortality. HLA matching had no significant impact on relapse (siblings: 24% (21-27); WMUD: 35% (26-44), p=0.11 and MM: 21% (18-24), p=0.81); alemtuzumab T-cell depletion and stem cell source (peripheral blood) were associated with an increased risk. As the toxicity of haploidentical transplants have been greatly decreased with the use of post-transplant cyclophosphamide, donor availability for transplantation has increased. The EBMT has reported the outcome of 117 CLL patients who had received an allogeneic SCT with a haploidentical donor, with results appearing almost identical to those with HLA-matched donors; 5-yr OS 38%, PFS 31%, CI of relapse 26%, and NRM 44%[6].

Myeloablative conditioning (MAC) is associated with improved overall survival in acute myeloid leukemia (AML), where the increased risks of NRM and acute and chronic GVHD associated with MAC were offset by the significant reduction in relapse[7]. It is unclear if these results can be extrapolated to patients with CLL, given that CLL is an indolent disease with high susceptibility to GVL which may not necessarily require intensive chemotherapy; patients with CLL may be at higher risk of NRM due to older age and underlying immune dysregulation; allotransplant recipients with CLL are heavily pre-treated which may confer greater resistance to MAC; and there may be more options to treat relapse after allotransplant in CLL, such as donor lymphocyte infusion and emerging therapies (e.g. non-covalent BTK inhibitors, CAR-T cells). Retrospective and transplant registry studies conclude that reduced intensity conditioning (RIC) is associated with lower risks of NRM, less

acute and chronic GVHD, and similar or improved OS compared to MAC in CLL[8, 9, 10, 11, 12, 13]. Indeed, intensive conditioning is not necessarily indicated since CLL has among the lowest relapse risk after non-myeloablative (NMA) conditioning of any hematologic malignancy[14]. An EBMT registry study also concluded that selected patients receiving NMA conditioning have similar relapse incidence, relapse-free survival (RFS), and overall survival as recipients of RIC in CLL[15]. As a result, the majority of allotransplants (75-80%) performed for CLL in North America and Europe employ RIC or NMA conditioning, and ASTCT guidelines recommend RIC or NMA conditioning for all patients undergoing allotransplant for CLL[2, 16, 17]. MAC with FluBu4 was utilized for most allotransplant recipients with CLL in Alberta until 2022, at which time a review of local outcomes revealed high rates of acute and chronic GVHD and low mod/severe chronic GVHD and RFS (cGRFS) despite the use of ATG (Table 3). As a result, in February 2023 RIC was adopted as the preferring conditioning regimen for patients with CLL to reduce their risks of acute and chronic GVHD as well as other acute toxicities and NRM.

Table 1. Summary of transplant characteristics and survival in prospective studies of RIC HSCT in CLL (modified from Gribben 2018[18]).

	Fred Hutchinson Cancer Center[8]	German CLL Study Group[9, 10]	MD Anderson Cancer Center[11]	Dana-Farber Cancer Institute[12]
Number of patients	82	90	86	76
Conditioning regimen	Flu/low-dose TBI	Flu/Cy ± ATG	Flu/Cy ± R	Flu/Bu
Donors, % sibling/% MUR	63/37	41/59	50/50	37/63
Median follow-up, months	60	72	37	61
Median PFS, %	39 (at 5 y)	38 (at 6 y)	36 (at 6 y)	43 (at 6 y)
Median OS, %	50 (at 5 y)	58 (at 6 y)	51 (at 6 y)	63 (at 6 y)

Abbreviations: ATG = antithymocyte globulin; BU = busulfan; CLL = chronic lymphocytic leukemia; Cy = cyclophosphamide; Flu = fludarabine; HSCT = hematopoietic stem cell transplantation; MUR = matched unrelated donor; OS = overall survival; PFS = progression-free survival; R = rituximab; RIC = reduced-intensity conditioning; TBI = total body irradiation; y = years.

Table 2. Summary of recent studies using RIC HSCT in CLL

Outcome	Dana Farber retrospective[19]	Multicenter retrospective[12]	France phase II trial[13]
No. patients	30	65	42
Conditioning	FluBu1 or FluBu2	Various RIC (95%)	FluBu2
GVHD prophylaxis	CNI + MTX +/- Sir	CNI + MTX (84%)	ATG+CNI+MTX
Overall survival	3-yr 87%	2-yr 81%	3-yr 87%
PFS	3-yr 72%	2-yr 63%	3-yr 63%
Relapse	3-yr 21%	2-yr 27%	3-yr 30%
NRM	3-yr 7%	2-yr 13%	3-yr 10%
Mod-severe cGVHD	NR	27%	23%

The EBMT studied 44 patients with 17p- CLL who received allogeneic hematopoietic SCT between March 1995 and July 2006 from a matched sibling (n = 24) or an alternative donor (n = 20)[20]. Patients had received a median of 3 lines of chemotherapy before SCT, and at the time of transplantation, 53% of patients were in remission. RIC was applied in 89% of patients. Acute or extensive GVHD occurred in 43% and 53% of patients, respectively. Nineteen patients were alive at the last follow-up (median observation time 39 months), and no late relapse occurred in 9 patients with a follow-up longer than 4 years. The 3-year OS and PFS rates were 44% and 37%, respectively.

It is clear that with the approval of novel agents including BTK inhibitors (e.g. ibrutinib, acalabrutinib), PI3 kinase inhibitors (e.g. idelalisib), and the BCL2 inhibitor venetoclax, the number of transplants being performed for CLL continues to decline, particularly for those patients without high risk cytogenetics. In a study of 65 patients with prior novel agent exposure who underwent alloSCT, the 24 month PFS, OS, NRM, and relapse incidence was 63%, 81%, 13%, and 27%, respectively[12]. Poor-risk disease characteristics, prior NA exposure, complete vs. partial remission status, and transplant characteristics were not independently associated with PFS; 1 vs. ≥ novel agents, or ibrutinib vs. venetoclax as the line of therapy immediately pre-alloHSCT had no impact on PFS or OS; only HCT-CI independently predicted for PFS. It remains to be seen whether combinations of these agents will alter the natural history of the disease, or whether they are just delaying the use of allogeneic SCT until later in the disease course. Allogeneic SCT will continue to have a role for patients who fail or are intolerant to these therapies.

Overall, allogeneic stem cell transplantation (HSCT) should be considered for fit patients who are younger than 65 years of age and have CLL that did not respond or have progressed after treatment with at least one novel agent (either BTKi and/or venetoclax). This is especially important in patients with higher disease risk, including complex karyotype, high risk cytogenetics (del17p/TP53), short duration of response, and MRD positive (on venetoclax).

Richter Transformation:

Richter transformation (RT) of CLL into an aggressive DLBCL occurs in 1-5% of patients with CLL. RT is associated with a dismal prognosis with PFS <25% with CHOP-based chemoimmunotherapy and median survival 6-12 months[21, 22, 23, 24]. Given these poor outcomes, consolidation with allogeneic HCT should be considered for eligible patients with responding disease who have relapsed RT or other high-risk features, such as previous therapy for CLL, failure to achieve a complete response to R-CHOP, TP53 aberrations, or clonally related RT[24, 25, 26, 27]. Although <10% of all patients with RT will ever undergo allogeneic HCT, this may represent a curative therapy for selected cases with 3-year PFS 43%, OS 52%, relapse incidence 30%, and NRM 27% in a CIBMTR study of 118 allogeneic HCT recipients[28]. Outcomes were best for patients in complete response (3-year PFS 66%) or partial response (3-year PFS 43%) at the time of HCT compared to those with resistant disease (3-year PFS 5%). The majority of patients with RT receive reduced intensity conditioning, which has been

associated with similar to improved outcomes in this setting compared to myeloablative conditioning[28, 29, 30, 31].

Importantly, patients with RT arising from treatment naïve CLL appear to have comparatively better outcomes with R-CHOP and may not necessarily require allogeneic HCT[23, 24]. In an Alberta study of 99 patients with RT, those with treatment naïve CLL had higher response rates to first line chemoimmunotherapy (71% versus 40%) and superior 2-year OS (51% versus 28%) compared to those with previously treated CLL. Nevertheless, 2-year OS remained suboptimal at 53% for the 13 patients ≤70 years old with RT and treatment naïve CLL, which suggests there may be a role to consider consolidation with autologous HCT for these patients, similarly as other high risk aggressive lymphomas. Although data is lacking on the outcomes of autologous HCT as part of first-line therapy for RT, a CIBMTR study of 53 patients undergoing autologous HCT for predominantly relapsed RT reported 3-year PFS 48%, OS 52%, and relapse incidence 37%[28]. In an EBMT study of 34 patients who underwent autologous HCT, only 11 of 17 relapses were related to RT (the remainder were due to CLL), suggesting autologous HCT may eradicate the RT component in many patients even though the underlying CLL may persist[29]. It should be noted that even if allogeneic HCT may not be required as a part of primary therapy for patients with lower-risk RT, a referral for transplant consultation and HLA typing is suggested at diagnosis in all patients who are eligible for allogenic HCT by age and/or comorbidities, given the significant risk of relapse/refractory disease with RT.

Less commonly, patients with CLL may develop a Hodgkin lymphoma variant of RT which is often clonally unrelated to the CLL. Available evidence suggests that Hodgkin-variant RT has similar outcomes with standard chemotherapy as de novo Hodgkin lymphoma in this age group[32, 33]. As such, there is not an established role for consolidation with HCT in these cases[27].

Autologous Stem Cell Transplantation in CLL

Case series from a number of institutions report high overall survival (4-year OS 65-94%) with low TRM (4-10%) of autologous stem cell transplantation (ASCT) for CLL; however, to date, no randomized study has demonstrated an OS advantage for the use of ASCT in CLL. Despite a strong PFS advantage in the published studies of ASCT, ASCT is now rarely used for CLL[17-19]. This is because FCR (fludarabine, cyclophosphamide, and rituximab) is now used as front-line therapy for most young CLL patients, as it has been shown in a randomized, controlled trial, to provide an OS advantage. Published studies of ASCT in CLL predate the introduction of FCR chemotherapy so the role that ASCT could play in the era of FCR is unclear. Additionally, the use of 6 cycles of a fludarabine-containing regimen significantly impairs the subsequent ability to mobilize and collect autologous blood stem cells. With the emergence of novel agents for relapsed CLL, the role of ASCT is even more unclear. At present, there are no definite indications for ASCT for CLL.

Figure 1A: Progression-free survival and overall survival of patients with CLL undergoing allotransplant in Calgary between 2000-2021

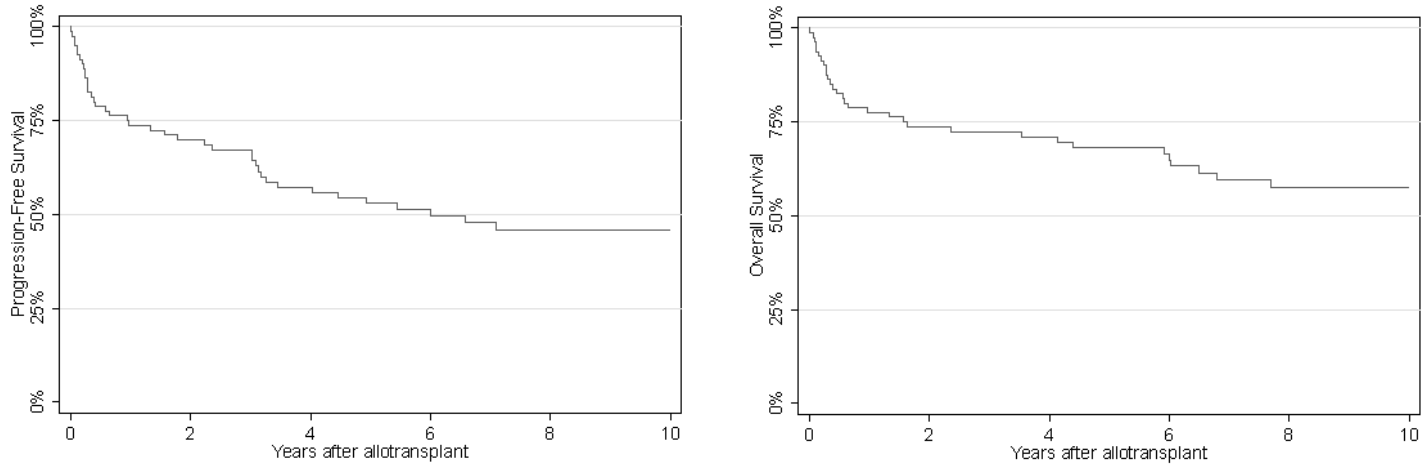


Figure 1B: Progression-free survival and overall survival of patients with DLBCL-type Richter transformation of CLL undergoing allotransplant in Calgary between 2000-2021

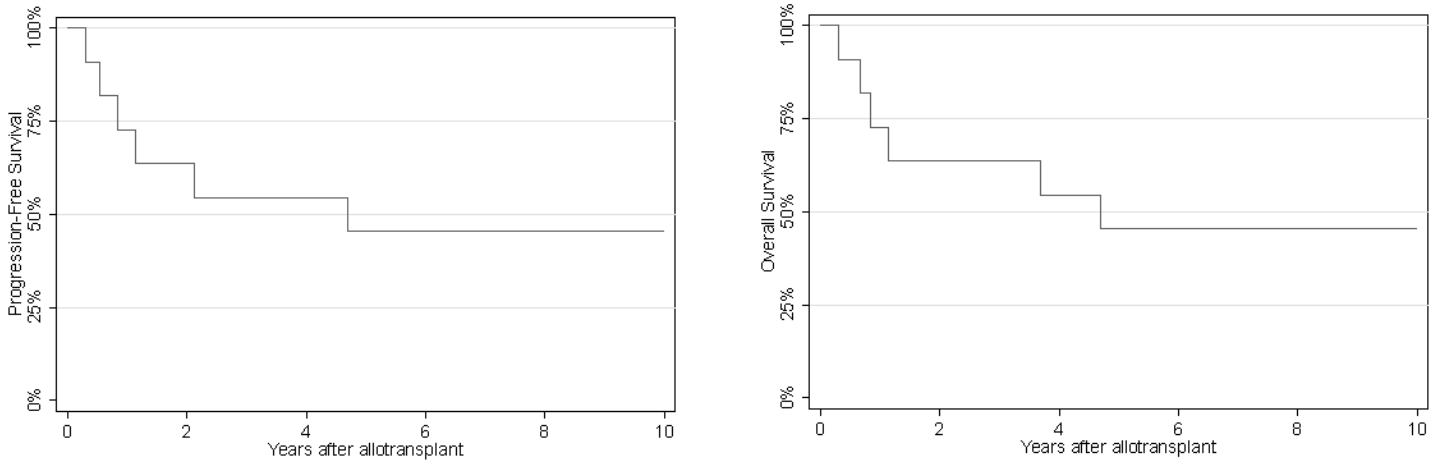


Table 3. Outcomes of patients undergoing allogeneic HCT with FluBu4 +/- TBI MAC for CLL or DLBCL-type Richter transformation in Calgary between 2000-2021

Outcome (at 5 years)	CLL (n=79)	Richter (n=11)
Overall survival	68%	45%
Progression-free survival	53%	45%
Relapse	28%	18%
Non-relapse mortality	20%	36%
Grade II-IV acute GVHD	43%	27%
Grade III-IV acute GVHD	18%	9%
Moderate-to-severe chronic GVHD	41%	45%
Chronic GVHD and RFS (cGRFS)	24%	18%

References

1. O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016;17(10):1409-18.
2. van Gelder M, de Wreede LC, Bornhäuser M, Niederwieser D, Karas M, Anderson NS, et al. Long-term survival of patients with CLL after allogeneic transplantation: a report from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2017;52(3):372-80.
3. van Gelder M, Ziagkos D, de Wreede L, van Biezen A, Dreger P, Gramatzki M, et al. Baseline Characteristics Predicting Very Good Outcome of Allogeneic Hematopoietic Cell Transplantation in Young Patients With High Cytogenetic Risk Chronic Lymphocytic Leukemia - A Retrospective Analysis From the Chronic Malignancies Working Party of the EBMT. Clin Lymphoma Myeloma Leuk. 2017;17(10):667-75.e2.
4. Krämer I, Stilgenbauer S, Dietrich S, Böttcher S, Zeis M, Stadler M, et al. Allogeneic hematopoietic cell transplantation for high-risk CLL: 10-year follow-up of the GCLLSG CLL3X trial. Blood. 2017;130(12):1477-80.
5. Michallet M, Sobh M, Milligan D, Morisset S, Niederwieser D, Koza V, et al. The impact of HLA matching on long-term transplant outcome after allogeneic hematopoietic stem cell transplantation for CLL: a retrospective study from the EBMT registry. Leukemia. 2010;24(10):1725-31.
6. van Gorkom G, van Gelder M, Eikema DJ, Blok HJ, van Lint MT, Koc Y, et al. Outcomes of haploidentical stem cell transplantation for chronic lymphocytic leukemia: a retrospective study on behalf of the chronic malignancies working party of the EBMT. Bone Marrow Transplant. 2018;53(3):255-63.
7. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. J Clin Oncol. 2017;35(11):1154-61.
8. Sobecks RM, Leis JF, Gale RP, Ahn KW, Zhu X, Sabloff M, et al. Outcomes of human leukocyte antigen-matched sibling donor hematopoietic cell transplantation in chronic lymphocytic leukemia: myeloablative versus reduced-intensity conditioning regimens. Biol Blood Marrow Transplant. 2014;20(9):1390-8.
9. Hill BT, Ahn KW, Hu ZH, Aljurf M, Beitinjaneh A, Cahn JY, et al. Assessment of Impact of HLA Type on Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia. Biol Blood Marrow Transplant. 2018;24(3):581-6.
10. Kharfan-Dabaja MA, Moukalled N, Reljic T, El-Asmar J, Kumar A. Reduced intensity is preferred over myeloablative conditioning allogeneic HCT in chronic lymphocytic leukemia whenever indicated: A systematic review/meta-analysis. Hematol Oncol Stem Cell Ther. 2018;11(2):53-64.

11. Brown JR, Kim HT, Armand P, Cutler C, Fisher DC, Ho V, et al. Long-term follow-up of reduced-intensity allogeneic stem cell transplantation for chronic lymphocytic leukemia: prognostic model to predict outcome. Leukemia. 2013;27(2):362-9.
12. Roeker LE, Dreger P, Brown JR, Lahoud OB, Eyre TA, Brander DM, et al. Allogeneic stem cell transplantation for chronic lymphocytic leukemia in the era of novel agents. Blood Adv. 2020;4(16):3977-89.
13. Tournilhac O, Le Garff-Tavernier M, Nguyen Quoc S, Forcade E, Chevallier P, Legrand-Izadifar F, et al. Efficacy of minimal residual disease driven immune-intervention after allogeneic hematopoietic stem cell transplantation for high-risk chronic lymphocytic leukemia: results of a prospective multicenter trial. Haematologica. 2021;106(7):1867-75.
14. Kahl C, Storer BE, Sandmaier BM, Mielcarek M, Maris MB, Blume KG, et al. Relapse risk in patients with malignant diseases given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. Blood. 2007;110(7):2744-8.
15. Andersen NS, Bornhäuser M, Gramatzki M, Dreger P, Vitek A, Karas M, et al. Reduced intensity conditioning regimens including alkylating chemotherapy do not alter survival outcomes after allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia compared to low-intensity non-myeloablative conditioning. J Cancer Res Clin Oncol. 2019;145(11):2823-34.
16. Kim HT, Ahn KW, Hu ZH, Davids MS, Volpe VO, Antin JH, et al. Prognostic Score and Cytogenetic Risk Classification for Chronic Lymphocytic Leukemia Patients: Center for International Blood and Marrow Transplant Research Report. Clin Cancer Res. 2019;25(16):5143-55.
17. Kharfan-Dabaja MA, Kumar A, Hamadani M, Stilgenbauer S, Ghia P, Anasetti C, et al. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2016;22(12):2117-25.
18. Gribben JG. How and when I do allogeneic transplant in CLL. Blood. 2018;132(1):31-9.
19. Kim HT, Shaughnessy CJ, Rai SC, Reynolds C, Ho VT, Cutler C, et al. Allogeneic hematopoietic cell transplantation after prior targeted therapy for high-risk chronic lymphocytic leukemia. Blood Adv. 2020;4(17):4113-23.
20. Schetelig J, van Biezen A, Brand R, Caballero D, Martino R, Itala M, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol. 2008;26(31):5094-100.
21. Elnair R, Ellithi M, Kallam A, Shostrom V, Bociek RG. Outcomes of Richter's transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): an analysis of the SEER database. Ann Hematol. 2021;100(10):2513-9.
22. Al-Sawaf O, Robrecht S, Bahlo J, Fink AM, Cramer P, V Tresckow J, et al. Richter transformation in chronic lymphocytic leukemia (CLL)-a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. Leukemia. 2021;35(1):169-76.
23. Abrisqueta P, Delgado J, Alcoceba M, Oliveira AC, Loscertales J, Hernández-Rivas JA, et al. Clinical outcome and prognostic factors of patients with Richter syndrome: real-world study of the Spanish Chronic Lymphocytic Leukemia Study Group (GELLC). Br J Haematol. 2020;190(6):854-63.
24. Wang Y, Tschautscher MA, Rabe KG, Call TG, Leis JF, Kenderian SS, et al. Clinical characteristics and outcomes of Richter transformation: experience of 204 patients from a single center. Haematologica. 2020;105(3):765-73.
25. Montesinos P, Cabrero M, Valcárcel D, Rovira M, García-Marco JA, Loscertales J, et al. The addition of ofatumumab to the conditioning regimen does not improve the outcome of patients with high-risk CLL undergoing reduced intensity allogeneic haematopoietic cell transplantation: a pilot trial from the GETH and GELLC (CLL4 trial). Bone Marrow Transplant. 2016;51(10):1404-7.
26. Rossi D, Spina V, Deambrogi C, Rasi S, Laurenti L, Stamatopoulos K, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. Blood. 2011;117(12):3391-401.
27. Eyre TA, Riches JC, Patten PEM, Walewska R, Marr H, Follows G, et al. Richter transformation of chronic lymphocytic leukaemia: a British Society for Haematology Good Practice Paper. Br J Haematol. 2022;196(4):864-70.
28. Herrera AF, Ahn KW, Litovich C, Chen Y, Assal A, Bashir Q, et al. Autologous and allogeneic hematopoietic cell transplantation for diffuse large B-cell lymphoma-type Richter syndrome. Blood Adv. 2021;5(18):3528-39.
29. Cwynarski K, van Biezen A, de Wreede L, Stilgenbauer S, Bunjes D, Metzner B, et al. Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): A retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2012;30(18):2211-7.
30. Bacher U, Klyuchnikov E, Le-Rademacher J, Carreras J, Armand P, Bishop MR, et al. Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? Blood. 2012;120(20):4256-62.

31. Fenske TS, Ahn KW, Graff TM, DiGilio A, Bashir Q, Kamble RT, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. Br J Haematol. 2016;174(2):235-48.
32. Stephens DM, Boucher K, Kander E, Parikh SA, Parry EM, Shadman M, et al. Hodgkin lymphoma arising in patients with chronic lymphocytic leukemia: outcomes from a large multi-center collaboration. Haematologica. 2021;106(11):2845-52.
33. Zhu K, Jamroz A, Huang S, Villa D, Freeman CL, Scott DW, et al. Outcomes of Hodgkin variant Richter transformation in chronic lymphocytic leukaemia and small lymphocytic lymphoma in British Columbia. Br J Haematol. 2022;198(4):684-92.

Hematopoietic Cell Transplantation/Cellular Therapy for Lymphoma

Presented by: Robert Puckrin

Summary

CAR-T Cell Therapy

- Axicabtagene autoleucel is expected to soon be funded as second-line therapy for diffuse large B-cell lymphoma (DLBCL) which is refractory or has relapsed within 12 months of the end of first-line therapy
- Axicabtagene autoleucel, tisagenlecleucel, and soon lisocabtagene maraleucel are funded for relapsed or refractory DLBCL after ≥2 lines of systemic therapy
    - Eligibility includes most subtypes of DLBCL, including transformed indolent lymphoma and follicular large B-cell lymphoma (previously known as follicular lymphoma grade 3B)
    - Patients with Richter transformation arising from previously-treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are not currently eligible
    - Patients with rare subtypes of DLBCL which typically lack B-cell antigens should have demonstration of CD19 expression to be eligible for CD19-directed CAR-T
- Brexucabtagene autoleucel is funded for relapsed or refractory mantle cell lymphoma after ≥2 lines of systemic therapy including a BTK inhibitor
- Axicabtagene autoleucel is expected to be funded for relapsed or refractory follicular lymphoma after ≥2 lines of systemic therapy
- Tisagenleceucel is expected to be funded for follicular lymphoma which is refractory to a second or later line of systemic therapy, relapsed within 6 months after completion of a second or later line of systemic therapy, relapsed during anti-CD20 antibody maintenance (following at least 2 lines of therapies as above) or within 6 months after maintenance completion, or relapsed after autologous HSCT.
- Lymphodepletion is typically with fludarabine and cyclophosphamide.
- Patients must meet the following criteria in addition to the above disease criteria:
    - Clinically stable and expected to remain so until the planned CAR-T cell infusion date with adequate organ function and performance status (ECOG 0-2)
    - No prior treatment with a CAR-T cell product targeting the same antigen
    - Patients with previous or active secondary CNS involvement are eligible for CAR-T but patients with active primary CNS lymphoma are not currently eligible

Autologous HCT (ASCT) and Allogeneic HCT- Eligibility and Conditioning

- Patients are generally considered eligible for autologous stem cell transplant (ASCT) or allogeneic HCT if they are approximately ≤75 years old and have controlled disease status (e.g. complete or partial response), a good performance status (e.g. ECOG 0-2), no serious uncontrolled infections, adequate organ function, and >$2x10^6$ CD34+ cells/kg (ASCT) or an available stem cell donor (allogeneic HCT)

- Conditioning for ASCT:

Aggressive NHL (DLBCL, PTCL)	(R) + Bu(13500uM.min) + Mel(140mg/m2)
Indolent NHL (FL, MZL, LPL)	(R) + Mel(180mg/m2) + TBI(5Gy x1)
Mantle cell lymphoma	(R) + Mel(180mg/m2) + TBI(5Gy x1)
Hodgkin lymphoma	Gemcitabine 1500 mg/m2 + Melphalan 200 mg/m2
Primary CNS lymphoma	(R) + Thiotepa(600mg/m2) + Bu(13500 uM.min)
Secondary CNS lymphoma	(R) + Thiotepa(500mg/m2) + Bu(13500uM.min) + Mel (100mg/m2)

- Reduced intensity conditioning allogeneic HCT is recommended for most patients who have heavily pretreated lymphoma (e.g. relapse after ASCT or multiply-relapsed disease), intrinsically chemoresistant lymphomas (e.g. TP53-mutated mantle cell lymphoma or cutaneous T-cell lymphomas), or indolent lymphomas with high susceptibility to the graft-versus-lymphoma effect (e.g. SLL/CLL or follicular lymphoma).

Indications for HCT/CT

Diffuse Large B-Cell Lymphoma:

- Consolidative ASCT may be considered for high-risk patients with DLBCL responding to first-line therapy, such as those with (1) high IPI score 4-5 and partial metabolic response on interim PET or (2) high-grade B-cell lymphoma with MYC and BCL2 rearrangements with IPI score 2-5 (1-5). This practice will require re-evaluation once second-line CAR-T cell therapy and novel first-line therapies are available.
- Once funded, second-line CAR-T cell therapy is recommended for eligible patients with DLBCL refractory to or relapsing within 12 months of the end of first-line chemoimmunotherapy (6-9)
- ASCT is recommended for eligible patients with chemosensitive relapse of DLBCL occurring >12 months after completion of first-line chemoimmunotherapy (10). Examples of appropriate salvage regimens before ASCT include R-DICEP, R-GDP, R-DHAP, or R-ICE (11-15).
- Third-line CAR-T cell therapy is recommended for patients with relapsed/refractory DLBCL after ≥2 lines of therapy who have not previously received CAR-T cell therapy (16-19).
- Allogeneic HCT is rarely performed for DLBCL but may be considered for fit, motivated patients who relapse after CAR-T cell therapy and achieve an adequate response to pre-transplant therapy (20, 21).

Central Nervous System (CNS) Lymphoma:

- Thiotepa/busulfan-based ASCT is recommended for eligible patients with primary CNS lymphoma responding to high-dose methotrexate and cytarabine based induction (see Lymphoma guideline) (22-27)

- Thiotepa/busulfan/melphalan-based ASCT is recommended for eligible patients with chemosensitive secondary CNS lymphoma (SCNSL), with favorable outcomes observed among those with SCNSL at diagnosis or isolated CNS relapse of systemic lymphoma (see Lymphoma guideline) (28, 29)
- The prognosis of patients with early concurrent CNS and systemic relapse is poor and the optimal treatment is unclear, so these patients should be considered for ASCT or second-line CAR-T cell therapy once funded on a case-by-case basis (28-30).
- Patients with SCNSL undergoing CAR-T cell therapy should receive appropriate CNS-directed bridging therapy before infusion since outcomes appear poor if there is active CNS disease at the time of infusion (30).
- Allogeneic HCT is not well established for CNS lymphoma (31).

Transformed Lymphoma:

- ASCT is recommended as consolidation therapy of R-CHOP for patients with chemosensitive transformed DLBCL if they have previously received chemotherapy for indolent B-cell lymphoma (32, 33)
- Patients who develop transformed DLBCL within 12 months of receiving R-CHOP or R-CEOP for indolent lymphoma may be considered for second-line CAR-T cell therapy once funded (6-9). Otherwise, CAR-T cell therapy is recommended for patients with relapsed/refractory transformed lymphoma after ≥2 lines of therapy (e.g. 1 for indolent lymphoma and 1 for DLBCL) (16, 18, 19)
- Allogeneic HCT is rarely performed for transformed lymphoma but may be considered for fit, motivated patients who relapse after CAR-T cell therapy and achieve an adequate response to pre-transplant therapy (20, 21, 33).

Burkitt Lymphoma:

- Relapsed Burkitt lymphoma has a poor prognosis but ASCT or rarely allogeneic HCT may be considered for patients with chemosensitive relapses (34)

Mantle Cell Lymphoma:

- Consolidative ASCT is recommended for eligible patients responding to first-line cytarabine-containing chemoimmunotherapy (35-40)
- Maintenance rituximab is recommended every 2 months for 3 years after ASCT (41, 42)
- CAR-T cell therapy is recommended for eligible patients with relapsed MCL after ≥2 lines of therapy including a BTK inhibitor (43, 44)
- Allogeneic HCT may be considered for fit, motivated patients who relapse after CAR-T cell therapy and achieve an adequate response to pre-transplant therapy (45)
- Patients with TP53-mutated mantle cell lymphoma have poor outcomes with chemotherapy and do not benefit from ASCT (46). These patients should be prioritized for first-line allogeneic HCT or third-line CAR-T cell therapy on a case-by-case basis.

Follicular Lymphoma:

- Given the poor prognosis with standard chemotherapy, ASCT is recommended for eligible patients with chemosensitive relapse of follicular lymphoma occurring within 24 months of first-line treatment (POD24) (47)
- ASCT achieves durable remissions and is also a recommended option for fit patients with first or second relapse of follicular lymphoma arising >24 months after first-line treatment (48-50)
- Once funded, CAR-T cell therapy is a recommended option for eligible patients with relapsed/refractory follicular lymphoma after ≥2 lines of systemic therapy (51, 52)
- Allogeneic HCT is rarely performed for follicular lymphoma but may be considered for fit, motivated patients who have relapsed after, or are unable to receive, ASCT and/or CAR-T cell therapy and who achieve an adequate response to pre-transplant therapy (53).

Other Indolent B-Cell Lymphomas:

- ASCT may be considered for selected patients with first or second chemosensitive relapse of marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), or nodular lymphocyte-predominant B-cell lymphoma (NLPBL), particularly for those with early relapses, aggressive clinical behavior, and in patients who prioritize the possibility of long-term disease control or who lack other treatment options (54-56)
- Allogeneic HCT is seldomly performed for rare indolent B-cell lymphomas but may be considered for fit, motivated patients who lack other therapeutic options and have relapsed after, or are unable to receive, ASCT and achieve an adequate response to pre-transplant therapy (57)

Hodgkin Lymphoma (HL):

- ASCT is recommended for eligible patients with relapsed/refractory HL who respond to second-line chemotherapy or immune checkpoint inhibitors (ICI) (58-62)
- Maintenance brentuximab vedotin (BV) every 3 weeks for 16 cycles starting 4-6 weeks after ASCT is funded for patients with primary refractory HL, relapsed HL <12 months from the end of frontline therapy, or extranodal disease at relapse. The benefits must be weighed against the risks given the lack of survival benefit, increased toxicity, and potential overtreatment of patients already cured by ASCT. The benefit of maintenance BV may be more pronounced in patients with 2-3 risk factors or with a positive PET before ASCT (63, 64).
- Allogeneic HCT is recommended for fit, motivated patients with HL who have exhausted other treatment options (65). Eligible patients should be referred for discussion of allogeneic HCT when starting their second novel agent (i.e. ICI or BV). For patients with highly refractory disease or short duration of remissions, consider using the second novel agent to achieve a response as a bridge to allogeneic HCT. Other patients who achieve a complete response to the second novel agent may reasonably defer allotransplant to the next relapse provided that effective bridging therapy is expected to be available. A washout period of the ICI for 6-12 weeks before allogeneic HCT is recommended to reduce the risk of GVHD (65, 66).

Peripheral T-Cell Lymphomas (PTCL) and Natural Killer-Cell (NK) Lymphomas:

- Given the poor prognosis with standard chemotherapy, consolidative ASCT is recommended for eligible patients responding to first-line therapy with advanced stage or high IPI score PTCL NOS, angioimmunoblastic T-cell lymphoma, ALK-negative anaplastic large cell lymphoma (ALCL), advanced-stage NK/T-cell lymphoma, or enteropathy-associated T-cell lymphoma (67-73). Although ALK-positive ALCL usually has a favorable prognosis with BV-CHP, consolidative ASCT may be considered for selected cases with a high IPI score given their poorer outcomes with standard chemotherapy and the uncertain benefit of brentuximab vedotin in this high-risk subgroup (72-75).
- First-line allogeneic HCT is recommended for eligible patients with certain poor prognosis lymphomas responding to first-line therapy, such as hepatosplenic T-cell lymphoma, acute or lymphoma-type adult T-cell leukemia/lymphoma, aggressive NK cell leukemia, and selected cases of advanced-stage NK/T-cell lymphoma (71, 73)
- ASCT is recommended for patients with relapsed PTCL who have not previously received ASCT and who demonstrate a good response to second-line chemotherapy (e.g. DICEP or GDP) (76, 77)
- Allogeneic HCT is also recommended for patients with PTCL who relapse after ASCT or who are unable to receive ASCT due to chemorefractory disease, provided that an adequate response to pre-transplant therapy is achieved (78)

Cutaneous T-Cell Lymphomas (CTCL):

- ASCT is not routinely recommended for patients with mycoses fungoides or Sezary syndrome (MF/SS) but allogeneic HCT may be considered for selected high-risk cases (79, 80)

References

1. *Stiff PJ, Unger JM, Cook JR, Constine LS, Couban S, Stewart DA, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med. 2013;369(18):1681-90.*
2. *Landsburg DJ, Falkiewicz MK, Maly J, Blum KA, Howlett C, Feldman T, et al. Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission. J Clin Oncol. 2017;35(20):2260-7.*
3. *Puckrin R, Sterrett R, Chua N, Owen C, Duggan P, Shafey M, et al. Consolidative Autotransplantation Achieves High Cure Rates in Adverse-Risk Large B Cell Lymphoma. Transplant Cell Ther. 2023;29(12):763.e1-.e5.*
4. *Puckrin R, Sterrett R, Shafey M, Chua N, Stewart D. Favorable Outcomes with R-CHOP Induction and Consolidative Autologous Stem Cell Transplantation for Double-Hit Lymphoma. Transplant Cell Ther. 2022;28(11):762.e1-.e4.*
5. *Stewart DA, Bahlis N, Valentine K, Balogh A, Savoie L, Morris DG, et al. Upfront double high-dose chemotherapy with DICEP followed by BEAM and autologous stem cell transplantation for poor-prognosis aggressive non-Hodgkin lymphoma. Blood. 2006;107(12):4623-7.*
6. *Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2021.*
7. *Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023.*
8. *Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399(10343):2294-308.*
9. *Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-84.*
10. *Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540-5.*
11. *Stewart D, Shepherd L, Dudebout J, Larouche J, Chua N, Baetz T, et al. Canadian Cancer Trials Group (CCTG) LY. 17: A Randomized Phase II Study Evaluating Novel Salvage Therapy Pre-Autologous Stem Cell Transplant (ASCT) in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (RR-DLBCL)-Outcome of Rituximab-Dose-Intensive Cyclophosphamide, Etoposide, Cisplatin (R-DICEP) Versus R-GDP. . Blood. 2022;140(Supplement 1)::3734-6.*
12. *Vijay A, Duan Q, Henning JW, Duggan P, Daly A, Shafey M, et al. High dose salvage therapy with dose intensive cyclophosphamide, etoposide and cisplatin may increase transplant rates for relapsed/refractory aggressive non-Hodgkin lymphoma. Leuk Lymphoma. 2013;54(12):2620-6.*
13. *Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-6.*
14. *van Imhoff GW, McMillan A, Matasar MJ, Radford J, Ardeshna KM, Kuliczkowski K, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. J Clin Oncol. 2017;35(5):544-51.*
15. *Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90.*
16. *Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-44.*
17. *Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-15.*
18. *Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.*
19. *Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-52.*
20. *Zurko J, Ramdial J, Shadman M, Ahmed S, Szabo A, Iovino L, et al. Allogeneic transplant following CAR T-cell therapy for large B-cell lymphoma. Haematologica. 2023;108(1):98-109.*

21. *Hamadani M, Gopal AK, Pasquini M, Kim S, Qiu X, Ahmed S, et al. Allogeneic transplant and CAR-T therapy after autologous transplant failure in DLBCL: a noncomparative cohort analysis. Blood Adv. 2022;6(2):486-94.*
22. *Illerhaus G, Ferreri AJ, Binder M, Borchmann P, Hasenkamp J, Stilgenbauer S, et al. Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation (HDC-ASCT) As Consolidation Therapy in Patients with Primary CNS Lymphoma-Results of an International Randomized Phase III Trial (MATRix/IELSG43). Blood. 2022;140 (Supplement 2), pp.LBA-3.*
23. *Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, La Rosée P, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017;4(11):e510-e23.*
24. *Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, Celico C, et al. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. Leukemia. 2022;36(7):1870-8.*
25. *Houillier C, Taillandier L, Dureau S, Lamy T, Laadhari M, Chinot O, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. J Clin Oncol. 2019;37(10):823-33.*
26. *Houillier C, Dureau S, Taillandier L, Houot R, Chinot O, Moluçon-Chabrot C, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients Age 60 Years and Younger: Long-Term Results of the Randomized Phase II PRECIS Study. J Clin Oncol. 2022;40(32):3692-8.*
27. *Sanders S, Chua N, Larouche JF, Owen C, Shafey M, Stewart DA. Outcomes of Consecutively Diagnosed Primary Central Nervous System Lymphoma Patients Using the Alberta Lymphoma Clinical Practice Guideline Incorporating Thiotepa-Busulfan Conditioning for Transplantation-Eligible Patients. Biol Blood Marrow Transplant. 2019;25(8):1505-10.*
28. *Ferreri AJM, Doorduijn JK, Re A, Cabras MG, Smith J, Ilariucci F, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. Lancet Haematol. 2021;8(2):e110-e21.*
29. *Puckrin R, Chua N, Shafey M, Stewart DA. Improving the outcomes of secondary CNS lymphoma with high-dose thiotepa, busulfan, melphalan, rituximab conditioning and autotransplant. Leuk Lymphoma. 2022;63(10):2444-52.*
30. *Ahmed G, Alsouqi A, Szabo A, Rojek AE, Riedell PA, Awan FT, et al. Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Secondary Central Nervous System Large B-Cell Lymphoma (SCNSL): A Multicenter Retrospective Analysis. . Blood. 2023;142:3088.*
31. *Sterling CH, Tsai HL, Holdhoff M, Bolaños-Meade J, Luznik L, Fuchs EJ, et al. Allogeneic Blood or Marrow Transplantation with Nonmyeloablative Conditioning and High-Dose Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis for Secondary Central Nervous System Lymphoma. Transplant Cell Ther. 2021;27(10):863.e1-.e5.*
32. *Kuruvilla J, MacDonald DA, Kouroukis CT, Cheung M, Olney HJ, Turner AR, et al. Salvage chemotherapy and autologous stem cell transplantation for transformed indolent lymphoma: a subset analysis of NCIC CTG LY12. Blood. 2015;126(6):733-8.*
33. *Villa D, Crump M, Panzarella T, Savage KJ, Toze CL, Stewart DA, et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. J Clin Oncol. 2013;31(9):1164-71.*
34. *Maramattom LV, Hari PN, Burns LJ, Carreras J, Arcese W, Cairo MS, et al. Autologous and allogeneic transplantation for burkitt lymphoma outcomes and changes in utilization: a report from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2013;19(2):173-9.*
35. *Dreyling M, Lenz G, Hoster E, Van Hoof A, Gisselbrecht C, Schmits R, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood. 2005;105(7):2677-84.*
36. *Zoellner AK, Unterhalt M, Stilgenbauer S, Hübel K, Thieblemont C, Metzner B, et al. Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial. Lancet Haematol. 2021;8(9):e648-e57.*
37. *Hermine O, Hoster E, Walewski J, Bosly A, Stilgenbauer S, Thieblemont C, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet. 2016;388(10044):565-75.*

38. *Hermine O, Jiang L, Walewski J, Bosly A, Thieblemont C, Szymczyk M, et al. High-Dose Cytarabine and Autologous Stem-Cell Transplantation in Mantle Cell Lymphoma: Long-Term Follow-Up of the Randomized Mantle Cell Lymphoma Younger Trial of the European Mantle Cell Lymphoma Network. J Clin Oncol. 2023;41(3):479-84.*
39. *Merryman RW, Edwin N, Redd R, Bsat J, Chase M, LaCasce A, et al. Rituximab/bendamustine and rituximab/cytarabine induction therapy for transplant-eligible mantle cell lymphoma. Blood Adv. 2020;4(5):858-67.*
40. *Stewart C, Owen C, Chua N, Peters A, Shafey M, Stewart DA, et al. Long-Term Remissions after First-Line Autologous Stem Cell Transplantation for Mantle Cell Lymphoma. . Blood. 2023;142:3599.*
41. *Le Gouill S, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Dartigeas C, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. N Engl J Med. 2017;377(13):1250-60.*
42. *Sarkozy C, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Damaj G, et al. Long-Term Follow-Up of Rituximab Maintenance in Young Patients With Mantle-Cell Lymphoma Included in the LYMA Trial: A LYSA Study. J Clin Oncol. 2024;42(7):769-73.*
43. *Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020;382(14):1331-42.*
44. *Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. J Clin Oncol. 2022:JCO2102370.*
45. *Robinson SP, Boumendil A, Finel H, Peggs KS, Chevallier P, Sierra J, et al. Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: a retrospective study from the EBMT Lymphoma Working Party. Bone Marrow Transplant. 2018;53(5):617-24.*
46. *Eskelund CW, Dahl C, Hansen JW, Westman M, Kolstad A, Pedersen LB, et al. mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood. 2017;130(17):1903-10.*
47. *Casulo C, Friedberg JW, Ahn KW, Flowers C, DiGilio A, Smith SM, et al. Autologous Transplantation in Follicular Lymphoma with Early Therapy Failure: A National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant. 2018;24(6):1163-71.*
48. *Schouten HC, Qian W, Kvaloy S, Porcellini A, Hagberg H, Johnsen HE, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol. 2003;21(21):3918-27.*
49. *Oh DH, Li H, Duan Q, Villa D, Peters A, Chua N, et al. Quantifying Benefit of Autologous Transplantation for Relapsed Follicular Lymphoma Patients via Instrumental Variable Analysis. Biol Blood Marrow Transplant. 2016;22(5):941-8.*
50. *Puckrin R, Chua N, Chin K, Peters A, Duggan P, Shafey M, et al. Long-term follow-up demonstrates curative potential of autologous stem cell transplantation for relapsed follicular lymphoma. Br J Haematol. 2023;201(2):319-25.*
51. *Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.*
52. *Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325-32.*
53. *Robinson SP, Boumendil A, Finel H, Schouten H, Ehninger G, Maertens J, et al. Reduced intensity allogeneic stem cell transplantation for follicular lymphoma relapsing after an autologous transplant achieves durable long-term disease control: an analysis from the Lymphoma Working Party of the EBMT†. Ann Oncol. 2016;27(6):1088-94.*
54. *Avivi I, Arcaini L, Ferretti VV, Boumendil A, Finel H, Milone G, et al. High-dose therapy and autologous stem cell transplantation in marginal zone lymphomas: a retrospective study by the EBMT Lymphoma Working Party and FIL-GITMO. Br J Haematol. 2018;182(6):807-15.*
55. *Kyriakou C, Canals C, Sibon D, Cahn JY, Kazmi M, Arcese W, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2010;28(13):2227-32.*
56. *Akhtar S, Montoto S, Boumendil A, Finel H, Masszi T, Jindra P, et al. High dose chemotherapy and autologous stem cell transplantation in nodular lymphocyte-predominant Hodgkin lymphoma: A retrospective study by the European society for blood and marrow transplantation-lymphoma working party. Am J Hematol. 2018;93(1):40-6.*
57. *Cornell RF, Bachanova V, D'Souza A, Woo-Ahn K, Martens M, Huang J, et al. Allogeneic Transplantation for Relapsed Waldenström Macroglobulinemia and Lymphoplasmacytic Lymphoma. Biol Blood Marrow Transplant. 2017;23(1):60-6.*
58. *Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341(8852):1051-4.*

59. *Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002;359(9323):2065-71.*
60. *Shafey M, Duan Q, Russell J, Duggan P, Balogh A, Stewart DA. Double high-dose therapy with dose-intensive cyclophosphamide, etoposide, cisplatin (DICEP) followed by high-dose melphalan and autologous stem cell transplantation for relapsed/refractory Hodgkin lymphoma. Leuk Lymphoma. 2012;53(4):596-602.*
61. *Merryman RW, Redd RA, Nishihori T, Chavez J, Nieto Y, Darrah JM, et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. Blood Adv. 2021;5(6):1648-59.*
62. *Mei MG, Lee HJ, Palmer JM, Chen R, Tsai NC, Chen L, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. Blood. 2022;139(25):3605-16.*
63. *Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853-62.*
64. *Moskowitz CH, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018;132(25):2639-42.*
65. *Merryman RW, Castagna L, Giordano L, Ho VT, Corradini P, Guidetti A, et al. Allogeneic transplantation after PD-1 blockade for classic Hodgkin lymphoma. Leukemia. 2021;35(9):2672-83.*
66. *Herbaux C, Merryman R, Devine S, Armand P, Houot R, Morschhauser F, et al. Recommendations for managing PD-1 blockade in the context of allogeneic HCT in Hodgkin lymphoma: taming a necessary evil. Blood. 2018;132(1):9-16.*
67. *d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093-9.*
68. *Savage KJ, Horwitz SM, Advani R, Christensen JH, Domingo-Domenech E, Rossi G, et al. Role of stem cell transplant in CD30+ PTCL following frontline brentuximab vedotin plus CHP or CHOP in ECHELON-2. Blood Adv. 2022;6(19):5550-5.*
69. *Schmitz N, Truemper L, Bouabdallah K, Ziepert M, Leclerc M, Cartron G, et al. A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. Blood. 2021;137(19):2646-56.*
70. *Brink M, Meeuwes FO, van der Poel MWM, Kersten MJ, Wondergem M, Mutsaers PGNJ, et al. Impact of etoposide and ASCT on survival among patients aged <65 years with stage II to IV PTCL: a population-based cohort study. Blood. 2022;140(9):1009-19.*
71. *Kharfan-Dabaja MA, Kumar A, Ayala E, Hamadani M, Reimer P, Gisselbrecht C, et al. Clinical Practice Recommendations on Indication and Timing of Hematopoietic Cell Transplantation in Mature T Cell and NK/T Cell Lymphomas: An International Collaborative Effort on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2017;23(11):1826-38.*
72. *Vose J, Armitage J, Weisenburger D, Project IT-CL. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30.*
73. *Fox CP, Ahearne MJ, Pettengell R, Dearden C, El-Sharkawi D, Kassam S, et al. Guidelines for the management of mature T- and natural killer-cell lymphomas (excluding cutaneous T-cell lymphoma): a British Society for Haematology Guideline. Br J Haematol. 2022;196(3):507-22.*
74. *Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229-40.*
75. *Horwitz S, O'Connor OA, Pro B, Trümper L, Iyer S, Advani R, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol. 2022;33(3):288-98.*
76. *Skamene T, Crump M, Savage KJ, Reiman T, Kuruvilla J, Good D, et al. Salvage chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: a subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study. Leuk Lymphoma. 2017;58(10):2319-27.*
77. *Ngu HS, Parkin S, Scott DW, Villa D, Gerrie AS, Toze CL, et al. Outcome of relapsed and refractory peripheral T-cell lymphoma (PTCL) with intention for curative therapy incorporating high dose chemotherapy and hematopoietic stem cell transplant (HDC/SCT). . Blood. 2021;138.*
78. *Hamadani M, Ngoya M, Sureda A, Bashir Q, Litovich CA, Finel H, et al. Outcome of allogeneic transplantation for mature T-cell lymphomas: impact of donor source and disease characteristics. Blood Adv. 2022;6(3):920-30.*

79. *de Masson A, Beylot-Barry M, Ram-Wolff C, Mear JB, Dalle S, d'Incan M, et al. Allogeneic transplantation in advanced cutaneous T-cell lymphomas (CUTALLO): a propensity score matched controlled prospective study. Lancet. 2023;401(10392):1941-50.*
80. *Domingo-Domenech E, Duarte RF, Boumedil A, Onida F, Gabriel I, Finel H, et al. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sézary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2021;56(6):1391-401.*

Myeloma and Amyloidosis

Presented by: The Myeloma Group

Summary

(Also see AHS Myeloma Guidelines)

1. For **symptomatic multiple myeloma**, an autologous stem cell transplant (ASCT) should be offered to patients who are ≤65 years old, without significant co-morbidities, and have achieved at least partial response after induction chemotherapy.
    - For individuals between ages 65 and 70 years, ASCT will be considered if the IMWG Frailty index is <1. (http://www.myelomafrailtyscorecalculator.net/)
        i. This is particularly pertinent where upfront use of Daratumumab/Lenalidomide and dexamethasone (DRd) may provide better outcomes than ASCT.
    - We do NOT recommend ASCT for individuals ≥ 70 years.
    - We recommend an early referral (after 2 cycles of induction chemotherapy) to the transplant team for ASCT consideration
2. Collecting enough stem cells for 2 transplants (for salvage, tandem or boost) is recommended but will be discussed on a case-by-case basis
    - Adequate stem cells will be collected for 2 ASCT in patients <60 years and adequate stem cells will be collected for 1 ASCT in patients >60 years.
    - Other considerations include 1) patient factors, 2) disease factors, 3) evolving myeloma therapies, and 3) local resource factors
3. The preferred conditioning chemotherapy for ASCT is Melphalan 200mg/m^2
    - The use of Busulfan with melphalan conditioning is reasonable
    - Dose reductions of melphalan is reasonable in those with renal dysfunction and/or frailty.
4. The preference is to offer an upfront ASCT post-induction as opposed to an ASCT on relapse.
5. Offering a second ASCT on relapse is reasonable if the disease has been in control for at least 2 years (no maintenance) and at least 4 years (with maintenance).
6. Tandem ASCT is not recommended. However, for patients with high-risk disease that may benefit from this approach, tandem ASCT will be considered on a case-by-case basis.
7. The use of consolidation therapy post-ASCT is recommended in patients with high-risk disease and in patients who achieved < very good partial response (VGPR) after ASCT.
8. The use of maintenance therapy with lenalidomide is recommended post-ASCT until disease progression (in contrast to fixed duration). The use of combination lenalidomide with bortezomib or carfilzomib, but not ixazomib as maintenance is reasonable in patients with high-risk disease.
9. Overall, the use of daratumumab with induction, consolidation and maintenance therapy is strongly recommended in those with access to funding. It would be ideal to have Minimal

Residual Disease (MRD) testing to guide potential discontinuation of therapy after 2 years (PERSEUS study), where up to 65% of patients may achieve this outcome.

10. Allogeneic transplant is not indicated.
11. For **systemic AL amyloidosis**, ASCT may be offered to patients with the following eligibility criteria:
    - Age <65 years,
    - Performance status (Eastern Cooperative Oncology Group) 0 to 2,
    - NT-proBNP is <5000 ng/l and/or cardiac troponin T is <0.06 ng/ml,
    - Estimated glomerular filtration rate >30 ml/min per 1.73 m2 unless on dialysis,
    - New York Heart Association class <III, cardiac ejection fraction >45%, systolic blood pressure >90 mm Hg (standing), and
    - Lung CO diffusion capacity >50%.
12. Induction chemotherapy for patients with AL amyloidosis should be recommended for patients with >10% monoclonal plasma cells in the bone marrow at presentation.
13. A salvage ASCT for AL amyloidosis will be considered on a case-by-case basis.

Symptomatic Myeloma

Background

Multiple myeloma is a chemotherapy-responsive tumor that demonstrates significant dose-response effects. The availability of increased and superior therapeutic options has led to improvements in depth and duration of response. Ultimately, this translates to better Progression-Free Survival (PFS), Overall Survival (OS) and Health related Quality of Life (HRQOL). A more thorough discussion on myeloma care can be found within the AHS Myeloma Guidelines.

Hematopoietic stem cell transplantation involves the use of high-dose chemotherapy followed by an infusion of either autologous, allogeneic, or syngeneic stem cells. Data from the CIBMTR, suggests improvements in myeloma outcomes with autologous stem cell transplantation (ASCT)[1]. In historical randomized controlled trials (RCT), the use of high-dose chemotherapy with ASCT to standard induction protocols demonstrates improved PFS, OS and HRQOL (Table 1).

Table 1. Review of Historic RCTs Comparing Standard Therapy (SDT) to High-Dose Chemotherapy (HDT) with ASCT.

Study	N	Age	SDT versus HDT (p-value)		
			CR/nCR (%)	Median EFS/PFS(mths)	Median OS (mths)
Attal *et al.* 1996 IFM90[2]	200	≤ 65	5 vs. 22 (p<.001)	18 vs. 28 (p=.01)	44 vs. 57 (p=.03)
Fermand *et al.* 1998 MAG-95[3]	190	55-65	20 vs. 36 (p=NR)	18.7 vs. 25.3 (p=.07)	47.6 vs. 47.8 (p=.91)
Child *et al.* 2003 MRC VII[4]	407	≤ 65	8 vs. 44 (p<.001)	19 vs. 31 (p=.001)	42 vs. 54 (p<.001)
Palumbo *et al.* 2004 M97G[5]	194	50-70	25 vs. 6 (p=0.002)	16 vs. 37 (p<0.001)	62 vs. 77 (p<0.001
Blade *et al.* 2005 PETHEMA[6]	216	≤ 65	11 vs. 30 (p=.002)	33 vs. 42 (p=NS)	61 vs. 66 (p=NS)
Barlogie *et al.* 2006 US Intergroup[7]	516	≤ 70	15 vs. 17 (p=NS)	21 vs. 25 (p=.05)	53 vs. 58 (p=NS)

.

Rationale For Use of Autologus Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) represents a significant advancement in care for patients with myeloma, where the chemotherapeutic options were historically limited. Multiple randomized controlled trials (RCT) have demonstrated the superiority of ASCT over standard care/conventional cytotoxic chemotherapy – improved depth of response, PFS/EFS and OS (Table 1). A meta-analysis of these historic studies supports the use of ASCT with improvements in PFS, but not OS[8]. Additionally, one RCT demonstrates better HRQOL as evaluated by a composite endpoint of a longer period without symptoms, treatment, and treatment toxicity (TwisTT)[9].

With the availability of newer chemotherapeutics such as proteasome inhibitors and immunomodulatory agents, they have been incorporated into myeloma care[10]. Such combinations have led to deeper and more durable responses either in induction, consolidation, and maintenance therapy[11,12]. Given these improved outcomes, many have challenged whether ASCT still has a role in myeloma care. Table 2 summarizes more recent Phase III RCTs performed in the current era of chemotherapeutics for induction. These studies have been variably subject to pooled analyses and meta-analyses demonstrating ACST's value[13,14]. More recently, the Determination study led by Richardson *et al.* compared 8 cycles of lenalidomide, bortezomib and dexamethasone (RVD) to 3

cycles of RVD, ASCT with 2 cycles of RVD consolidation. Subsequently, both groups received lenalidomide maintenance. With a median follow-up of 76 months, they demonstrate a median PFS that favors the ASCT group (46.2 vs. 67.5 months) affirming the continued role of ASCT.

Table 2: Review of RCTs Comparing Standard Therapy (SDT) to High-Dose Chemotherapy (HDT) with ASCT in the era of novel agent therapy.

Study	N	Age	SDT versus HDT (p-value)		
			VGPR/CR (%)	Median PFS (mths)/*3 yr PFS*	3-,4- or 5 year OS (%)
Palumbo *et al.* 2014[15]	402	<65	15.7 vs. 20	22.4 vs. 43 (p<0.001)	65.3 vs. 81.6 (p=0.02)
Gay *et al.* 2015[16]	389	≤65	?20s vs. 30s	28.6 vs. 43.3 (p<0.001)	84 vs. 87
Cavo *et al.* 2017[17]	1503	≤65	75 vs. 84	57% vs. 64% (p=0.002)	NR
Attal *et al.* 2017 IFM/DFCI2009[18]	700	≤65	48 vs. 59 (p=0.03)	36 vs. 50 (p<0.001)	82 vs. 81 (p=0.87)
Richardson *et al.* 2022 DETERMINATION[19]	722	≤65	42 vs.46.8	46.2 vs.67.5	79.2 vs. 80.7 (p=1.0)

Collectively, these studies suggest that ASCT consistently improves responses, PFS and OS. ASCT continues to be a key intervention in the current era of chemotherapeutics.

Timing of ASCT

The optimal timing of ASCT has been debated – should it be offered after successful induction therapy or on relapse? The only Phase III RCT was performed prior to the availability of novel agent, where it demonstrates similar survival, but patients undergoing early ASCT had superior HRQOL as measured by TwisTT[9]. In the current therapeutic era, there are several single institution observational studies compared early vs. delayed ASCT[20-23]and systematic reviews[14] suggesting a superior depth of response and PFS but similar OS with early ASCT. The IFM-DFCI RCT by Attal *et al.* compared 3 cycles of RVD induction with ASCT vs. 8 x RVD. In the 8 x RVD group, 79% of symptomatic patients received a salvage (delayed) ASCT[18]. This study may allow an indirect comparison of early vs. delayed ASCT. Both PFS and HRQOL was favored in the patients receiving early ASCT in the IFM-DFCI study[18]. More recently, patients participating in phase III EMN02/HO95 study who were randomized to upfront ASCT were compared (not randomized) to those who received ASCT at the time of progression after primary randomization to VMP[24]. After a median follow-up of 85 months in the upfront auto-HSCT group with a median follow-up of 51 months in the delayed auto-HSCT group, the median PFS2 rate was 55% vs 32% (HR, 0.52; 95% CI, 0.40–0.66; p < 0.0001) respectively. Moreover, median OS was not reached in the upfront auto-HSCT group vs 81 months in the delayed auto-HSCT group, with OS rates of 69% vs 58% (HR, 0.68; 95% CI, 0.51–0.93; p = 0.0164).

Table 3: Review of RCTs Comparing Upfront or Delayed ASCT

Study	**N**	**Age (yrs)**	**Upfront versus Delayed (p-value)**		
			Response	**Median EFS/PFS (mths)**	**Median OS (mths)**
Fermand *et al.*1998[9]	202	≤56	NR	39 vs. 13 p=S	64.6 vs. 64 p=0.92
Attal *et al.* 2017 IFM/DFCI2009[18]	700	≤65	59% vs. 48% (CR)	50 vs. 36 p<0.001	81% vs. 82% at 4yrs p=NS

Taken together, it is ideal that ASCT be considered upfront in patients who are eligible. However, it is reasonable to delay ASCT due to personal and/or psychosocial reasons given similar OS. It must be recognized that by deferring an ASCT may mean that in the future, an ASCT may not be possible or warranted. This risk has been estimated to be around 10% from a single institution study[25]. Moreover, it may be preferable to strongly consider an upfront ASCT in individuals who are deemed high risk by disease presentation, cytogenetics, or gene expression profiling.

Eligibility for ASCT

Chronologic Age:

Given that most RCTs evaluate patients who are ≤65 years for ASCT, this constitutes the highest level of evidence for practice. However, there have been numerous observational studies that suggest that ASCT is feasible in patients > 65 years with careful selection[26-30]. In addition, there have been movements to consider physiologic age as opposed to chronologic age[31]. As such, it is reasonable to consider ASCT in patients >65 with careful attention to comorbidities and assessments of frailty. Assessments of frailty[32-34] are nuanced and in the myeloma setting, the IMWG Frailty score[35] is often used: http://www.myelomafrailtyscorecalculator.net/

As such, it is reasonable to consider the IMWG Frailty score as an anchor to help determined ASCT eligibility[36]. A more in-depth assessment of frailty may be required, and a review is available in the AHS BMT guidelines chapter: Patient Eligibility.

However, given the advancements in myeloma therapeutics, the relative value of ASCT in older patients will likely decrease. For instance, the use of Daratumumab/Lenalidomide and dexamethasone (DRd) can provide a 5-year PFS rate of 52.5%[37].

Patient Variables:

See AHS BMT guidelines section: Patient Eligibility

Depth of Response:

In general depth of response pre-ASCT correlates with post-ASCT outcomes[38]. However, a historic registry study at IBMTR suggests deepening responses beyond partial response (PR) did not translate to better OS. More recent data from the CIBMTR suggest that patients achieving less than a PR to initial induction therapy, including with novel agent combinations, additional pre-ASCT salvage chemotherapy improved the depth of response and pre-ASCT disease status but was not associated with survival benefit[39]. Additionally, patients with refractory myeloma (<PR) might still derived benefit from ASCT. Notably, current induction therapies (e.g., CYBORD or RVD) do not generally include cytotoxic therapy – meaning that a less than responsive disease might still derived benefit from ASCT where high dose melphalan is used for conditioning[40].

In the “novel therapy” era, the MRC XI[41] evaluated whether there is value in deepening responses prior to ASCT. They randomized patients who only achieved a MR or PR after immunomodulatory

based triplet therapy to receive either no additional therapy or additional therapy with bortezomib, cyclophosphamide and dexamethasone (CYBORD). The additional therapy improved the pre-ASCT responses (PR improved to VGPR in 41% of evaluable cases) and translated to improved PFS (55 months vs. 30 months, p=0.0003), but no differences in OS.

Stem Cell Mobilization

See AHS BMT guidelines section: Donor Management, Mobilization

Should We Be Collecting Enough Stem Cells for 2 ASCTs:

Table 4 illustrates ASCTs performed in Calgary from 2010, including the proportion of 2nd and 3rd ASCT (planned tandem, delayed ASCT or stem cell boost).

Considerations for collection amount include: 1) patient factors such as age, co-morbidities, 2) disease factors such as high-risk disease, 3) evolving myeloma therapies, and 3) local resource factors. Taken together, collecting for 1 or 2 ASCT will be discussed on a case-by-case basis.

Table 4: ASCTs performed in Calgary from 2010

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
1st ASCT	28	29	24	27	40	41	40	25	43	32	38	38
≤65 years[1]	28	28	24	25	38	32	33	23	40	31	32	31
>65 years[1]	0	1	0	2	2	9	7	2	3	1	6	7
2nd ASCT	3	0	1	1	5	6	6	5	7	3	2	5
≤65 years[2]	3	0	1	1	4	5	5	3	4	2	1	4
>65 years[2]	0	0	0	0	1	1	1	2	3	1	1	1
3rd ASCT	0	0	0	0	2	0	0	1	0	0	1	0
≤65 years[3]	0	0	0	0	2	0	0	1	0	0	0	0
>65 years[3]	0	0	0	0	0	0	0	0	0	0	1	0
Total ASCT	31	29	25	28	47	47	46	31	50	35	41	43

2nd/3rd ASCT may include tandem ASCT or stem cell boosts

Conditioning Regimen

The current standard for conditioning is Melphalan 200mg/m^2 following a RCT demonstrating that Melphalan 200mg/m^2 (Mel200) was superior to Melphalan 140mg/m^2 (Mel140) with 8 Gy Total Body Irradiation[42]. A large database study from EBMT suggests that Mel200 may be preferable to Mel140 to patients who do not achieve a ≥PR post-induction chemotherapy. In contrast, patients appear to do just as well with Mel140 in those with ≥VGPR post-induction chemotherapy[43].

More recently, Roussel *et al.* compared Mel200 with Mel200+Bortezomib. In this RCT carried out by the IFM, the combination of Mel200+Bortezomib did not result in superior depth of response, PFS or OS[44]. Additionally, Bashir *et al.* evaluated the combination of Mel140+Busulfan 130mg/m^2 vs. Mel200 in a RCT with the combination therapy associated with an improved PFS (65 months vs. 44 months)[45]. Interestingly, this trial showed an improvement in PFS with the Bu-Mel conditioning regimen in patients with newly diagnosed myeloma with HR cytogenetics, where the median PFS was 44.7 months and 25.7 months in the Bu-Mel and Mel arms, respectively (P = .044)[46]. A meta-analysis

of 10 observation studies with a total of 2855 patients examined the use of Bu-Mel conditioning compared with Mel200 alone. Bu-Mel conditioning correlates with longer PFS (HR 0.77; p=0.0002) but similar OS (HR 1.08; p=0.35)[47].

The dose of melphalan should be reduced to 140mg/m^2 in individuals with renal dysfunction or on dialysis[48-50]. Further, consideration could be given to a 140mg/m^2 melphalan dosing in those who >65 years with deemed frailty[50-52].

Table 5: Review of RCTs Comparing Conditioning Regimens in ASCT

Study	N	Age (yrs) Median	Mel200 versus "other" (p-value)		
			CR (%)	Median EFS/PFS	OS (%)
Moreau *et al.* 2002 IFM 9502[42]	282	<65	NA	EFS of 20.5 mths vs. 21 mths (p=0.6)	65.8 vs. 45.5 (at 45mths) p=0.05
Roussel *et al.* 2022 IFM 2014-02[44]	300	58	22.1 vs. 20.5	PFS of 34 mnths vs. 29.6 mnths (p=0.244)	89.5 vs. 89.5 (at 3 years)
Bashir *et al.* 2019[53]	202	58-59	26 vs. 33	PFS of 43.5 mths vs. 64.7 mths (p=0.022)	NS at (p=0.75)

Role of Tandem ASCT

Tandem ASCT with Historic Induction Chemotherapy:

A tandem ASCT can be defined as a pre-planned second ASCT within 6 months of the first ASCT, where the goal is avail of additional high dose melphalan to achieve a deeper hematological response.

There has been several RCTs comparing tandem with single ASCTs prior modern induction chemotherapy[52,54-56]. These older studies demonstrate that tandem RCTs can improve either EFS or PFS with only one demonstrating OS advantage limited to the subgroup of patients not achieving VGPR after the 1st ASCT[54]. Two meta-analyses would confirm these observations[57,58].

Table 6: Review of historic RCTs Comparing Tandem ASCT with Single ASCT

Study	N	Age (yrs)	Tandem versus single (p-value)		
			Responses (%)	Median EFS/PFS (mths)	Median OS (mths)
Attal *et al.* 2003[54]	399	<60	50 vs. 42 (>VGPR)	20% vs. 10% at 7yrs p=0.03	42% vs. 21% (at 7 years) p=0.01
Cavo *et al.* 2007 Bologna 96[55]	321	≤60	47 vs. 33 (≥nCR)	25 vs. 32 p=0.19	NR
Sonnevald *et al.* 2007[52]	303	≤65	32 vs. 13 (CR)	17% vs. 9% at 6yrs p=0.006	39% vs. 36% at 6yrs p=0.51
Mai *et al.* 2016 GMMG-HD2[56]	358	≤66	19.4 vs. 16 (CR)	33.1 vs. 26.2 p=NS	75.3 vs. 73.0 p=NS

Tandem ASCT with Modern Induction Chemotherapy:

More recently, a post-hoc analyses using pooled data from 3 independent Phase III RCTs was performed to elucidate the potential value of tandem ASCT[59]. All 3 RCTs utilized bortezomib-based

induction regimen. There was a significant improvement in the median PFS and 5-year OS in favor of tandem ASCT. This benefit was more apparent in patients with high-risk cytogenetics such as t(4;14) and/or deletion 17p who had not achieved a CR after induction therapy (70% vs. 17%). Additionally, these results were further affirmed with their 10 year follow-up data where patients with ISS stage II+III, high-risk cytogenetics and failure to achieve CR benefitted from a tandem ASCT approach[60].

These findings were also echoed by the preliminary findings in the EMN02/HO95 MM study[17], where there was a significant improvement in the 3-year PFS (73% vs. 64%) and 3-year OS (89% vs. 82%) in favor of tandem ASCT compared to single ASCT. The superiority of a tandem ASCT was again evident in patients with high-risk cytogenetics in both 3-year PFS and OS. In this study, most patients received bortezomib based induction (i.e., no lenalidomide).

In contrast, the BMT-CTN 0702 STAMINA study[61] did not demonstrate any difference between patients (after initial ASCT who either received a 1) tandem ASCT followed by maintenance lenalidomide, 2) 4 cycles of consolidation (lenalidomide, bortezomib and dexamethasone (RVD)) followed by maintenance lenalidomide, or 3) maintenance lenalidomide alone. Of note, most patients in this study received RVD induction therapy prior to initial ASCT.

Table 7: Review of recent RCTs Comparing Tandem ASCT with Single ASCT

Study	N	Age	Tandem versus single/other		
			Randomized Gps	Median PFS	Median OS
Stadtmauer *et al.* 2016 STAMINA[61]	758	<71yrs	Mel200 x1 - R maint	52 mths	83 mths
			Mel200 x2 - R maint	57 mths	86 mths
			Mel200 x1- RVD conso- R maint	57 mths	82 mths
Cavo *et al.* 2017 EMN02/HO95[17]	1503	≤65yrs	Mel200 x1 - +/- RVD - R maint	64% (3yr PFS)	82% (3yr PFS)
			Mel200 x2 - +/- RVD - R maint	73% (3yr PFS)	89% (3yr PFS)

Consolidation Post-ASCT

The goal of consolidation therapy post-ASCT is to improve and augment responses – to suppress residual disease. There have several RCTs suggesting that consolidation can deepen responses and prolong PFS. However, its effect on OS is less clear.

Indeed, the above mentioned BMT-CTN 0702 STAMINA study[61] did not demonstrate benefit of consolidation therapy. In contrast, preliminary data from the EMN02/HO95 MM study[62] suggest a PFS benefit with 2 cycles of lenalidomide, bortezomib and dexamethasone (VRD) consolidation (p=0.013) without OS benefit (p>0.05).

Both the CASSIOPEIA and PERSEUS seek to understand the value of Daratumamab in patients eligible for ASCT. The PERSEUS randomly assigned 709 transplantation-eligible patients with newly diagnosed multiple myeloma to receive either subcutaneous daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy (D-VRd group) or VRd induction and consolidation therapy and lenalidomide maintenance therapy alone (VRd group). Similarly, the CASSIOPEIA evaluated daratumumab in combination with bortezomib, thalidomide,

and dexamethasone (D-VTd) as induction therapy before and consolidation therapy after autologous stem-cell transplantation (ASCT), followed by a second randomization to daratumumab maintenance therapy (up to 2 years) or observation alone. This means that the independent value of consolidation post-ASCT in these 2 studies cannot be assessed – see Section Maintenance with anti-CD38 monoclonal antibody for more details.

Table 8: Review of recent RCTs Comparing Consolidation Therapy with No Consolidation Therapy

Study	N	Age	Consolidation versus none		
			Randomized Gps	Median PFS (mths)	Median OS (mths)
Stadtmauer *et al.* 2019 STAMINA[63]	758	<71yrs	Mel200 x1 - R maint	52	83
			Mel200 x2 - R maint	57	86
			Mel200 x1- RVD conso- R maint	57	82
Sonneveld *et al.* 2020 EMN02/HO95[62]	903	≤65yrs	RVD consolidation x 2	59	75% at 6yrs
			No consolidation	43	69% at 6yrs

Maintenance Post-ASCT

A typical maintenance therapy is low dose with limited toxicity administered over a prolonged period to deepen responses and/or maintain responses. Thalidomide was historically for maintenance therapy post-ASCT with improvements in depth of responses, PFS and possibly OS. This came at a cost of clinically significant peripheral neuropathy and therapy related fatigue. Interestingly, thalidomide maintenance therapy has been associated with worse outcomes in patients with high-risk cytogenetics.

Maintenance with Lenalidomide Monotherapy

Maintenance with lenalidomide has been considered standard of care following the publications by CALGB[64] and IFM[65]. Both studies demonstrate improvements in PFS but only the CALGB study demonstrates improvements with OS on lenalidomide maintenance. Both the GIMEMA[15] and Myeloma IX[41] study would confirm the benefit of maintenance lenalidomide on PFS. The results of these studies have been subject to systematic reviews/meta-analyses which confirms the efficacy of maintenance lenalidomide[66-70].

The duration of maintenance therapy with lenalidomide has been subject to some discussion. In the IFM/DFCI2009 study[18] by Attal *et al.*, maintenance therapy with lenalidomide post-ASCT was for 1 year. In contrast, the Determination study[19] by Richardson *et al.* employed maintenance therapy with lenalidomide until progression. An indirect comparison suggests a median PFS of 35 months and 46.2 months respectively. This would support a preference for lenalidomide maintenance until progression.

Table 9: Review of recent RCTs Comparing Maintenance Therapy with Lenalidomide with No Maintenance Therapy

Study	N	Age	Lenalidomide Maintenance versus none (p-value)		
			>VGPR	Median PFS (mths)	Median OS (mths)
Attal *et al.* 2012 IFM[65]	614	<65	84% vs. 76% (p=0.009)	41 vs. 23 (p<0.001)	73% vs. 75% at 4yrs (p=NS)
McCarthy 2012 CALGB*64*	460	<71	NR	46 vs. 27 (P<0.001)	88% vs. 80% at 3yrs (p=0.03)
Palumbo *et al.* 2014 GIMEMA[15]	273	<65	NR	41.9 vs. 21.6 (p<0.001)	88% vs. 79.2% at 3yrs (p=NS)
Jackson *et al.* Myeloma IX[41]	2568	NR	NR	57 vs. 30 (p<0.0001)	87.5% vs. 80.2% at 3yrs (p=0.014)

Maintenance with Proteosome Inhibition Monotherapy:

The effect of maintenance bortezomib post-ASCT has also been evaluated. The HOVON-65/GMMG-HD4 study suggest that patients with del 17p might benefit from a proteasome inhibitor maintenance[71,72]. More recently, the TOURMALINE MM3 study[73] evaluated ixazomib maintenance post-ASCT compared to placebo. After a median follow-up of 31 months with 54% of PFS events, there was a 28% reduction in the risk of progression/death, corresponding to a 39% improvement in PFS with ixazomib vs placebo (median 26.5 vs 21.3 months; hazard ratio [HR] 0.72; 95% CI: 0.582, 0.890; p=0.002). In a landmark analysis from ASCT, PFS was 30.7 vs 24.9 months (HR 0.684; 95% CI: 0.551, 0.848; p<0.001).

Table 10: Review of recent RCTs Comparing Maintenance Therapy with Proteosome Inhibition (PI) with No Maintenance Therapy

Study	N	Age (yrs)	Proteosome Inhibition versus other (p-value)		
			Response (%)	Median PFS (mths)	OS
Goldschmidt *et al.* 2018 HOVON-65/GMMG-HD4[71,72]	827	57	36 vs. 24 CR	35 vs. 28 (p=0.002)	61% vs. 55% at 5yrs
Dimopoulos *et al.* 2019 TOURMALINE MM3[73]	656	57	12 vs. 7 MRD -ve	26.5 vs. 21.3 (p=0.002)	NR

Dual Maintenance with Proteosome Inhibition and Lenalidomide:

Maintenance therapy with Ixazomib, lenalidomide and dexamethasone (IRd) was compared to lenalidomide with dexamethasone in the GEM2014MAIN trial led by Rosinol *et al*[74]. With a median follow-up of 56 months, they demonstrate there was no difference in PFS between the two maintenance arms (median not reached, PFS at 5 years: 62% vs. 63% with IRd and Rd, respectively, p=0.785).

Similarly, concurrent carfilzomib with lenalidomide was also compared with lenalidomide as part of a second randomization in the FORTE study[75]. Here, the 3-year PFS from the second randomization was 75% in patients treated with carfilzomib + lenalidomide (95% CI, 68–82, median, not reached [NR]; 95% CI, NR–NR) versus 65% with lenalidomide alone (95% CI, 58–72, median, NR; 95% CI, NR–NR) (hazard ratio, 0.64; 95% CI ,0.44–0.94; p = 0.023).

Table 11: Review of recent RCTs Comparing Dual Maintenance Therapy with PI and Lenalidomide with Lenalidomide alone Therapy

Study	N	Age (yrs.)	Proteosome Inhibition and Lenalidomide versus other (p-value)		
			Response (%)	Median PFS (mths)	OS
Gay *et al.* 2021 FORTE[75]	356	56-57	68 vs. 65 sCR	75% vs. 65% at 3 years (p=0.023)	94% vs. 90% at 3 years
Rosinol *et al.* 2021 GEM2014MAIN[74]	332	58-59	73.7 vs. 65.2 sCR/CR	62% vs. 63% at 5 years	Not available

Maintenance with Anti-CD38 Monoclonal Antibody:
Again, CASSIOPEIA was a two-part, randomized phase 3 trial that evaluated daratumumab in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) as induction therapy before and consolidation therapy after autologous stem-cell transplantation (ASCT), followed by a second randomization to daratumumab maintenance therapy (up to 2 years) or observation alone, in transplant-eligible patients with newly diagnosed multiple myeloma. With a follow-up of 80.1 months, progression-free survival from second randomization was significantly longer in the daratumumab maintenance group than the observation-alone group (see Table 12).

Likewise, the PERSEUS randomly assigned 709 transplantation-eligible patients with newly diagnosed multiple myeloma to receive either subcutaneous daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy (D-VRd group) or VRd induction and consolidation therapy and lenalidomide maintenance therapy alone (VRd group). Daratumumab was stopped at 2 years if complete response or better and had sustained minimal residual disease (MRD)–negative status (the absence of malignant cells at a sensitivity threshold of $10^{-}5$ or lower) for at least 12 months. PERSEUS trial did NOT have a second randomization to maintenance therapy – meaning the independent value of maintenance daratumumab is less clear.

It is ideal to have Minimal Residual Disease (MRD) testing to guide potential discontinuation of therapy after 2 years, a management strategy validated by the PERSEUS study, where up to 65% patients may achieve this outcome.

Table 12: Review of recent RCTs Comparing anti-CD38 antibody with No maintenance/ Lenalidomide alone Therapy

Study	N	Age (yrs.)	Anti-CD38 versus other (p-value)		
			Response (%)	Median PFS (mths)	OS
Sonneveld *et al.* 2023 PERSEUS	709	60	65.1 vs. 32.2 (MRD 10^{-6})	84.3% vs 67.7% at 4 years	
Moreau *et al.* 2024 CASSIOPEIA	886	58	58.1 vs. 48.9 (MRD 10^{-6})*	Not reached vs. 72.1 (p=0.0481))*	85% vs.84% at 80 mths
			43.7 vs 26.5 (MRD 10^{-6})^	Not reached vs. 32.7 (p<0.0001)^	

*received D-VTD induction; ^received VTD induction

Role of Second ASCT for Salvage Therapy

Given that most if not all patients will relapse, a second ASCT can be considered as salvage treatment. There has been 1 RCT that evaluates the use of 2nd salvage ASCT vs. conventional care, demonstrating that a 2nd salvage improves PFS but not OS[76]. In contrast, there have been numerous observational studies that support the use of a 2nd salvage ASCT[77-83]. Given that the duration of response with a 2nd ASCT will be shorter than the 1st ASCT, an arbitrary cutoff of at least 2 years from the 1st ASCT before 2nd ASCT should be considered. However, the routine use of consolidation and maintenance may change this duration of response "cutoff".

Table 13: Review of RCTs of 2nd salvage ASCT.

Study	N	Age	Salvage 2nd ASCT vs. conventional (p-value)		
			Overall Response (%)	Median PFS (mths)	3-Year OS (%)
Cook *et al.* 2014 NCRI myeloma X Relapse[76]	297	61	83 vs. 75	19 vs. 11 (p<0.001)	80.3 vs. 62.9 (p=0.19)

Role of Allogeneic Transplant

Evidence for a graft-versus-myeloma effect has been weak. Allogeneic transplants (myeloablative) are associated with significant treatment related toxicity with unclear long-term benefits. Given these toxicities, reduced intensity conditioning (RIC) allogeneic transplants have been advocated to mitigate concerns surrounding transplant related mortality. There have been several RCTs and quasi-RCTs that have evaluated tandem ASCT vs. ASCT followed by RIC allogeneic transplants[84-89]. In general, there is a lack of meaningful benefit with an ASCT-RIC allogeneic transplant approach to myeloma care[90,91]. Allogeneic transplant in relapsed disease is poorly tolerated with marginal effectiveness over other available therapies[90,91].

Table 14: Review of RCT and quasi-RCTs comparing studies Tandem ASCT vs. ASCT-RIC Allo

Study	N	Mean/Median Age (yrs)	Tandem ASCT vs. ASCT-RIC Allo (p-value)		
			CR (%)	Median PFS/EFS	Median OS
Moreau *et al.* 2008 IFM99-03 and IFM99-04[87]	284	58 vs. 54 (p=0.006)	38 vs. 62	22mths vs. 19mths EFS (p=0.58)	48mths vs. 34mths (p=0.07)
Rosinol *et al.* 2008 PETHEMA[88]	752	55 vs. 52	11 vs. 40 (p=0.001)	31mths vs. NR PFS (p=0.08)	34mths vs. 58mths (p=0.9)
Krishnan *et al.* 2011 BMT-CTN0102[85]	710	<70	45 vs. 58	46% vs. 43% at 3 yrs (p=0.671)	80% vs. 77% at 3 yrs (p=0.191)
Giaconne *et al.* 2011[86]	162	55	26 vs. 55	2.4yrs vs. 2.8yrs EFS (p=0.005)	4.25yrs vs. NR (p=0.001)
Gahrton *et al.* 2013 EBMT-NMAM2000[84]	357	≤69	41 vs. 50	12% vs. 22% at 8 yrs (p=0.027)	36% vs. 49% at 8 yrs (p=0.154)
Knop et al. 2014[89]	199	53	31 vs. 59	23mths vs. 35mths PFS (p=0.005)	72mths vs. 70mths (p=NS)

Systemic AL Amyloidosis

Background
Systemic immunoglobulin light chain amyloidosis is a protein misfolding disease caused by the conversion of immunoglobulin light chains from their soluble functional states into highly organized amyloid fibrillar aggregates that lead to organ dysfunction[92]. Light-chain (AL) amyloidosis is the most common form of systemic amyloidosis, accounting for 70% of patients with amyloidosis[93]. AL amyloidosis (historically referred to as primary amyloidosis) is an uncommon disorder and its exact incidence is unknown. However, in the USA the incidence ranges from 9–14 cases per million person years[94]. AL amyloidosis is a disease of the elderly with a median age at diagnosis of 63 years[95]. There is a male predominance, with men accounting for 55% of cases[96]. AL amyloidosis occurs in all races and geographic locations, but data are limited regarding the incidence of AL amyloidosis across different ethnic groups.

Patients with a new diagnosis of AL amyloidosis should be referred to a center with expertise in the treatment of this entity, especially if considering for autologous stem cell transplantation (ASCT).

Autologous Stem Cell Transplantation (ASCT):
Most AL amyloidosis patients are not eligible for ASCT due to the presence of significant comorbidities. Early studies reported high mortality rates during ASCT for AL patients, however, due to improved supportive care and careful patient selection, the mortality in ASCT has decreased significantly[97].

A recent report by the Mayo Clinic showed an early mortality rate (before day 100) of only 1.1% when Mayo stage III patients are excluded from transplant[98]. In addition, a recent long-term report on 20 years of experience with ASCT for AL amyloidosis at the Mayo Clinic Rochester highlighted the benefits of supportive care and patient selection in the setting of ASCT for AL Amyloidosis[99]. In brief, 672 consecutive patients receiving ASCT for AL amyloidosis were divided into three cohorts based on date of transplantation (cohort 1, 1996-2002 [n = 124]; cohort 2, 2003-2009 [n = 302]; and cohort 3, 2010-2016 [n = 246]). The median age for the entire cohort was 59 years, with patients in cohort 3 being slightly older than those in the other two cohorts (60 vs 58 vs 54 years for cohorts 3, 2, and 1, respectively; $p < 0.001$). More patients received pre-transplantation therapy in cohort 3 compared with earlier time periods (49% vs 38% vs 42% for cohorts 3, 2, and 1, respectively; $p = 0.02$). Hematologic response was higher in cohort 3 (84% vs 79% vs 69% for cohorts 3, 2, and 1, respectively; $p = 0.002$). Median overall survival for the entire cohort was 122 months and improved over time (not reached vs 120 months vs 75 months for cohorts 3, 2, and 1, respectively; $p < 0.001$). Treatment-related mortality declined over time (2.4% vs 8.6% vs 14.5% for cohorts 3, 2, and 1, respectively; $p < 0.001$).

The improved survival and markedly reduced treatment-related mortality in eligible patients indicate that this will remain an important first-line option even in the era of treatment approaches.

Eligibility Criteria

ASCT was reported in 1996 as a form of treatment for AL amyloidosis[100]. High-dose dexamethasone was introduced later in 1997[101]. Since then, multiple advances in the treatment (novel agents) and supportive care have been developed. The first randomized clinical trial on AL amyloidosis led by the MAG and IFM group reported that the outcome of treatment of AL amyloidosis with high-dose melphalan plus ASCT was not superior to the outcome with standard-dose melphalan plus dexamethasone[102]. However, no cardiac biomarker selection was made on those patients and 29 centers were included for the study.

Requirements for safe ASCT currently include[97,98,103-105]:

1. Age <65 years,
2. Performance status (Eastern Cooperative Oncology Group) 0 to 2,
3. NT-proBNP is <5000 ng/l and/or cardiac troponin T is <0.06 ng/ml,
4. Estimated glomerular filtration rate >30 ml/min per 1.73 m2 unless on dialysis,
5. New York Heart Association class <III, cardiac ejection fraction >45%, systolic blood pressure >90 mm Hg (standing), and
6. Lung CO diffusion capacity >50%.

Non-transplant candidates can be offered melphalan-dexamethasone or cyclophosphamide-bortezomib-dexamethasone. Daratumumab appears to be highly active in AL amyloidosis. Currently, a clinical trial incorporating daratumumab to CyBorD is ongoing. Antibodies designed to dissolve existing amyloid deposits are under study. So far, only one amyloid removal antibody trial is ongoing (CAEL 101).

Induction and Stem Cell Collection

One of the first issues to consider for AL patients eligible for ASCT is the stem cell collection process[106]. Patients with AL commonly suffer from kidney and heart involvement and during the collection process often tend to accumulate fluids during filgrastim (granulocyte colony stimulating factor) mobilization[107] and thus, fluid balance should be meticulously followed and maintained.

The second issue in transplantation of AL amyloidosis patients is whether an induction before SCT improves outcomes. A single-center, prospective randomized trial reported on the role of induction (two cycles of bortezomib and dexamethasone) versus no induction in 56 AL amyloidosis patients. Overall hematologic (ORR) and organ response rates (OR) in the whole cohort after ASCT were 77% and 58%. The ORR and OR in the bortezomib pretreated group were 92% and 75% vs. 69% and 54% in the group that received no pretreatment. The median time to maximum hematologic response after ASCT was reduced in the group that received bortezomib induction (3 vs. 14 months). Overall cardiac response rate was 60%; 100% in patients pretreated with bortezomib and 43% in those without induction treatment. With a median follow-up of 2.9 years, the 3-year progression-free and overall survival rates in the entire cohort were 66% and 73% and in those with cardiac involvement, 73% and 80%[108].

In a study from the MDACC the type of induction therapy and its impact on the outcome of autologous hematopoietic stem cell transplantation in AL was evaluated in 128 patients. The patients were

divided into 3 groups: no induction (20 patients), conventional chemotherapy-based induction (melphalan and steroids; 25 patients), and IMiD/proteasome inhibitor (PI)-based induction (83 patients). Overall, the hematological response on day 100 was highest in the IMiD/PI group, and organ response at 1 year was highest in the conventional chemotherapy-based induction. The 2-year PFS rates were 67, 56, and 73% in the no induction, CC, and IMiD/PI groups, respectively, and OS rates at 2 years were 73, 76, and 87%, respectively[109].

Among 415 AL patients, 35% had induction prior to ASCT at the Mayo Clinic[110]. Post-ASCT hematologic CR plus VGPR rates were significantly higher in those with baseline BMPC ≤ 10% compared to BMPC >10% (58% vs 40%, p = 0.0013). Significant risk factors for lack of attainment of CR included attenuated dose melphalan conditioning, baseline BMPC > 10%, no induction, and male gender. The 5-year OS for the entire group was 65%. Mayo Clinic patients eligible for ASCT that have bone marrow plasma cells lower that 10% are sent directly to ASCT.

We recommend induction therapy for those with >10% BMPC's as outcomes appear to be better.

Conditioning

In immunoglobulin light-chain (AL) amyloidosis, the depth of hematologic response to treatment is associated with improved survival and organ responses. A recent clinical trial using bortezomib in induction and in conditioning with melphalan before ASCT for AL amyloidosis was reported by the Boston University (BU) group[111]. The long-term results of this clinical trial with a median follow-up of 77 months in 35 patients enrolled showed a hematologic complete response and very good partial response (VGPR) of 100% (27 of 27) of the evaluable patients at 6 months post-ASCT. Four patients (15%) had hematologic relapse at a median of 42 months, and 1 patient (3.7%) had organ progression despite maintaining a VGPR at 37 months. The median overall survival and progression-free survival have not yet been reached at the time of the report. Renal and cardiac responses occurred in 65% and 88%, respectively, at 5 years post-ASCT. The median time to renal and cardiac response was 12 months and 6 months, respectively.

In conclusion, incorporating bortezomib into induction and conditioning yielded durable hematologic responses of AL amyloidosis, with corresponding organ responses and prolonged survival. At our center bortezomib and melphalan as well as melphalan are the recommended conditioning regimens for transplantation in AL amyloidosis. It should be noted that recent data from the IFM in MM showed that Bor-HDM did not improve clinical outcomes or degree of response[112] and thus this conditioning regimen has been discouraged in MM, no data is available in this regard for AL amyloidosis.

Consolidation

It has been reported that bortezomib in combination with dexamethasone (BD) followed by ASCT can significantly improve both the hematological and organ response rates of AL amyloidosis patients compared to ASCT alone.

An initial phase II trial using bortezomib and dexamethasone (BD) as consolidation was reported by Landau *et al.*[112]. Forty untreated patients with renal (70%), cardiac (65%), liver/gastrointestinal (15%) or nervous system (13%) AL were assigned MEL 100, 140 or 200 mg/m^2 based on age, renal function, and cardiac involvement. Hematological response was assessed at 3 months post stem cell transplant (SCT); patients with less than complete hematological response (CR) received BD consolidation. Four patients with advanced cardiac AL died within 100 days of SCT (10% treatment-related mortality). Survival at 12- and 24-months post treatment start was 88 and 82% overall and was 81 and 72% in patients with cardiac AL. At 3 months post SCT, 45% had ≥ partial response (PR) including 27% CR. Twenty-three patients received consolidation and in 86% response improved; all patients responded in one cycle. At 12 and 24 months, 79 and 60% had ≥ PR, 58 and 40% CR. Organ responses occurred in 55 and 70% at 12 and 24 months. Eight patients relapsed/progressed. One patient with serologic progression had organ impairment at time of progression.

Based on this study, a small non-randomized trial has been recently conducted to evaluate the efficacy and safety of bortezomib in combination with ASCT in the induction, conditioning, and consolidation of patients with newly diagnosed AL amyloidosis[113]. The overall response (OR) rate after induction therapy of two cycles of BD was 57.1% and the CR rate was 28.5%. Eight (8/20, 40%) patients achieved hematologic CR after ASCT and 10 (10/20, 50%) after consolidation therapy. According to intention-to-treat (ITT) analysis, the CR rate was 47.6% (10/21) at 12 months after ASCT. The hematologic very good partial response (VGPR) rate reached 40% (8/20) after ASCT and 30% (6/20) after consolidation therapy. The OR rate was 90% (18/20) at 12 months after ASCT in evaluable patients and 85.7% (18/21) according to ITT analysis. The hematologic response rate of CR and VGPR increased from 52.4% to 80% after ASCT treatment. The OR rate was similar after ASCT, and the CR rate increased from 40% to 50% after consolidation therapy.

Based the paucity of data, consolidation is not recommended as the standard treatment for patients with AL amyloidosis undergoing ASCT at our center.

Deferred ASCT

Modern chemotherapy agents can induce hematologic and organ responses in AL, including those with cardiac involvement, but durability of response remains uncertain[114,115]. No study has demonstrated the prolonged progression-free survival (PFS) patients treated with non-transplant regimes akin to that achieved with ASCT.

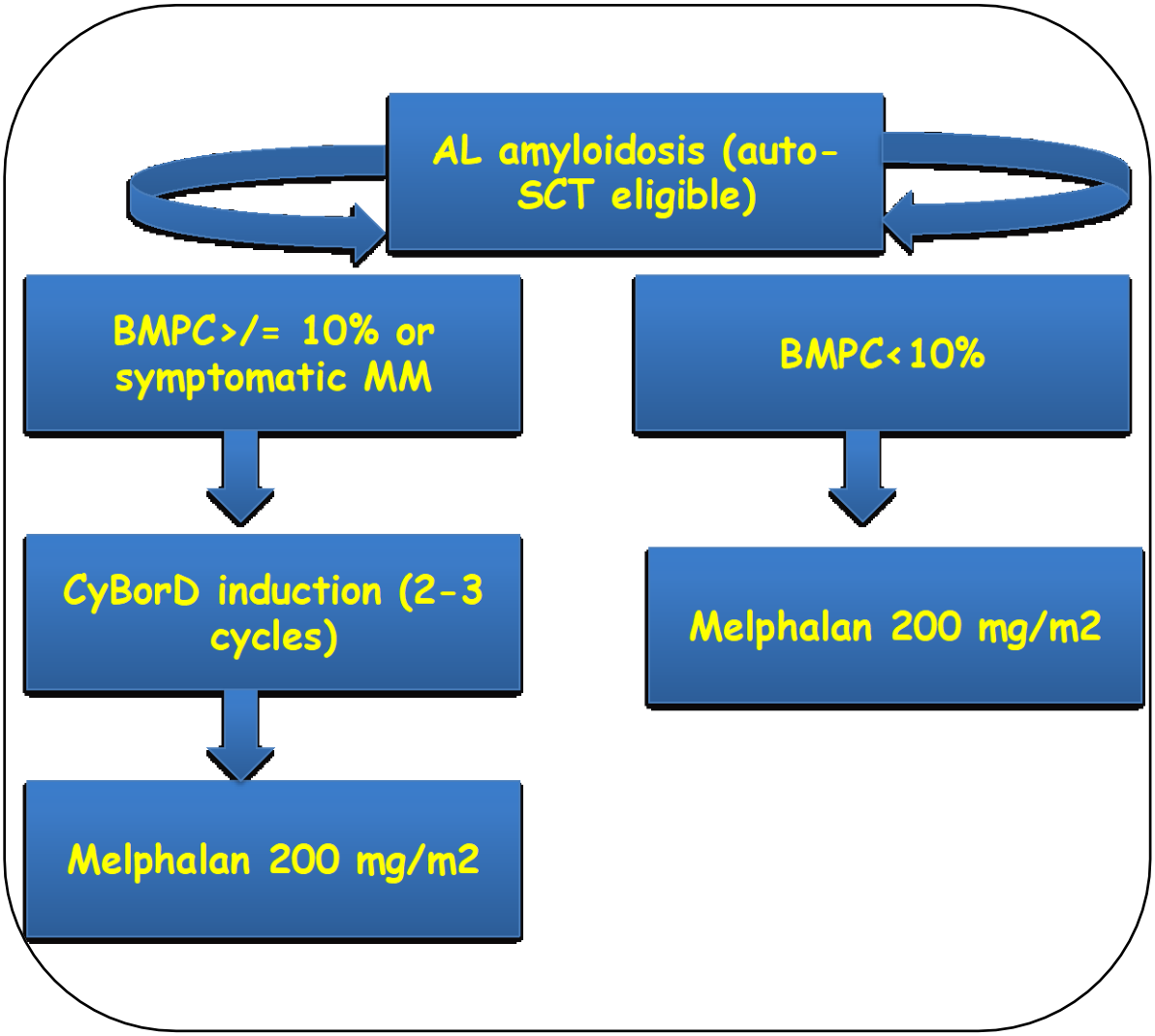
It is now apparent that a proportion of patients with significant cardiac involvement will substantially improve after achieving a good response to chemotherapy. While studies have examined the role of bortezomib-based induction chemotherapy immediately prior to ASCT, no studies to date have specifically focused on the role of deferred ASCT in transplant-ineligible patients.

A recent study by Manwani *et al.*[116] reported on 22 AL patients who underwent deferred ASCT. All patients were transplant-ineligible at presentation, predominantly due to advanced cardiac involvement. All received bortezomib-based therapy, with 100% hematologic response (86% complete response (CR)/very good partial response (VGPR)), enabling reversal of ASCT exclusion criteria. Patients underwent deferred ASCT for hematologic progression (45%) or consolidation

(55%). There was no transplant-related mortality. Hematologic responses post-ASCT: CR 50%, VGPR 27%, PR 18%, non-response 5%. In all, 85.7% achieved cardiac responses. Median overall survival (OS) was not reached, and median progression-free survival (PFS) was 54 months. This selected cohort achieved excellent hematologic responses, organ responses, PFS and OS with deferred ASCT.

If larger studies confirm these findings, this may widen the applicability of ASCT in AL Amyloidosis.

Figure 1: Recommended algorithm for ASCT in AL amyloidosis at Tom Baker Cancer Center.



References

1. J.J. A, J. K, M. C, B.E. S. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021. 20 May 2022: 1:24 PM (https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx).
2. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996;335(2):91-7. DOI: 10.1056/NEJM199607113350204.
3. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23(36):9227-33. DOI: 10.1200/JCO.2005.03.0551.
4. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348(19):1875-83. DOI: 10.1056/NEJMoa022340.
5. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood 2004;104(10):3052-7. DOI: 10.1182/blood-2004-02-0408.
6. Blade J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood 2005;106(12):3755-9. DOI: 10.1182/blood-2005-03-1301.
7. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006;24(6):929-36. DOI: 10.1200/JCO.2005.04.5807.
8. Koreth J, Cutler CS, Djulbegovic B, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. Biol Blood Marrow Transplant 2007;13(2):183-96. DOI: 10.1016/j.bbmt.2006.09.010.
9. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood 1998;92(9):3131-6. (https://www.ncbi.nlm.nih.gov/pubmed/9787148).
10. Gandolfi S, Prada CP, Richardson PG. How I treat the young patient with multiple myeloma. Blood 2018;132(11):1114-1124. DOI: 10.1182/blood-2017-05-693606.
11. Sekine L, Ziegelmann PK, Manica D, et al. Frontline treatment for transplant-eligible multiple myeloma: A 6474 patients network meta-analysis. Hematol Oncol 2019;37(1):62-74. DOI: 10.1002/hon.2552.
12. Nooka AK, Kaufman JL, Behera M, et al. Bortezomib-containing induction regimens in transplant-eligible myeloma patients: a meta-analysis of phase 3 randomized clinical trials. Cancer 2013;119(23):4119-28. DOI: 10.1002/cncr.28325.
13. Dhakal B, Szabo A, Chhabra S, et al. Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4(3):343-350. DOI: 10.1001/jamaoncol.2017.4600.
14. Jain T, Sonbol MB, Firwana B, et al. High-Dose Chemotherapy with Early Autologous Stem Cell Transplantation Compared to Standard Dose Chemotherapy or Delayed Transplantation in Patients with Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis. Biol Blood Marrow Transplant 2019;25(2):239-247. DOI: 10.1016/j.bbmt.2018.09.021.
15. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014;371(10):895-905. DOI: 10.1056/NEJMoa1402888.
16. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol 2015;16(16):1617-29. DOI: 10.1016/S1470-2045(15)00389-7.
17. Cavo M, Hájek R, Pantani L, et al. Autologous Stem Cell Transplantation Versus Bortezomib-Melphalan-Prednisone for Newly Diagnosed Multiple Myeloma: Second Interim Analysis of the Phase 3 EMN02/HO95 Study. Blood 2017;130(Suppl 1):397-397.
18. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med 2017;376(14):1311-1320. DOI: 10.1056/NEJMoa1611750.

19. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. N Engl J Med 2022;387(2):132-147. DOI: 10.1056/NEJMoa2204925.
20. Leng S, Moshier E, Tremblay D, et al. A Comparison of the Outcomes of Early Versus Delayed Autologous Stem Cell Transplantation for Multiple Myeloma in the Era of Novel Therapies. Blood 2015;126(23):1993-1993. DOI: 10.1182/blood.V126.23.1993.1993.
21. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. Cancer 2012;118(6):1585-92. DOI: 10.1002/cncr.26422.
22. Dunavin NC, Wei L, Elder P, et al. Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma. Leuk Lymphoma 2013;54(8):1658-64. DOI: 10.3109/10428194.2012.751528.
23. Remenyi P, Varga G, Mikala G, et al. Early Versus Delayed Autologous Stem Cell Transplantation and Interferon Maintenance in Multiple Myeloma: Single-Center Experience of 18 Years. Transplant Proc 2016;48(1):177-84. DOI: 10.1016/j.transproceed.2015.12.031.
24. Cavo M, Gay F, Beksac M, et al. Upfront Autologous Hematopoietic Stem-Cell Transplantation Improves Overall Survival in Comparison with Bortezomib-Based Intensification Therapy in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the Randomized Phase 3 EMN02/HO95 Study. Blood 2020;136(Supplement 1):37-38. DOI: 10.1182/blood-2020-137575.
25. Kansagra A, Gonsalves WI, Gertz MA, et al. Analysis of Clinical Factors and Outcomes Associated with Nonuse of Collected Peripheral Blood Stem Cells for Autologous Stem Cell Transplants in Transplant-Eligible Patients with Multiple Myeloma. Biol Blood Marrow Transplant 2018;24(10):2127-2132. DOI: 10.1016/j.bbmt.2018.04.007.
26. Sharma M, Zhang MJ, Zhong X, et al. Older patients with myeloma derive similar benefit from autologous transplantation. Biol Blood Marrow Transplant 2014;20(11):1796-803. DOI: 10.1016/j.bbmt.2014.07.013.
27. Dhakal B, Nelson A, Guru Murthy GS, et al. Autologous Hematopoietic Cell Transplantation in Patients With Multiple Myeloma: Effect of Age. Clin Lymphoma Myeloma Leuk 2017;17(3):165-172. DOI: 10.1016/j.clml.2016.11.006.
28. Muchtar E, Dingli D, Kumar S, et al. Autologous stem cell transplant for multiple myeloma patients 70 years or older. Bone Marrow Transplant 2016;51(11):1449-1455. DOI: 10.1038/bmt.2016.174.
29. Garderet L, Beohou E, Caillot D, et al. Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients: a prospective multicenter study. Haematologica 2016;101(11):1390-1397. DOI: 10.3324/haematol.2016.150334.
30. Merz M, Neben K, Raab MS, et al. Autologous stem cell transplantation for elderly patients with newly diagnosed multiple myeloma in the era of novel agents. Ann Oncol 2014;25(1):189-95. DOI: 10.1093/annonc/mdt509.
31. Shah N, Callander N, Ganguly S, et al. Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2015;21(7):1155-66. DOI: 10.1016/j.bbmt.2015.03.002.
32. Moller MD, Gengenbach L, Graziani G, Greil C, Wasch R, Engelhardt M. Geriatric assessments and frailty scores in multiple myeloma patients: a needed tool for individualized treatment? Curr Opin Oncol 2021;33(6):648-657. DOI: 10.1097/CCO.0000000000000792.
33. Li Y, Zhang J, Xu J, et al. Retrospective Analysis of Four Frailty Assessment Tools in Elderly Patients with Multiple Myeloma. Blood 2023;142(Supplement 1):1975-1975. DOI: 10.1182/blood-2023-184676.
34. Sim S, Kalff A, Tuch G, et al. The importance of frailty assessment in multiple myeloma: a position statement from the Myeloma Scientific Advisory Group to Myeloma Australia. Intern Med J 2023;53(5):819-824. (In eng). DOI: 10.1111/imj.16049.
35. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood 2015;125(13):2068-74. DOI: 10.1182/blood-2014-12-615187.
36. Wu X, Fu C, Shen H, et al. IMWG /ECOG Frailty Score Was a Good Indicator for ASCT Candidate Selection for NDMM in China from a Hcmmd Retrospective Study. Blood 2023;142(Supplement 1):7061-7061. DOI: 10.1182/blood-2023-185763.
37. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22(11):1582-1596. DOI: 10.1016/S1470-2045(21)00466-6.
38. Chakraborty R, Muchtar E, Kumar SK, et al. Impact of pre-transplant bone marrow plasma cell percentage on post-transplant response and survival in newly diagnosed multiple myeloma. Leuk Lymphoma 2017;58(2):308-315. DOI: 10.1080/10428194.2016.1201572.

39. Vij R, Kumar S, Zhang MJ, et al. Impact of pretransplant therapy and depth of disease response before autologous transplantation for multiple myeloma. Biol Blood Marrow Transplant 2015;21(2):335-41. DOI: 10.1016/j.bbmt.2014.10.023.
40. Parrish C, Rahemtulla A, Cavet J, et al. Autologous Stem Cell Transplantation Is an Effective Salvage Therapy for Primary Refractory Multiple Myeloma. Biol Blood Marrow Transplant 2015;21(7):1330-4. DOI: 10.1016/j.bbmt.2015.03.026.
41. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2019;20(1):57-73. DOI: 10.1016/S1470-2045(18)30687-9.
42. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood 2002;99(3):731-5. DOI: 10.1182/blood.v99.3.731.
43. Auner HW, Iacobelli S, Sbianchi G, et al. Melphalan 140 mg/m(2) or 200 mg/m(2) for autologous transplantation in myeloma: results from the Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study. A report by the EBMT Chronic Malignancies Working Party. Haematologica 2018;103(3):514-521. DOI: 10.3324/haematol.2017.181339.
44. Roussel M, Lauwers-Cances V, Macro M, et al. Bortezomib and high-dose melphalan conditioning regimen in frontline multiple myeloma: an IFM randomized phase 3 study. Blood 2022;139(18):2747-2757. (In eng). DOI: 10.1182/blood.2021014635.
45. Bashir Q, Thall PF, Milton DR, et al. Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial. Lancet Haematol 2019;6(5):e266-e275. (In eng). DOI: 10.1016/s2352-3026(19)30023-7.
46. Saini N, Bashir Q, Milton DR, et al. Busulfan and melphalan conditioning is superior to melphalan alone in autologous stem cell transplantation for high-risk MM. Blood Advances 2020;4(19):4834-4837. DOI: 10.1182/bloodadvances.2020002590.
47. Gao F, Lin MS, You JS, et al. Long-term outcomes of busulfan plus melphalan-based versus melphalan 200 mg/m(2) conditioning regimens for autologous hematopoietic stem cell transplantation in patients with multiple myeloma: a systematic review and meta-analysis. Cancer Cell Int 2021;21(1):601. (In eng). DOI: 10.1186/s12935-021-02313-z.
48. Badros A, Barlogie B, Siegel E, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. Br J Haematol 2001;114(4):822-9. DOI: 10.1046/j.1365-2141.2001.03033.x.
49. Ali H, Jyoti B, Paneesha S, et al. Efficacy and Safety of Melphalan 140mg/m2 Conditioned Autologous Stem Cell Transplantation in Elderly Pre-Dialysis and Dialysis Patients with Multiple Myeloma. Blood 2016;128(22):5822-5822. DOI: 10.1182/blood.V128.22.5822.5822.
50. Gulbis AM, Champlin RE, Qazilbash MH. A Lower Dose Of Melphalan (140 mg/m²) As Preparative Regimen For Multiple Myeloma In Patients >65 Or With Renal Dysfunction. Blood 2013;122(21):5536-5536.
51. Engelhardt M, Ihorst G, Caers J, Gunther A, Wasch R. Autotransplants in older multiple myeloma patients: hype or hope in the era of novel agents? Haematologica 2016;101(11):1276-1278. DOI: 10.3324/haematol.2016.154807.
52. Sonneveld P, van der Holt B, Segeren CM, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. Haematologica 2007;92(7):928-35. DOI: 10.3324/haematol.11168.
53. Qazilbash MH, Bashir Q, Thall PF, et al. A Randomized Phase III Trial of Busulfan + Melphalan Vs Melphalan Alone for Multiple Myeloma. Blood 2017;130(Supplement 1):399-399. DOI: 10.1182/blood.V130.Suppl_1.399.399.
54. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349(26):2495-502. DOI: 10.1056/NEJMoa032290.
55. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol 2007;25(17):2434-41. DOI: 10.1200/JCO.2006.10.2509.
56. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. Br J Haematol 2016;173(5):731-41. DOI: 10.1111/bjh.13994.
57. Naumann-Winter F, Greb A, Borchmann P, Bohlius J, Engert A, Schnell R. First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. Cochrane Database Syst Rev 2012;10:CD004626. DOI: 10.1002/14651858.CD004626.pub3.

58. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. J Natl Cancer Inst 2009;101(2):100-6. DOI: 10.1093/jnci/djn439.
59. Cavo M, Salwender H, Rosiñol L, et al. Double Vs Single Autologous Stem Cell Transplantation After Bortezomib-Based Induction Regimens For Multiple Myeloma: An Integrated Analysis Of Patient-Level Data From Phase European III Studies. Blood 2013;122(21):767-767. DOI: 10.1182/blood.V122.21.767.767.
60. Cavo M, Goldschmidt H, Rosinol L, et al. Double Vs Single Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: Long-Term Follow-up (10-Years) Analysis of Randomized Phase 3 Studies American Society of Hematology. San Diego2018.
61. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial. J Clin Oncol 2019;37(7):589-597. DOI: 10.1200/JCO.18.00685.
62. Sonneveld P, Beksac M, Van Der Holt B, et al. Consolidation Treatment with VRD Followed By Maintenance Therapy Versus Maintenance Alone in Newly Diagnosed, Transplant-Eligible Patients with Multiple Myeloma (MM): A Randomized Phase 3 Trial of the European Myeloma Network (EMN02/HO95). Blood 2020;136(Supplement 1):46-48. DOI: 10.1182/blood-2020-139337.
63. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Comparison of Autologous Hematopoietic Cell Transplant (autoHCT), Bortezomib, Lenalidomide (Len) and Dexamethasone (RVD) Consolidation with Len Maintenance (ACM), Tandem Autohct with Len Maintenance (TAM) and Autohct with Len Maintenance (AM) for up-Front Treatment of Patients with Multiple Myeloma (MM): Primary Results from the Randomized Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 - StaMINA Trial). Blood 2016;128(22):LBA-1-LBA-1.
64. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366(19):1770-81. DOI: 10.1056/NEJMoa1114083.
65. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366(19):1782-91. DOI: 10.1056/NEJMoa1114138.
66. Al-Ani F, Louzada M. Post-transplant consolidation plus lenalidomide maintenance vs lenalidomide maintenance alone in multiple myeloma: A systematic review. Eur J Haematol 2017;99(6):479-488. DOI: 10.1111/ejh.12961.
67. Gay F, Jackson G, Rosinol L, et al. Maintenance Treatment and Survival in Patients With Myeloma: A Systematic Review and Network Meta-analysis. JAMA Oncol 2018;4(10):1389-1397. DOI: 10.1001/jamaoncol.2018.2961.
68. Liu X, He CK, Meng X, et al. Bortezomib-based vs non-bortezomib-based post-transplantation treatment in multiple myeloma patients: a systematic review and meta-analysis of Phase III randomized controlled trials. Onco Targets Ther 2015;8:1459-69. DOI: 10.2147/OTT.S84828.
69. Wang Y, Yang F, Shen Y, et al. Maintenance Therapy With Immunomodulatory Drugs in Multiple Myeloma: A Meta-Analysis and Systematic Review. J Natl Cancer Inst 2016;108(3). DOI: 10.1093/jnci/djv342.
70. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol 2017;35(29):3279-3289. DOI: 10.1200/JCO.2017.72.6679.
71. Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. Leukemia 2018;32(2):383-390. DOI: 10.1038/leu.2017.211.
72. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 2012;30(24):2946-55. DOI: 10.1200/JCO.2011.39.6820.
73. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2019;393(10168):253-264. DOI: 10.1016/S0140-6736(18)33003-4.
74. Rosinol L, Oriol A, Ríos Tamayo R, et al. Ixazomib Plus Lenalidomide/Dexamethasone (IRd) Versus Lenalidomide /Dexamethasone (Rd) Maintenance after Autologous Stem Cell Transplant in Patients with Newly Diagnosed Multiple Myeloma: Results of the Spanish GEM2014MAIN Trial. Blood 2021;138:466. DOI: https://doi.org/10.1182/blood-2021-146798.
75. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol 2021;22(12):1705-1720. DOI: 10.1016/S1470-2045(21)00535-0.

76. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15(8):874-85. DOI: 10.1016/S1470-2045(14)70245-1.
77. Gonsalves WI, Gertz MA, Lacy MQ, et al. Second auto-SCT for treatment of relapsed multiple myeloma. Bone Marrow Transplant 2013;48(4):568-73. DOI: 10.1038/bmt.2012.183.
78. Michaelis LC, Saad A, Zhong X, et al. Salvage second hematopoietic cell transplantation in myeloma. Biol Blood Marrow Transplant 2013;19(5):760-6. DOI: 10.1016/j.bbmt.2013.01.004.
79. Lemieux E, Hulin C, Caillot D, et al. Autologous stem cell transplantation: an effective salvage therapy in multiple myeloma. Biol Blood Marrow Transplant 2013;19(3):445-9. DOI: 10.1016/j.bbmt.2012.11.013.
80. Jimenez-Zepeda VH, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. Biol Blood Marrow Transplant 2012;18(5):773-9. DOI: 10.1016/j.bbmt.2011.10.044.
81. Shah N, Ahmed F, Bashir Q, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer 2012;118(14):3549-55. DOI: 10.1002/cncr.26662.
82. Olin RL, Vogl DT, Porter DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant 2009;43(5):417-22. DOI: 10.1038/bmt.2008.334.
83. Yhim HY, Kim K, Kim JS, et al. Matched-pair analysis to compare the outcomes of a second salvage auto-SCT to systemic chemotherapy alone in patients with multiple myeloma who relapsed after front-line auto-SCT. Bone Marrow Transplant 2013;48(3):425-32. DOI: 10.1038/bmt.2012.164.
84. Gahrton G, Iacobelli S, Bjorkstrand B, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood 2013;121(25):5055-63. DOI: 10.1182/blood-2012-11-469452.
85. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol 2011;12(13):1195-203. DOI: 10.1016/S1470-2045(11)70243-1.
86. Giaccone L, Storer B, Patriarca F, et al. Long-term follow-up of a comparison of nonmyeloablative allografting with autografting for newly diagnosed myeloma. Blood 2011;117(24):6721-7. DOI: 10.1182/blood-2011-03-339945.
87. Moreau P, Garban F, Attal M, et al. Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous transplantation in high-risk de novo multiple myeloma. Blood 2008;112(9):3914-5. DOI: 10.1182/blood-2008-07-168823.
88. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood 2008;112(9):3591-3. DOI: 10.1182/blood-2008-02-141598.
89. Knop S, Liebisch P, Hebart H, et al. Autologous Followed By Allogeneic Versus Tandem-Autologous Stem Cell Transplant in Newly Diagnosed FISH-del13q Myeloma. Blood 2014;124(21):43-43. DOI: 10.1182/blood.V124.21.43.43.
90. Armeson KE, Hill EG, Costa LJ. Tandem autologous vs autologous plus reduced intensity allogeneic transplantation in the upfront management of multiple myeloma: meta-analysis of trials with biological assignment. Bone Marrow Transplant 2013;48(4):562-7. DOI: 10.1038/bmt.2012.173.
91. Kharfan-Dabaja MA, Hamadani M, Reljic T, et al. Comparative efficacy of tandem autologous versus autologous followed by allogeneic hematopoietic cell transplantation in patients with newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. J Hematol Oncol 2013;6:2. DOI: 10.1186/1756-8722-6-2.
92. Merlini G, Dispenzieri A, Sanchorawala V, et al. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers 2018;4(1):38. DOI: 10.1038/s41572-018-0034-3.
93. Vaxman I, Gertz M. Recent Advances in the Diagnosis, Risk Stratification, and Management of Systemic Light-Chain Amyloidosis. Acta Haematol 2019;141(2):93-106. DOI: 10.1159/000495455.
94. Merlini G. AL amyloidosis: from molecular mechanisms to targeted therapies. Hematology Am Soc Hematol Educ Program 2017;2017(1):1-12. DOI: 10.1182/asheducation-2017.1.1.
95. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992;79(7):1817-22. (https://www.ncbi.nlm.nih.gov/pubmed/1558973).
96. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2018;2(10):1046-1053. DOI: 10.1182/bloodadvances.2018016402.

97. D'Souza A, Dispenzieri A, Wirk B, et al. Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study. J Clin Oncol 2015;33(32):3741-9. DOI: 10.1200/JCO.2015.62.4015.
98. Gertz MA, Lacy MQ, Dispenzieri A, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplant 2013;48(4):557-61. DOI: 10.1038/bmt.2012.170.
99. Sidiqi MH, Aljama MA, Buadi FK, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. J Clin Oncol 2018;36(13):1323-1329. DOI: 10.1200/JCO.2017.76.9554.
100. Comenzo RL, Vosburgh E, Simms RW, et al. Dose-intensive melphalan with blood stem cell support for the treatment of AL amyloidosis: one-year follow-up in five patients. Blood 1996;88(7):2801-6. (https://www.ncbi.nlm.nih.gov/pubmed/8839879).
101. Dhodapkar MV, Jagannath S, Vesole D, et al. Treatment of AL-amyloidosis with dexamethasone plus alpha interferon. Leuk Lymphoma 1997;27(3-4):351-6. DOI: 10.3109/10428199709059690.
102. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007;357(11):1083-93. DOI: 10.1056/NEJMoa070484.
103. Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood 2016;128(2):159-68. DOI: 10.1182/blood-2016-01-629790.
104. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood 2011;118(16):4346-52. DOI: 10.1182/blood-2011-01-330738.
105. Dispenzieri A, Buadi F, Kumar SK, et al. Treatment of Immunoglobulin Light Chain Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement. Mayo Clin Proc 2015;90(8):1054-81. DOI: 10.1016/j.mayocp.2015.06.009.
106. Gertz MA. Immunoglobulin light chain amyloidosis: 2018 Update on diagnosis, prognosis, and treatment. Am J Hematol 2018;93(9):1169-1180. DOI: 10.1002/ajh.25149.
107. Bashir Q, Langford LA, Parmar S, Champlin RE, Qazilbash MH. Primary systemic amyloid light chain amyloidosis decompensating after filgrastim-induced mobilization and stem-cell collection. J Clin Oncol 2011;29(4):e79-80. DOI: 10.1200/JCO.2010.31.4161.
108. Scott EC, Heitner SB, Dibb W, et al. Induction bortezomib in Al amyloidosis followed by high dose melphalan and autologous stem cell transplantation: a single institution retrospective study. Clin Lymphoma Myeloma Leuk 2014;14(5):424-430 e1. DOI: 10.1016/j.clml.2014.02.003.
109. Afrough A, Saliba RM, Hamdi A, et al. Impact of Induction Therapy on the Outcome of Immunoglobulin Light Chain Amyloidosis after Autologous Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2018;24(11):2197-2203. DOI: 10.1016/j.bbmt.2018.07.010.
110. Hwa YL, Kumar SK, Gertz MA, et al. Induction therapy pre-autologous stem cell transplantation in immunoglobulin light chain amyloidosis: a retrospective evaluation. Am J Hematol 2016;91(10):984-8. DOI: 10.1002/ajh.24453.
111. Gupta VK, Brauneis D, Shelton AC, et al. Induction Therapy with Bortezomib and Dexamethasone and Conditioning with High-Dose Melphalan and Bortezomib Followed by Autologous Stem Cell Transplantation for Immunoglobulin Light Chain Amyloidosis: Long-Term Follow-Up Analysis. Biol Blood Marrow Transplant 2019;25(5):e169-e173. DOI: 10.1016/j.bbmt.2019.01.007.
112. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. Leukemia 2013;27(4):823-8. DOI: 10.1038/leu.2012.274.
113. Huang X, Fu C, Chen L, et al. Combination of bortezomib in the induction, conditioning and consolidation with autologous hematopoietic stem cell transplantation in patients with immunoglobulin light chain amyloidosis. Am J Hematol 2019;94(4):E101-E104. DOI: 10.1002/ajh.25404.
114. Jaccard A, Comenzo RL, Hari P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naive patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Haematologica 2014;99(9):1479-85. DOI: 10.3324/haematol.2014.104109.
115. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood 2012;119(19):4387-90. DOI: 10.1182/blood-2011-10-388462.
116. Manwani R, Hegenbart U, Mahmood S, et al. Deferred autologous stem cell transplantation in systemic AL amyloidosis. Blood Cancer J 2018;8(11):101. DOI: 10.1038/s41408-018-0137-9.

Hematopoietic Cell Transplantation for Severe Aplastic Anemia

Presented by: Lynn Savoie

Summary

- All patients with severe aplastic anemia should have HLA typing and a search for a related donor carried out at diagnosis.
- Patients less than 40 years old with a matched sibling donor should proceed directly to stem cell transplantation provided no contraindication to transplant exists.
- Patients greater than 40 years old and patients less than 40 years old without a matched sibling donor should receive immunosuppressive therapy with cyclosporine and equine anti-thymocyte globulin. They should proceed to stem cell transplantation from a matched sibling, matched unrelated donor, or a haploidentical donor if there is no clinically significant response after 6 months or if relapse.
- Expert opinion is divided on whether platelet transfusion-dependent patients should receive immunosuppressive therapy given the propensity of this treatment to increase platelet requirements and induce platelet refractoriness. These patients should be considered for early HCT if an appropriate donor can be identified in a suitable timeframe.
- A search for a MUD or a haploidentical donor should be initiated on patients without a matched sibling who show no response to immunosuppressive therapy after 3 months to allow a transplant to take place at 6 months.
- Conditioning
    - For matched sib HCT, fludarabine, cyclophosphamide and rabbit ATG. Additional GVHD prophylaxis will consist of methotrexate (day 1, 3, 6, 11), and cyclosporine for at least 6 months.
    - For matched unrelated donor and haploidentical HCT, rabbit ATG (day -9 to -7), fludarabine, low dose cyclophosphamide, and 2 Gy TBI (4 Gy if no previous immuno-suppressive therapy). GVHD prophylaxis will consist of post-transplant cyclophosphamide (day 3 and 4), mycophenolate mofetil until day 35 and tacrolimus for at least 6 months.
    - See chapters on Conditioning and GVHD prophylaxis for details.
- Bone marrow will be the preferred source of stem cells in aplastic anemia. If considering an unrelated donor, choose one from a donor center that has a history of collecting consistently $>2.5 \times 10^8$ NC/kg.
- Patients with recurrence of SAA after stem HCT may be considered for repeat transplantation or immunosuppressive therapy.

Background[1-4]

Severe aplastic anemia (SAA) is an uncommon condition with an annual incidence rate of approximately 2 per million. While the majority of cases seen clinically are idiopathic, acquired SAA

has been described in relation to medications (chloramphenicol, gold salts, anticonvulsants), infection (e.g. non-A, B, C hepatitis or HIV), immune diseases (thymoma, eosinophilic fasciitis, graft-versus-host disease) and paroxysmal nocturnal hemoglobinuria (PNH). In children and young adults, hereditary conditions such as Fanconi anemia, dyskeratosis congenita and Schwachman- Diamond syndrome are important considerations and are frequently associated with non-hematological abnormalities. The manifestations of SAA occur as a result of damage to the hematopoietic stem cell compartment, making stem cell transplantation a natural treatment choice in this disease. For the purposes of these guidelines, SAA will be defined as follows:

- Bone marrow cellularity < 25% on an adequate biopsy and any two of the following:
- ANC (absolute neutrophil count) < 0.5 x 10^9 / L
- Platelets < 20 x 10^9/L
- Reticulocyte index < 1.0

Results with Standard Treatment[5-17]

Immunosuppressive treatment with the combination of antithymocyte globulin (ATG) and cyclosporine has become standard treatment in SAA. Recent trials outlined in the table below show response rates of 65 to 75% and survival rates of 75 to 80% using this approach. Responses are generally delayed, with 85% of responses occurring in the first 3 months after treatment. As a general rule, response rates at 3, 6 and 12 months are 67%, 71% and 78%, respectively.

Table 1. Results of recent trials of standard treatment for severe aplastic anemia

Study	N	Ages	Response	OS	Relapse
NIH	122	35	61%	55% (7 y)	35% (5 year)
EBMT	182	25	83-85%	NA	NA
Germany	51	43	70% (6 m)	64% (3.5 y)	11%
EBMT	46	29	74% (6 m)	93% (4 y)	NA
Korea	83	14 – 40	47% (6 m)	69% (6 y)	7.1%

Complications of immunosuppressive treatment include serum sickness due to heterologous protein in ATG, renal dysfunction and infectious illnesses. Over the longer term, patients are at risk of developing secondary myelodysplasia or AML: clonal disorders occur in 10 to 20% of SAA patients treated in this way. Relapses are not uncommon and may coincide with discontinuation of cyclosporine. Patients who fail a first course of immunosuppressive therapy (IST) for SAA may respond to retreatment with a similar regimen. Response rates in this situation are 43 to 77%. Response to IST is poorly defined, but at a minimum should include freedom from transfusions and neutropenic infections. Many patients will continue with abnormal blood counts indefinitely following successful IST.

In a randomized phase III study, the addition of Eltrombopag to standard immunosuppressive therapy

increased the rapidity of response and the number of complete and overall responses without increased toxicity, as reported by Peffault de Latour in 2022. The percentage of patients who had a complete response at 3 months increased to 22% from 10% and the percentage of overall response at 6 months increased to 68% from 41%. The median time to first response decreased to 3.0 months from 8.8 months. EFS increased to 46% from 34% but this is an early timepoint for this assessment as many events happen late.

Bone Marrow Transplantation in SAA[17-26]

Matched sibling bone marrow transplantation is the treatment of choice for young patients with a suitable donor, as these patients enjoy excellent long-term survival with few relapses. Outcome of transplantation in this group of patients is limited by graft rejection (reported in 3 to 23% of recipients) and GVHD but overall survival is reported to be 63 to 93% in single institution reports. The CIBMTR reported results on 1699 recipients of allogeneic transplantation for this disease, with 5 year survival rates of 75%, 68% and 35% for patients aged <20, 20-40 and >40, respectively.

Age at transplant has emerged as the major determinant of outcome and is used in most clinical algorithms to direct patients to the most appropriate treatment. Few quality of life studies have been carried out in this field; one such report found similar survival, event-free survival and quality-adjusted time without symptoms and toxicity (Q-TWiST) for bone marrow transplantation (BMT) and immunosuppression (IS), with BMT-treated patients enjoying longer periods free of symptoms and IS-treated patients requiring closer medical care, transfusion support and medications.[24]

The existing literature fails to distinguish outcomes for patients who undergo SCT as up-front treatment from those in whom it is used as second-line or salvage therapy. Small reports suggest that the outcome of SCT after failure of immunosuppressive therapy may approach that of first-line therapy,[6] while others have found a higher rate of graft rejection when transplant is undertaken in these circumstances.[25] The table below summarizes selected reports of outcome of BMT in SAA.

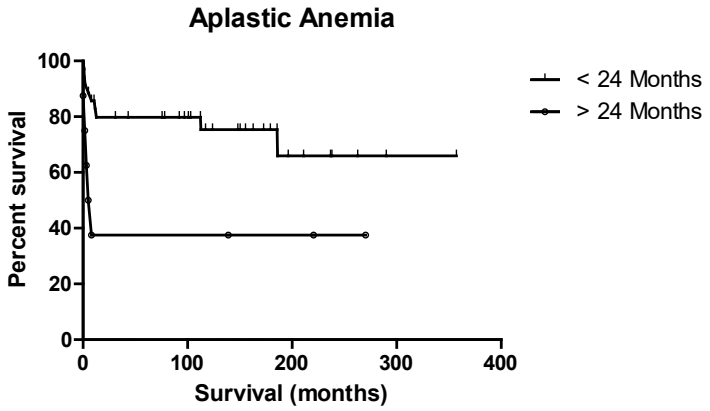
Table 2. Outcomes of BMT in severe aplastic anemia

Study	Regimen	N	Age	Engraftment	OS (time)	GVHD % (a/c)
FHCRC	Cy-ATG	94	26	96%	88% (6y)	29/32
GITMO	CyA-Mtx	37	20	97%	94% (5y)	30/44
EBMT	BMT	1567	NR	NR	73% (10y)	NR
	IS	912	NR	NR	68% (10y)	
IBMTR	Various	471	20	84%	66%	19/32

Abbreviations: Cy-ATG = cyclosporine + antithymocyte globulin; CyA-Mtx = cyclosporine + methotrexate; GVHD = graft-versus-host-disease.

Early application of HCT to patients with IST-refractory SAA is essential. Our local results are in keeping with those of other groups, which have shown that patients who receive a transplant for SAA

more than two years after diagnosis have poor outcomes as shown below. It is essential that patients be taken to transplant as soon as possible (provided there are no contraindications) once patients are identified as being IST-refractory.



Results of HCT for SAA in Alberta based on time from diagnosis to transplant. P=0.0068

Figure 1. Percent survival over time for patients with aplastic anemia

Experience has been developed in the area of haploidentical HCT for SAA. Previous experience with haploidentical donors for transplantation in other contexts has demonstrated a high rate of graft failure, infection and treatment-related mortality. In aplastic anemia experience is limited but the results appear promising. Two publications have described the outcome of SAA patients who have received non-myeloablative HCT followed by G-CSF (granulocyte colony stimulating factor) mobilized peripheral blood stem cell (PBSC) grafts.[31,32] GVHD prophylaxis was with post-transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil. Informal meta-analysis of these two reports indicates that engraftment occurs in approximately 90% of cases, and that overall survival at 1-2 years is 70-80%.[33] Further improvement appears to have been achieved by including rabbit antithymocyte globulin into the conditioning. The Johns Hopkins (Baltimore) group reported on 20 patients with relapsed/refractory SAA, who received ATG, fludarabine, low dose cyclophosphamide, 200 cGy TBI, marrow graft, and posttransplant cyclophosphamide, MMF and tacrolimus for haploidentical translants[35]. Overall survival with a median follow-up of 32 months was 100%, and no graft failure or moderate to severe cGVHD occurred. They also report on 17 treatment naïve patients treated with the same protocol with similar results, the exception being an increase in graft failure that was resolved by increasing the TBI to 400cGy. A BMT CTN study using this same protocol[36] in 31 patients for haploidentical transplants in relapsed/refractory patients produced a 1-year OS of 81%, with deaths due to disease and unsuccessful bone marrow transplant (mostly graft failure?). A similar protocol has been used in 42 published patients with hemoglobinopathies (no previous immunosuppression other than hydroxyurea). In this setting, it was found that a higher dose of TBI may be associated with a decreased incidence of graft failure (6/14 haploidentical HCT recipients developed GF after 200 cGy,[37] 1/8 after 300 cGy,[38] and 1/17 after 400 cGy TBI[39]). Given the

encouraging results, we will offer haploidentical HCT to patients with relapsed/refractory SAA, using the Baltimore protocol with 200 cGy TBI. Despite we do not yet plan to routinely offer haploidentical HCT as primary treatment for SAA (without previous immunosuppressive therapy), if such a need arose, it would be prudent to use 400 instead of 200 cGy TBI.

Transplant Details

In transplantation for malignant disease, the presence of graft-versus-host disease is associated with improved disease control and translates into superior disease-free survival. In aplastic anemia, graft-versus-host disease is deleterious to survival and has significant impact on patients' quality of life. Given the association between transplantation of stem cells from G-CSF mobilized peripheral blood and chronic GVHD (cGVHD), we will use bone marrow as the primary source of stem cells for transplantation in SAA.[30] Cyclosporine and short-course methotrexate will be used for GVHD prophylaxis given the results of randomized studies showing greater overall survival among patients treated in this way.

The conditioning regimen for patients undergoing stem cell transplantation for severe aplastic anemia has consisted of cyclophosphamide and ATG. With this approach it has been difficult to reduce the graft rejection rate below 10%, with consequent high transplant-related mortality (TRM) especially among older patients or those receiving transplants from mismatched or unrelated donors. The addition of fludarabine to Cy-ATG (FCA) has probably improved engraftment rates, and some series report engraftment rates of as much as 100% (see table below).[27] Retrospective comparisons of FCA with Cy-ATG show a trend to reduced rates of engraftment failure among those treated with FCA (0% vs. 11%, p=0.09).[28] We plan to use fludarabine 30 mg/m^2 daily x 4 days (days -5, -4, -3, -2), cyclophosphamide 60 mg/kg daily x 2 days (-3 and -2) and thymoglobulin 4.5 mg/kg (0.5 mg/kg day -2 followed by 2 mg/kg on day -1 and day 0) for patients receiving transplants from HLA-matched related donors

For matched unrelated donor and haploidentical transplants, we will use the Baltimore protocol.[34,39] Conditioning will consist of Thymoglobulin (0.5 mg/kg on day -9, 2 mg/kg on day -8, and 2 mg/kg on day -9), fludarabine (30 mg/m^2/day on days -6 to -2), cyclophosphamide (14.5 mg/kg/day on days -6 and -5), and TBI 2 Gy on day -1 (4 Gy in a single fraction on day -1 if no previous immunosuppressive therapy). Marrow graft will be infused on day 0. Patients will receive cyclophosphamide 50 mg/kg/day on days +3 and +4, they will begin tacrolimus on day +5. Dosing will target trough level 10-15 mcg/L until 6 months and then taper it slowly to discontinue at 6 months.. They will also receive mycophenolate mofetil 15 mg/kg tid (max 1 g tid) from day +5 to day +35.

Evidence has repeatedly shown that cell dose is important in order to avoid graft failure in patients with SAA, including in the haploidentical setting using ATG, fludarabine, low dose cyclophosphamide, low dose TBI, and additional GVHD prophylaxis with PTCy, MMF, and tacrolimus[36]. If using an unrelated donor we will prioritize the use of donor centers with histories of collecting consistently >2.5x10e8 NC/kg.

Table 3.

Study	N	Conditioning	Product	Graft Failure	aGVHD II-IV	cGVHD	TRM	OS (%)
Bacigalupo EBMT MUD	38	Flu/CY/rATG	BM=36; PBSC=2	18%	11%	27%		72 (2 years)
Kang	5	Flu/CY/rATG	BM	0	0 (1/5, grade I)	0		80
Gupta	7	Flu/CY/ alemtuzumab	BM	0	3/7	1/6	2/7	
Chan	5	Flu/CY/ATG		0	80%	80%	0	
Urban	3	Flu + other	PBSC/CD34+ cells	0				
Vassiliou	8	Alemtuzumab/ CY/TBI	MUD=7; haplo sib=1	0	25% (grade II)	0	0	100
MRD								
George	35	Flu/CY ± ATG	G stim; BM=7; PBSC=28	2.8%	29% (I-IV)	32%	17.1% (day 100)	82
Resnick	13	Flu/CY/ATG	BM=4; PBSC=9	0	8.3%	12.5%		84 (5 years)
Koh	8	Flu/TBI	PBSC; MRD=7; MUD=1	0	37.5%	60%	25%	75
Rzepeki	5	Flu/ alemtuzumab/ Mel	BM=2; PBSC=2	0	0	0	0	100
Srinivasan	26	Flu/CY/ATG	PBSC; MRD=22; MMRD=4	0	65%	56%	3.8%	92
Gupta	33	CY/ alemtuzumab	BM=32; PBSC=1	24%	14%	4%	6/33	81 (5 years)
Gomez-Almaguer	23	Bu/CY/Flu	PBSC=23	26%	17.3%	26%	2/23	91

Abbreviations: aGVHD = acute GVHD; Bu = busulfan; cGVHD = chronic GVHD; CY = cyclophosphamide; Flu = fludarabine; MMRD = mismatched related donor; MRD = matched related donor; MUD = matched unrelated donor; PBSC = peripheral blood stem cells; TRM = treatment/transplant-related mortality.

Table 4. Results of haploidentical transplants in SAA (from Bacigalupo, Hematology 2018)[33]

Ref.	No. of Patients	Age, y	Conditioning	GVHD Proph	SC source	Engraftment	GVHD 2-4	Alive at 1 y
36	26	30	RIC	ATG CsA	BM	92%	10%	84%
37	21	14	NMA	CD3 dep	PB	96%	30%	94%
38	8	30	NMA	PTCY, FN, MMF	GPregimen; B			75%
39	17	19	NMA	ATG, Basilix, CsA	GBM + GPB	90%	25%	65%
40	26	30	NMA	ATG, CsA, MTX, MMF	GBM + GPB	92%	12%	84%
41	77	8	NMA	ATG, CsA, MTX, MMF + MSC	GBM + GPB	92%	12%	93%
42	13	30	RIC	PTCY, FK, MMF	BM	100%	10%	100%
43	89	25	RIC	ATG, CsA, MTX, MMF	GBM + GPB	97%	30%	86%
Total	277	27				92%	12%	85%

BM, bone marrow; FK, tacrolimus; GVHD Proph, GVHD prophylaxis; MMF, mycophenolate; NMA, nonmyeloablative regimen; PB, peripheral blood; PTCY, high-dose posttransplant cyclophosphamide; RIC, reduced intensity conditioning regimen; SC source, stem cell source.

References

1. Ball S. The modern management of severe aplastic anemia. Br J Haematol 2000 Jul;110(1):41-53.
2. Killic S, Marsh J. Aplastic anemia: management. Blood Rev 2000 Sep;14(3):157-71.
3. Young N. Acquired aplastic anemia. Ann Intern Med 2002 Apr;136(7):534-46.
4. Brodsky R, Jones R. Aplastic anemia. Lancet 2005 May;365(9471):1647-56.
5. Frickhofen N, Kaltwasser J, Schrezenmeier H, Raghavachar A, Vogt HG, Herrmann F, et al. Treatment of aplasticanemia with antilymphocyte globulin and methylprednisolone with or without cyclosporine. The German Aplastic Study Group. N Engl J Med 1991 May;324(19):1297-304.
6. Crump M, Larrat L, Maki E, Curtis JE, Minden MD, Meharchand JM, et al. Treatment of adults with severe aplastic anemia: primary therapy with antithymocyte globulin (ATG) and rescue of ATG failures with bone marrow transplantation. Am J Med 1992 Jun;92(6):596-602.
7. Rosenfeld S, Kimball J, Vining D, Young NS. Intensive immunosuppression with antithymocyte globulin and cyclosporine as treatment for severe acquired aplastic anemia. Blood 1995 Jun;85(11):3058-65.
8. Marsh JC, Gordon-Smith EC. Treatment of aplastic anemia with antilymphocyte globulin and cyclosporin. Int J Hematol 1995 Oct;62(3):133-44.
9. Doney K, Leisenring W, Storb R, Appelbaum FR. Primary treatment of acquired aplastic anemia: outcomes with bone marrow transplantation and immunosuppressive therapy. Seattle Bone Marrow Transplant Team. Ann Inter Med 1997 Jan;126(2):107-15.
10. Marsh JC, Gordon-Smith EC. Treatment options in severe aplastic anemia. Lancet 1998 Jun;351(9119):1830-1.
11. Marsh J, Schrezenmeier H, Marin P, Ilhan O, Ljungman P, McCann S, et al. Prospective randomized multicenter study comparing cyclosporin alone versus the combination of antithymocyte globulin and cyclosporin for treatment of patients with nonsevere aplastic anemia: a report from the European Blood and Marrow Transplant (EBMT) Severe Aplastic Anemia Working Party. Blood 1999 Apr;93(7):2191-5.
12. Tichelli A, Socié G, Henry-Amar M, Marsh J, Passweg J, Schrezenmeier H, et al. Effectiveness of immunosuppressive therapy in older patients with aplastic anemia. European Blood and Marrow Transplant Severe Aplastic Anemia Working Party. Ann Inter Med 1999 Feb;130(3):193-201.
13. Deeg H, Seidel K, Casper J, Anasetti C, Davies S, Gajeweski JL, et al. Marrow transplantation from unrelated donors for patients with severe aplastic anemia who have failed immunosuppressive therapy. Biol Blood Marrow Transplant 1999;5(4):243-52.
14. Di Bona E, Rodeghiero F, Bruno B, Gabbas A, Foa P, Locasciulli A, et al. Rabbit antithymocyte globulin (r-ATG) plus cyclosporine and granulocyte colony stimulating factor is an effective treatment for aplastic anemia patients unresponsive to a first course of intensive immunosuppressive therapy. Groupo Italiano di Midollo Osseo (GITMO). Br J Haematol 1999 Nov;107(2):330-4.
15. Bacigalupo A, Bruno B, Saracco P, Di Bona E, Locasciulli A, Locatelli F, et al. Antilymphocyte globulin, cyclosporine, prednisolone and granulocyte colony-stimulating factor for severe aplastic anemia: an update of the GITMO/EBMT study on 100 patients. European Blood and Marrow Transplant (EBMT) Working Party on Severe Aplastic Anemia and the Groupo Italiano di Midollo Osseo (GITMO). Blood 2000 Mar;95(6):1931-4.
16. Frickhofen N, Heimpel H, Kaltwasser J, Schrezenmeier H; German Aplastic Anemia Study Group. Antithymocyte globulin with or without cyclosporin A: 11-year follow-up of a randomized trial comparing treatments of aplastic anemia. Blood 2003 Feb;101(4):1236-42.
17. Marsh J, Ball S, Darbyshire P, Gordon-Smith EC, Keidan AJ, Martin A, et al. Guidelines for the diagnosis and management of acquired aplastic anemia. Br J Haematol 2003 Dec;123(5):782-801.
18. Locatelli F, Bruno B, Zecca M, Van-Lint MT, McCann S, Arcese W, et al. Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis in patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EBMT randomized trial. Blood 2000 Sept;96(5):1690-7.
19. Storb R, Blume K, O'Donnell M, Chauncey T, Forman SJ, Deeg HJ, et al. Cyclophosphamide and antithymocyte globulin to condition patients with aplastic anemia for allogeneic transplantations: the experience in four centres. Biol Blood Marrow Transplant 2001;7(1):39-44.
20. Georges E, Storb R. Stem cell transplantation for aplastic anemia. Int J Hematol 2002 Feb;75(2):141-6.
21. Kröger N, Zabelina T, Renges H, Krüger W, Kordes U, Rischewski J, et al. Long-term follow-up of allogeneic stem cell transplantation in patients with severe aplastic anemia after conditioning with cyclophosphamide plus antithymocyte globulin. Ann Hematol 2002 Nov;81(11):627-31.
22. Kojima S, Matsuyama T, Kato S, Kigasawa H, Kobayashi R, Kikuta A, et al. Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: The Japan Marrow Donor Program. Blood 2002

Aug;100(3):799-803.
23. Ades L, Mary J, Robin M, Ferry C, Porcher R, Esperou H, et al. Long-Term outcome after bone marrow transplantation for severe aplastic anemia. Blood 2004 Apr;103(7):2490-7.
24. Viollier R, Passweg J, Gregor M, Favre G, Kühne T, Nissen C, et al. Quality-adjusted survival analysis shows differences in outcome after immunosuppression or bone marrow transplantation in aplastic anemia. Ann Hematol 2005 Jan;84(1):47-55.
25. Kobayashi R, Yabe H, Hara J, Morimoto A, Tsuchida M, Mugishima H, et al. Preceding immunosuppressive with antithymocyte globulin and ciclosporin increases the incidence of graft rejection in children with aplastic anemia who underwent allogeneic bone marrow transplantation from HLA-identical siblings. Br J Haematol 2006 Dec;135(5):693-6.
26. Champlin R, Perez W, Passweg J, Klein JP, Camitta BM, Gluckman E, et al. Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens. Blood 2007 May;109(10):4582-5.
27. Resnick IB, Aker M, Shapira MY, Tsirigotis PD, Bitan M, Abdul-Haj A, et al. Allogeneic stem cell transplantation for severe aplastic anemia using a fludarabine-based preparative regimen. Br J Haematol 2006 Jun;133(6):649-54.
28. Maury S, Bacigalupo A, Anderlini P, Aljurf M, Marsh J, Socié G, et al. Improved outcome of patients older than 30 years receiving HLA-identical sibling hematopoietic stem cell transplantation for severe acquired aplastic anemia using fludarabine-based conditioning: a comparison with conventional conditioning regimen. Haematologica 2009 Sep;94(9):1312-5.
29. Bacigalupo A, Socie G, Lanino E, Prete A, Locatelli F, Locascuilli A, et al. Fludarabine, cyclophosphamide, anththymocyte globulin, with or without low-dose total body irradiation, for alternative donor transplants, in acquired severe aplastic anemia: a retrospective study from the EBMT-SAA working party. Haematologica 2010 Jun;95(6):976-82.
30. Bacigalupo A, Socie G, Hamladji RM, Aljurf M, Maschan A, Kyrcz-Krzemien S, et al., Current Outcome of HLA Identical Sibling versus unrelated donor transplants in severe aplastic anemia: An EBMT analysis. Haematologica 2015; 100(5): 696-702.
31. Clay J, Kulasekararaj A, Potter V, Grimaldi F, McLornan D, Raj K, et al., Nonmyeloablative peripheral blood haploidentical stem cell transplantation for severe aplastic anemia. Biol Blood Marrow Transplant 2014;20(11):1711-16.
32. Esteves I, Bonfirm C, Pasquini R, Funke V, Pereira NF, Rocha V, et al., Haploidentical BMT and posttransplant Cy for severe aplastic anemia: A multicenter retrospective study. Bone Marrow Transplant 2015;50(5):685-9.
33. Bacigalupo A. Alternative donor translants for severe aplastic anemia. Hematology (2018): 467-73
34. DeZern A et al: Alternative donor transplantion with high dose posttransplantation cyclophosphamide for refractory severe aplastic anemia. BBMT 23:498, 2017.
35. DeZern AE, Zahurak ML, Symons HJ et al. Haploidenitcal BMT for severe aplastic anemia with intensive GHVD propylaxis including posttransplant cyclophosphamide. Blood Advances 4(8): 1770-1779.
36. DeZern AE, Eapen M, Wu J et al. Haploidentical bone marrow transplantation in patients with relapsed or refractory severe aplastic anemia in the USA (BMT CTN 1502): a multicentre, single-are, phase 2 trial. Lancet Haemtol 9: e660-669.
37. Bolanos-Meade J et al: HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood 120:4285, 2012.
38. Saraf SL et al: Haploidentical peripheral blood stem cell transplantation demonstrates stable engraftment in adults with sickle cells disease. BBMT 24:1754, 2018.
39. Bolanos-Meade J et al: Effect of increased dose of total body irradiation on graft failure associated with HLA-haploidentical transplantation in patients with severe haemoglobinopathies: a prospective clinical trial. Lancet Haematol 6:e183, 2019.

Hemoglobinopathies

Presented by: Kareem Jamani

Summary

Sickle Cell Disease

- Referrals for allo-HCT for SCD (typically sickle cell anemia and sickle cell β^0 thalassemia) will be accepted from the Northern and Southern Alberta Rare Blood Disorders programs.
- Requirements for allo-HCT include:
    - An HLA-matched sibling or a haploidentical relative without SCD (sickle cell trait is acceptable).
    - Demonstrated compliance with medications and follow-up.
    - KPS >70, GFR >30 mL/minute, LVEF >40% and DLCO >50% predicted.
    - No evidence of cirrhosis or active hepatitis.
    - RBC allo-antibodies directed towards donor RBC antigens (including major ABO incompatibility) can lead to prolonged transfusion requirement post-HCT but do not appear to be associated with graft failure. The decision to proceed with HCT in this setting should be individualized.
- Indications for allo-HCT include any one of the following:
    - SCD-related end-organ complication (previous cerebrovascular event, sickle nephropathy, hepatopathy, or pulmonary artery hypertension by right heart catheterization or echocardiogram (TRV >2.5 m/s).
    - Reversible SCD-related complication not ameliorated by hydroxyurea (>2 vaso-occlusive crises/year requiring medical attention, >1 lifetime episode of acute chest syndrome, >1 episode of priapism/year requiring medical attention, proliferative retinopathy with visual impairment, >1 joint with avascular necrosis).
    - Red blood cell alloimmunization complicating chronic transfusion therapy.
    - Patients with combinations of clinical characteristics such as elevated WBC, elevated LDH, history of sepsis, age >35 and chronic transfusion who are at moderate-high risk of short-term mortality.
- Matched sibling donor HCT is performed according to the NIH protocol:
    - Conditioning is non-myeloablative and includes alemtuzumab (0.03 mg/kg D-7, 0.1 mg/kg D-6, 0.3 mg/kg D-5, -4, and -3) followed by TBI 3 Gy in a single fraction on D-2.
    - Grafts will be G-CSF mobilized PBSCs with a target of 10 x 10^6 CD34+ cells/kg recipient weight.
    - GVHD prophylaxis is in the form of sirolimus starting on D-1 with a trough serum level of 5-15 ng/mL. Sirolimus should be maintained for at least 1 year and should be tapered thereafter only when donor T-cell chimerism is >50% in the absence of GVHD.
    - In the setting of sirolimus toxicity, alternate immunosuppression with mycophenolate should be considered as posterior reversible encephalopathy syndrome has been reported with calcineurin inhibitor use in this setting.

    - Myeloid and T-cell chimerism should be measured at days 90, 180 and 365 post-HCT and yearly thereafter (however, if sirolimus is continued beyond 1 year, chimerism may be monitored more frequently, i.e., q. 3-6 months). RBC chimerism can also be monitored at these time points via Hb electrophoresis/HPLC.
- Haploidentical HCT is performed according to the Baltimore protocol:
    - Conditioning is non-myeloablative and includes Thymoglobulin (0.5 mg/kg on day -9, 2 mg/kg on day -8, 2 mg/kg on day -7), Thiotepa (10 mg/kg on day -7), Fludarabine (30 mg/m^2 daily from day -6 to -2), Cyclophosphamide (14.5 mg/kg daily on day -6 and -5), and TBI (2 Gy in a single fraction on day -1).
    - Bone marrow graft.
    - GVHD prophylaxis consists of posttransplant cyclophosphamide (50 mg/kg daily on day +3 and +4), mycophenolate mofetil from day +5 to +35 (15 mg/kg/d tid, max 1 g tid), and sirolimus from day +5 to (target 5 to 15 ng/dL). Sirolimus should be maintained for at least 1 year and should be tapered thereafter only when donor T-cell chimerism is >50% in the absence of GVHD.
- Supportive care measures will be provided as outlined in the ABMTP standard practice guidelines, with the following modifications:
    - Patients should undergo exchange transfusion with a goal HbS <30% and Hb 90-100 g/L on D-10. Extended phenotype-matched RBC units (ABO, Rh D, C/c, E/e & Kell) should be used for exchange transfusion (the need for, on average, 7 units should be communicated to transfusion medicine in advance).
    - The transfusion target for Hb and platelets post-HCT should be 90-100 and 50, respectively.
    - If RBC allo-antibodies are identified it should be ensured that enough antigen negative units will be available for transfusion post-HCT (on average 6 units).
    - Hydroxyurea should be discontinued on 1 day before starting ATG or alemtuzumab.
    - G-CSF should be avoided altogether given the adverse outcomes associated with this medication in SCD.
    - Penicillin V prophylaxis should be provided until completion of pneumococcal vaccination, i.e., 2 years posttransplant (in addition to trimethoprim-sulfamethoxazole until 3 mo after discontinuation of immunosuppression).
- Patients should be counseled regarding possible late toxicities of allo-HCT including infertility (and preservation options) and therapy-related myeloid neoplasms.

Thalassemia

- At this time, allo-HCT for adults with thalassemia should not be offered outside of a clinical trial.

Allo-HCT for Sickle Cell Disease

Background

Sickle cell disease (SCD) is a severe monogenic autosomal recessive multisystem disease characterized by "sickled" erythrocytes. While SCD is an overarching term referring to all genotypes that cause this clinical syndrome, sickle cell anemia (SCA) refers to the most common form of the disease (70% of cases) resulting from homozygosity for the sickle cell allele (the majority of remaining cases result from hemoglobin SC and sickle cell/β-thalassemia)[1]. Sickled hemoglobin (Hb S) results from a point mutation in the β-globin gene in which a single nucleotide of glutamic acid is replaced with valine. The consequence is a hydrophobic patch on the β-globin molecule, which allows binding of β-globin chains of two hemoglobin molecules when deoxygenated and thus polymerization of hemoglobin molecules[1]. Ultimately, the result is a distortion in the shape of the erythrocyte and a significant loss of its flexibility.

The underlying pathophysiology of SCD is complex. At the most basic level, sickled erythrocytes contribute to both chronic hemolysis and vaso-occlusion with resultant tissue hypoxia. Recent work has produced additional insights into SCD pathophysiology including the role of vasculopathy and endothelial cell dysfunction, dysregulated inflammatory responses and innate immunity, oxidant stress and iron dysregulation, and sensitization of the nervous system to pain stimuli[2]. The resultant clinical manifestations of SCD are summarized in Table 1.

Table 1. Clinical manifestations of sickle cell disease

SCD Pathology or Outcome	Clinical Manifestation
Chronic hemolysis	Pulmonary hypertension
	Gallstones
	Fatigue
Vaso-occlusive events	Acute pain
	Chronic pain
	Acute chest syndrome
	Osteonecrosis
	Priapism
Vasculopathy	Retinopathy
	Stroke/Moyamoya and neurologic impairment
	Nephropathy
	Hepatopathy
	Asplenia and infection
	Hypercoagulability
Chronic Transfusion	Iron overload
	RBC allo-immunization
Poor Quality of Life	Poor educational outcomes
	Lack of employment
	Mental illness
	Stigma

Advances in SCD care; notably newborn screening, penicillin prophylaxis, vaccination, transcranial Doppler monitoring with pre-emptive transfusion therapy for primary stroke prevention and hydroxyurea therapy[3]; have led to significant improvements in survival in children with SCD[4]. Hydroxyurea, the only approved disease-modifying pharmacotherapy for SCD, has been shown to reduce the incidence of vaso-occlusive pain crises, acute chest syndrome and red cell transfusion as well as improve survival in SCD[3]. Yet, over the last 30 years, there has been no improvement in the survival of adults with SCD. In a large American longitudinal study, mortality in adults with SCD appeared to increase by 1% in each year studied from 1979 to 2005 and the median age at death in 2005 was 42 and 38 years for females and males, respectively[5]. In another recent American prospective observational cohort, those with SCA had a median survival of 58 years[6]. In recent years, the most common cause of death in SCD is chronic cardiopulmonary disease, including chronic lung disease, pulmonary hypertension, congestive heart failure, myocardial ischemia and venous thromboembolic disease[7, 8]. There is no convincing evidence to suggest that hydroxyurea alters the incidence or course of chronic SCD-related cardiopulmonary disease[3, 9]. Thus, in adults, despite hydroxyurea and improvements in supportive care, SCD continues to reduce life expectancy.

Allo-HCT for SCD

The recognition that those with SCD continue to suffer poor outcomes has led to growing interest in the development of disease-modifying and potentially curative therapy, including allogeneic hematopoietic cell transplantation (allo-HCT). In 1996, Walters et al demonstrated that allo-HCT from HLA-matched siblings with myeloablative conditioning (Bu/Cy/ATG) was feasible in children and resulted in sustained engraftment, elimination of vaso-occlusive episodes and stability in SCD-related end-organ damage present pre-transplant[10]. In children, experience with allo-HCT has rapidly expanded since that time; outcomes with a variety of conditioning strategies are excellent with CIBMTR (Center for International Blood and Marrow Transplant Research) and EBMT (European Group for Blood and Marrow Transplantation) registries reporting >90% 1 year survival and low rates of graft-versus-host-disease (GVHD) for those receiving HLA-matched sibling HCT[11].

In adults, there are now several published reports of allo-HCT for SCD. Encouraging results, particularly with non-myeloablative approaches have been reported (summarized in table 2). In the earliest attempt at myeloablative conditioning, the Chicago group reported on 2 patients receiving HLA-matched sibling peripheral blood stem cells (PBSC) after conditioning with Flu/Mel/ATG. Both patients engrafted and neither had SCD-related complications post-HCT, however, both died before 1 year from GVHD/infection[12]. A French group reported on 15 patients receiving HLA-matched sibling bone marrow after conditioning with Bu/Cy/ATG. All patients engrafted and one patient experienced early mortality due to cerebral hemorrhage in the setting of severe cerebral vasculopathy. At a median follow-up of 3.4 years: DFS was 93%, half of patients developed steroid-responsive grade 2-3 aGVHD, 2 patients developed moderate cGVHD, donor chimerism was sustained with all patients off immunosuppression, and all patients enjoy normal quality of life per the authors[13]. More recently, a multi-centre prospective American pilot study reported on 22 patients receiving HLA-matched sibling

(17) or unrelated bone marrow (5) after conditioning with Flu/Bu/ATG. All patients engrafted and two patients experienced early mortality (intracranial hemorrhage and GVHD). One year OS and EFS were 91% and 86%. Four patients developed grades 2-3 acute GVHD, 3 developed moderate-severe chronic GVHD and one developed secondary graft failure and is alive after a second transplant. Significant improvements in health-related quality of life and pain were observed[14].

Table 2. Studies of allo-HCT for Sickle Cell Disease

Ref	N	Donors/ Graft	Conditioning and GVHD prophylaxis	Engraftment	GVHD	TRM	SCD-Specific Outcome
Myeloablative							
12	2	MSD / PBSC	Flu/Mel/ATG MTX/Tac	2/2	1 acute/1 chronic	2/2	No acute SCD complications
13	15	MSD / BM	Bu/Cy/ATG MTX/Csa	15/15	Acute: 7 grade II 1 grade III Chronic: 2 mod-severe	1/15	14/15 “normal” QoL & no immune suppression
14	22	MSD (17) or MUD (5) / BM	Flu/Bu/ATG MTX/Csa	22/22 (1 late graft failure)	Acute: 4 grade 2-3 Mod-Severe Chronic: 3	2/22	No SCD recurrence post HCT. ↑ HR-QoL and ↓ pain.
Non-myeloablative							
15	30	MSD / PBSC	Alem/TBI Sirolimus	26/30	None	0/30	↓TRV ↓Hospitalization ↓Narcs No recurrent neurologic events 15/26 off sirolimus @ med 2.1 yrs
16	13	MSD / PBSC	Alem/TBI Sirolimus	12/13	None	0/13	↑QoL ↓BNP ↑FEV1&FVC 4/12 off sirolimus at med f-up 22 mos
20	17	Haplo (14) or MSD (3) / BM	ATG/Flu/Cy/ TBI200/PTCy/ MMF/Tacro or Sirol	11/17	No gr 2-4 aGVHD, No mod-sev cGVHD	0/17	10/17 disease-free (transfusion-independent, off narcs)
21	8	Haplo / PBSC	ATG/Flu/Cy/ TBI300/PTCy/ MMF/Sirol	7/8	2 gr 2-4 aGVHD, 1 mod-sev cGVHD	1/8	6/8 disease-free
27	17	Haplo / BM	ATG/Flu/Cy/ TBI400/PTCy/ MMF/Sirol	16/17	5 gr 2-4 aGVHD, 1 mod-sev cGVHD	0/17	16/17 disease-free
28	42	Haplo/ BM	ATG/Flu/Thiotepa/Cy/TBI200/ PTCy/MMF/Sirol	39/42	26% gr 2-4 aGVHD, 7% mod-sev cGVHD	2/42	Not yet reported
29	38	Haplo/ BM	ATG/Flu/Thiotepa/Cy/TBI200/ PTCy/MMF/Sirol	38/38	8% gr 3-4 aGVHD, 3% mod-sev cGVHD	3/38	Not yet reported

Abbreviations: Alem = alemtuzumab; ATG = anti-thymocyte globulin; ATLG = anti-Jurkat T cell globulin; BM = bone marrow; Csa = cyclosporine; Flu = fludarabine; Mel = melphalan; MMF = mycophenolate mofetil; MSD = matched sibling donor; MTX = methotrexate; MUD = matched unrelated donor; PTCy = post-transplantation cyclophosphamide; Tac = tacrolimus; TBI = total body irradiation; TRM = treatment-related mortality.

The most extensively reported experience in adults, and the approach to be used in the Alberta Bone Marrow Transplant Program (ABMTP), is with non-myeloablative conditioning from matched sibling or haploidentical donors. This approach aims to produce mixed chimerism to alleviate the SCD phenotype while maintaining low non-relapse mortality (NRM). The group at the NIH has reported results of a phase 1/2 trial involving 30 patients given alemtuzumab and low dose TBI conditioning followed by infusion of sibling HLA-matched PBSCs and sirolimus for GVHD/graft failure prophylaxis[15]. Patients were followed for a median of 3.4 years. All patients initially engrafted but 4 subsequently experienced graft failure with recurrence of SCD and one of these patients died from intracranial hemorrhage. In patients who had sustained engraftment, mean donor T-cell and myeloid chimerism were 48% and 86%, respectively. Chimerism was monitored frequently and withdrawal of sirolimus was considered at 1 year or more post-HCT if T-cell chimerism was >50% donor. Fifteen patients were able to discontinue immunosuppression at a median of 2.1 years and the remainder continue due to inadequate T-cell chimerism. NRM and GVHD were not observed. In those with sustained engraftment, specific SCD outcomes included reduction in tricuspid regurgitant velocity (TRV), no recurrent neurologic events, reduction in hospitalization rate and reduction in narcotic use. These findings have recently been replicated by the Chicago group in 13 patients[16]. At a median follow-up of 22 months; 1 patient experienced secondary graft failure (non-compliant with sirolimus) and the rest had stable mixed chimerism, 4 were able to discontinue sirolimus, quality of life scores improved at 1-year post-HCT and no TRM or GVHD were observed. There was significant improvement in cardiopulmonary parameters at 1 year. Of note, 2 patients were transplanted across major ABO incompatibility without engraftment concerns.

Late Outcomes

Beyond improvements in quality of life and pain after allo-HCT as noted above, emerging data appears to confirm the protective effect of allo-HCT on organ function. Specifically (as well-reviewed by Hulbert *et al.*)[17], allo-HCT appears to be associated with: a reduced incidence of stroke, stable or improved neurocognitive outcomes, a reduction in glomerular hyperfiltration, stability or improvement in restrictive or obstructive lung disease, improvements in diastolic filling/cardiac size and a reduction in tricuspid regurgitant velocity.

Regarding toxicities: acute kidney injury and hypertension appear relatively common after allo-HCT, warranting careful attention to nephrotoxins in the peri-HCT period and careful monitoring of blood pressure post-transplant[17]. An additional concern is the development of therapy-related myeloid neoplasms (TRMN) after non-myeloablative conditioned allo-HCT for sickle cell disease: Investigators at the NIH recently reported that 5/120 recipients (4.2%) developed a TRMN, all in the setting of residual host hematopoiesis (4 graft failure and 1 loss of myeloid chimerism). The investigators hypothesize that the TRMNs after non-myeloablative HCT are a result of selective pressure, induced by graft failure, placed on autologous preleukemic myeloid clones (which are especially noted to be present in older adults with more severe sickle cell disease)[18].

Use of Alternative Donors

Most SCD patients will not have a suitable matched sibling donor available, thus, there is significant interest in the use of alternative donors. The use of MUDs has predominantly been described in children with the largest series (29 patients) reporting a 28% treatment-related mortality after reduced-intensity conditioning with alemtuzumab, melphalan, and fludarabine, predominantly due to GVHD[19]. Haploidentical allo-HCT with post-transplant cyclophosphamide is promising. Initially, it was hampered by high rates of graft failure[20, 21]. However, with the newest version of the Baltimore protocol (using pretransplant ATG and posttransplant cyclophosphamide), of 17 patients who underwent haploidentical HCT, all 17 survived, only one developed moderate-severe cGVHD, only one developed graft failure, and 13/16 engrafted patients demonstrated full donor chimerism[27]. A modification of the Baltimore protocol (addition of a single dose of thiotepa and reduction in the TBI dose to 200 cGy) was subsequently studied in two prospective clinical trials (the BMT CTN 1507 and the Vanderbilt International Learning Collaborative) enrolling a total of 80 patients.[28, 29] Combined, 77/80 patients engrafted, the rates of grade 3-4 aGVHD and moderate-severe cGVHD were <10% each and TRM was reported in 5/80. Importantly, all engrafted patients demonstrated 100% donor chimerism at the 1-year mark. Full donor chimerism is particularly important to reduce the risk of TRMN as described above. Thus, we will use the modification of the Baltimore protocol (thiotepa and 2 Gy TBI), as outlined in the Summary, above. Novel approaches involving ex-vivo T-cell depletion, such as α/β T-cell depletion, have shown promise but are in their infancy[22]. The use of umbilical cord grafts has not been described in adult SCD patients.

Patient Selection

SCD results in phenotypic diversity. Recent efforts have focused on identifying specific clinical features that are associated with risk of mortality with standard SCD care. In a recent review of observational SCD studies: elevated TRV, leukocytosis and chronic transfusion were associated with 10% 2-year mortality, while elevated NT-proBNP, history of sepsis, elevated LDH (lactate dehydrogenase) and age >35 were associated with 5-9% 2-year mortality. Having a combination of two of these features led to 7-24% 2-year mortality[23]. Other end organ complications like sickle hepatopathy, sickle nephropathy, cerebrovascular events and acute chest syndrome are also associated with mortality[24]. In addition, recurrent vaso-occlusive crises, sickle retinopathy and osteonecrosis lead to significant morbidity. Given the low NRM, patients with over 5% 2-year mortality are likely to benefit from matched sibling HCT. In contrast, only patients with higher (>10%) estimated 2-year mortality are likely to benefit from higher risk grafts (MUD, haploidentical and umbilical cord)[23]. Specific indications for allo-HCT in the SCD in the two non-myeloablative trials described above include: end-organ complication (previous cerebrovascular event, sickle nephropathy or hepatopathy, TRV >2.5 m/s), a reversible complication not ameliorated by hydroxyurea (>2 vaso-occlusive crises/year requiring medical attention, >1 lifetime episode of acute chest syndrome, >1 episode of priapism/year requiring medical attention, proliferative retinopathy with visual impairment or >1 joint with avascular necrosis) or red blood cell alloimmunization during chronic transfusion therapy[15, 20]. RBC allo-antibodies directed towards donor RBC antigens (including major ABO incompatibility) can

lead to prolonged transfusion requirement post-HCT but do not appear to be associated with graft failure. The decision to proceed with HCT in this setting should be individualized. Given the risk of secondary graft failure and infectious or toxic complications of allo-HCT, demonstrated compliance with medications and follow-up is crucial. Candidates for allo-HCT should be referred by an SCD expert after a comprehensive assessment of SCD status. Most patients who meet the above inclusion criteria will have an elevated HCT-CI (hematopoietic cell transplantation comorbidity index), making non-myeloablative conditioning an attractive option. Minimal functional status and organ function criteria, however, in the above trials has included: KPS >70, GFR >30 mL/minute, LVEF >40% and DLCO (diffuse capacity of lung for carbon monoxide) >50% predicted. Active hepatitis and a diagnosis of cirrhosis are exclusion criteria.

SCD-Specific Supportive Care for Allo-HCT

Because of the unique physiological circumstances in SCD and the potentially toxic nature of allo-HCT, additional supportive care measures will apply to these patients in addition to standard allo-HCT care.

1. There is a risk of gonadal failure after low dose TBI. Patients should be counseled about fertility preservation options. Testicular shielding will be used during TBI treatment. Our center does not have the capacity to provide ovarian shielding.
2. Medication management: hydroxyurea should be discontinued the day before conditioning begins and G-CSF should be avoided given its association with severe SCD-related acute complications (vaso-occlusive events, acute chest syndrome, multi-organ failure and death)[25].
3. Transfusion medicine: As per standard allo-HCT practice, transfused blood products should be irradiated. The target hemoglobin (Hb) in the peri-transplant period is 90-100 g/L. The need for extended phenotype-matched RBC units (ABO, Rh D, C, E & Kell) should be communicated to transfusion medicine. A median of 6 (range 0-15) units of RBCs transfused has been reported with the NIH non-myeloablative protocol. An RBC antibody screen should be performed during pre-HCT workup and if RBC allo-antibodies are identified, it should be ensured that enough antigen negative units will be available for transfusion post HCT. Given the physiologic stress (fever, infection, volume depletion etc.) likely to be encountered post-HCT and the associated risk of an SCD-related acute event, patients should undergo exchange transfusion with a goal HbS <30% and Hb 90-100 g/L (using the above noted RBC unit attributes) prior to beginning conditioning. Given the risk of CNS bleeding in the setting of vasculopathy and thrombocytopenia, the transfusion target for platelets post-HCT should be 50. A median of 4 platelet units (range 0-19) were required to achieve this target with the NIH protocol.
4. Additional supportive care measures should include careful attention to hydration status, encouraging mobilization and out of hospital passes when appropriate, pharmacologic venous thromboembolism prophylaxis if the patient remains on the inpatient unit and platelets are >50 and use of incentive spirometry when on the inpatient unit.
5. Infectious prophylaxis, including CMV monitoring and pre-emptive therapy, should be per current ABMTP practice guidelines, with the following modifications:

a. Penicillin V prophylaxis should be provided until completion of pneumococcal vaccination, i.e., 2-years posttransplant (in addition to trimethoprim-sulfamethoxazole until 3 mo after discontinuation of immunosuppression).
b. While EBV viremia is expected to be uncommon, the approach should be individualized given the risk of secondary graft failure or GVHD with tapering immunosuppression, i.e., use of rituximab only (without immunosuppression taper) should be considered.

Allo-HCT for Thalassemia

There is very limited experience with allo-HCT for adults with β-thalassemia major. Myeloablative approaches have resulted in high non-relapse mortality and outcomes are primarily determined by hepatic iron overload status[26]. There are no significant reports of reduced intensity or non-myeloablative approaches in this patient population. At this time, allo-HCT for adults with thalassemia should not be routinely offered outside of a clinical trial.

References

1. *Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018-2031.*
2. *Kato GJ. New insights into sickle cell disease: mechanisms and investigational therapies. Current opinion in hematology. 2016;23:224-232.*
3. *Chaturvedi S, DeBaun MR. Evolution of sickle cell disease from a life-threatening disease of children to a chronic disease of adults: The last 40 years. American journal of hematology. 2016;91:5-14.*
4. *Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010;115:3447-3452.*
5. *Lanzkron S, Carroll CP, Haywood C, Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public health reports. 2013;128:110-116.*
6. *Elmariah H, Garrett ME, De Castro LM, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. American journal of hematology. 2014;89:530-535.*
7. *Fitzhugh CD, Lauder N, Jonassaint JC, et al. Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. American journal of hematology. 2010;85:36-40.*
8. *Darbari DS, Kple-Faget P, Kwagyan J, Rana S, Gordeuk VR, Castro O. Circumstances of death in adult sickle cell disease patients. American journal of hematology. 2006;81:858-863.*
9. *Buckner TW, Ataga KI. Does hydroxyurea prevent pulmonary complications of sickle cell disease? Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program. 2014;2014:432-437.*
10. *Walters MC, Patience M, Leisenring W, et al. Bone marrow transplantation for sickle cell disease. The New England journal of medicine. 1996;335:369-376.*
11. *Gluckman E. Allogeneic transplantation strategies including haploidentical transplantation in sickle cell disease. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program. 2013;2013:370-376.*
12. *van Besien K, Bartholomew A, Stock W, et al. Fludarabine-based conditioning for allogeneic transplantation in adults with sickle cell disease. Bone marrow transplantation. 2000;26:445-449.*
13. *Kuentz M, Robin M, Dhedin N, et al. Is there still a place for myeloablative regimen to transplant young adults with sickle cell disease? Blood. 2011;118:4491-4492; author reply 4492-4493.*
14. *Krishnamurti L, Neuberg DS, Sullivan KM, et al. Bone marrow transplantation for adolescents and young adults with sickle cell disease: Results of a prospective multicenter pilot study. Am J Hematol. 2019.*
15. *Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. Jama. 2014;312:48-56.*

16. *Saraf SL, Oh AL, Patel PR, et al. Nonmyeloablative Stem Cell Transplantation with Alemtuzumab/Low-Dose Irradiation to Cure and Improve the Quality of Life of Adults with Sickle Cell Disease. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22:441-448.*
17. *Hulbert ML, King AA, Shenoy S. Organ function indications and potential improvements following curative therapy for sickle cell disease. Hematology Am Soc Hematol Educ Program. 2022;2022:277-282.*
18. *Lawal RA, Mukherjee D, Limerick EM, et al. Increased incidence of hematologic malignancies in SCD after HCT in adults with graft failure and mixed chimerism. Blood. 2022;140:2514-2518.*
19. *Shenoy S, Eapen M, Panepinto JA, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. Blood. 2016;128:2561-2567.*
20. *Bolanos-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120:4285-4291.*
21. *Fitzhugh CD, Hsieh MM, Taylor T, et al. Cyclophosphamide improves engraftment in patients with SCD and severe organ damage who undergo haploidentical PBSCT. Blood Adv. 2017;1:652-661.*
22. *Marzollo A, Calore E, Tumino M, et al. Treosulfan-Based Conditioning Regimen in Sibling and Alternative Donor Hematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease. Mediterr J Hematol Infect Dis. 2017;9:e2017014.*
23. *Rotz SJ, O'Riordan MA, Kim C, de Lima M, Gladwin MT, Little JA. Traffic Light: prognosis-based eligibility for clinical trials of hematopoietic SCT in adults with sickle cell anemia. Bone marrow transplantation. 2015;50:918-923.*
24. *Hsieh MM, Fitzhugh CD, Tisdale JF. Allogeneic hematopoietic stem cell transplantation for sickle cell disease: the time is now. Blood. 2011;118:1197-1207.*
25. *Fitzhugh CD, Hsieh MM, Bolan CD, Saenz C, Tisdale JF. Granulocyte colony-stimulating factor (G-CSF) administration in individuals with sickle cell disease: time for a moratorium? Cytotherapy. 2009;11:464-471.*
26. *Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. 2014;99:811-820.*
27. *Bolanos-Meade, J. Effect of increased dose of total body irradiation on graft failure associated with HLA-haploidentical transplantation in patients with severe haemoglobinopathies: a prospective clinical trial. Lancet Hematol. 2019*
28. *Kassim, A. Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe Sickle Cell Disease: BMT CTN 1507. ASH Abstract 2023.*
29. *Kassim, A. Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe Sickle Cell Disease: BMT CTN 1507. Blood 2023.*

Multiple Sclerosis

Presented by: Jodie Burton and Jan Storek

Summary

- Eligibility for autologous hematopoietic stem cell transplantation (autoHCT) includes poorly controlled relapsing-remitting multiple sclerosis (RRMS) or apparent pseudo-progression in highly select group of patients
- Relapsing-remitting patients will be eligible if they have failed a second disease modifying therapy (DMT), or are intolerant of multiple DMTs. In special cases, RRMS patients might be eligible having failed only one DMT (e.g., high risk of PML).
- "Pseudo-progressive" patients will be eligible if they meet stringent criteria and consensus agreement by an MS neurologist experienced with the use of AHSCT in MS and a transplant physician
- For transplant technique, we use mobilization with cyclophosphamide + GCSF + dexamethasone, no CD34 enrichment, and conditioning with cyclophosphamide (200 mg/m^2) + Thymoglobulin (4.5 mg/m^2), and more intense infection prophylaxis than for patients with malignancies.

Background

Multiple Sclerosis (MS) is the most common neurodegenerative disease of non-elderly adults in North America, with a prevalence of roughly 1/385 in Alberta, Canada[1,2]. It is characterized by central nervous system (CNS) demyelination and axonal loss/degeneration. Most patients present with the relapsing-remitting (RRMS) form of the disease, characterized by episodes of CNS dysfunction that typically last weeks with fair to good recovery[3]. The average patient is female, age 32, and while there is a small impact on life expectancy, it is typically in single digit years, thus patients will incur disability over decades and all the direct and indirect costs that entails[3].

First-Line Multiple Sclerosis Disease Modifying Treatment

Since the mid 1990s, parenteral agents, interferon beta (Avonex®, Rebif®, Betaseron®) and glatiramer acetate (Copaxone®), to reduce relapse frequency in RRMS have been available[4-7]. While mildly to moderately effective, these agents reduce relapse rates by roughly 30%, and 30% or more of patients on these agents are considered treatment failures[4-7]. An additional subset of patients fails to tolerate these agents due to common adverse events of flu-like symptoms, leucopenia, transaminitis and a variety of skin manifestations[4-7]. In 2013, dimethyl fumarate (Tecfidera®), an oral agent taken twice daily, was approved for RRMS, soon thereafter joining the approved first-line agents in Alberta. This agent has demonstrated roughly a 50% reduction relapse rate versus placebo and ~ 34% versus Copaxone®.[8,9]. Tecfidera® is associated with a small risk of lymphopenia, typically

manifesting in the first 6-months of use, which typically persists, and if grade 3 or higher, requires discontinuation to avoid immunosuppressive complications. There have also been a small number of cases of PML, most of which have been linked to ongoing lymphopenia and ongoing use of Tecfidera®.[10] Teriflunomide (Aubagio®), a once daily oral agent approved in 2013, has also been added to the first-line arsenal. In the pivotal trials, Aubagio® showed a 31-36% relative reduction in relapse activity, with adverse events that include hair thinning/loss and the risk of teratogenicity (based mostly on animal data)[11]. A proportion of patients, approximately 4-14%, have what is considered to be aggressive multiple sclerosis, defined as reaching a high degree of disability within 5 years of disease onset or age 40, or transitioning to progressive MS within only 3 years of disease onset[12].

Ocrelizumab/Ocrevus®, approved in Canada in 2018 for both RRMS and PPMS, is a humanized anti-CD20 monoclonal antibody given by infusion every 6 months (similar to rituximab which is not approved as a DMT in Canada). In pivotal trials in RRMS, relapse rates were reduced by 46-47% vs Rebif, with a relatively tolerable adverse event profile[13]. The apparent small increased risk of breast cancer associated with Ocrelizumab has since been disproven[14]. Extension and post-marketing trials of Ocrelizumab have shown it to be consistently highly efficacious in RRMS[15], but associated with hypogammaglobulinemia, albeit rarely symptomatic[16]. This agent was approved by Alberta Blue Cross as a first-line agent in April 2019.

Ofatumumab/Kesimpta®, approved in Canada in 2021 for RRMS, is a fully humanized monoclonal antibody targeting a different component of the CD20 receptor, and is given subcutaneously every month. In pivotal trials, relapse rates in patients receiving ofatumumab versus teriflunomide were 0.11 vs 0.22 and 0.10 vs 0.25[17]. A similar risk profile to Ocrelizumab with respect to typically asymptomatic hypogammaglobulinemia was seen[17]. This agent was approved by Alberta Blue Cross as a first-line agent in May 2022.

Of note, a sizable proportion of RRMS patients, particularly those who are newly diagnosed, start with ocrelizumab or ofatumumab.

Second Line-Escalation Disease Modifying Treatment

In truth, escalation agents (typically classic immunosuppressants such as azathioprine and cyclophosphamide) have been used for decades, but those with randomized control trial evidence have only been available since 2000. Mitoxantrone (Novantrone®) was approved for use in worsening RRMS and secondary progressive MS in 2000, although it's use has decreased considerably in the wake of relatively high rates of serious adverse events including cardiac dysfunction, leukemia and bone marrow damage[18]. In 2006, Natalizumab (Tysabri®) was approved for use in RRMS in the context of marked failure on conventional agents[19,20]. Although highly effective, it has become evident that the risk of progressive multifocal leukoencephalopathy (PML) from JC virus entry into the CNS is as high as 1/30 patients based on risk factor stratification[21,22]. In

Alberta, all currently approved therapies not categorized as first-line therapy are considered second-line (i.e. there are no therapies solely categorized by Alberta and Blur Cross as third-line). These agents include:

Fingolimod/Gilenya®:
Gilenya® was the first oral agent in RRMS was approved (for RRMS) in Canada. This agent has a novel mechanism of action characterized by activation of lymphocyte S1P1 via high-affinity receptor binding that subsequently induces S1P1 down-regulation, preventings lymphocyte egress from lymphoid tissues and thus reducing autoaggressive lymphocyte infiltration into the central nervous system (CNS)[23,24].
In pivotal trials, there was a 54% relative reduction in relapses versus placebo (52% versus Avonex®), as well as signigicant reductions in MRI lesion load, and markers of disability progression[23,24]. It is also associated with rare cardiac, respiratory adverse events as well as viral infectious (namely varicella zoster virus reactivation, i.e. shingles) and leads to an expected apparent lymphopenis due to its mechanism of action[23,24]. It, like all agents mentioned below is considered a second-line/escalation agent in Canada[25]. Since its approval, there have been upwards of 15 cases of PML associated with Gilenya® use, with a cited risk of 3.12 per 100,000[26]. The only risk factor identified thus far is duration of use.

Alemtuzumab/Lemtrada®:
As well, Alemtuzumab, a very potent intravenous escalation agent with compelling results was approved in Canada in December 2013[27]. It is currently covered in the province of Alberta as a second-line treatment. Use of Alemtuzumab requires long-term monitoring of a minimum of four to five years of monthly blood and urine testing for potentially significant side effects (thyroid dysfunction, idiopathic thrombocytopenia purpura and Goodpasture syndrome)[27]. More recently, additional risks including Acute acalculous cholecystitis and stroke during infusions have been reported[28,29].

Cladribine/Mavenclad®:
Cladribine, approved for use in RRMS in Canada in 2018, is a purine nucleoside analogue that selectively depletes peripheral lymphocytes without a major impact on cells of the innate immune system. It is given in oral form given as a weight-based dose in two relatively short courses over two annual cycles. Oral cladribine results in the peripheral depletion of lymphocytes that is gradual, occurring over several weeks, and is not associated with a cell lysis syndrome, has a greater impact on B cells than T cells, and is followed by gradual reconstitution of the peripheral lymphocyte counts over several months[30]. In pivotal trials, cladribine patients had a relative relapse reduction of 57% compared to placebo. Beyond typical mild adverse events, there is a risk of lymphopenia with cladribine, which may lead to a delay or cancellation of the second cycle of treatment if persistent[31]. Recent studies have demonstrated that the duration of “no evidence of disease activity” with Mavenclad® is relatively short, although not synonymous with needing further treatment[32].

The History of Transplantation Therapy in MS

Multiple randomized studies have been initiated comparing autologous transplantation to conventional therapy in MS or other autoimmune diseases. Over the history of these trials, both efficacy and toxicity has improved, due in part to improved patient selection restricting enrollment to less advanced patients. Transplant-related mortality for MS in Europe dropped from 7.3% in 1995-2000 to 1.3% in 2001-2007[33]. Trial regimens include the use of agents such as busulfan or BEAM. According to the European Bone Marrow Transplant Registry (EBMTR) and the Center for International Blood and Marrow Transplant Research (CIBMTR), more than 250 patients have received autologous stem cell transplants for the treatment of refractory MS. Current trials for the most part employ a non-ablative hematopoietic stem cell transplant regimen, and enrolment criteria of these modern trials have focused on younger patients who have yet to reach advanced disability, and have not required failure of multiple agents. These choices are likely contributory to the reduced morbidity, mortality and toxicity in present trials. Atkins et al recently published the results and pearls learned from over 600 cases of transplant in MS in the literature supporting these lesions.[34] And in 2016, Atkins et al published the results of their landmark autoHCT trial using busulfan, revealing that no patient has had any evidence of inflammatory disease activity (relapse, gadolinium (gd) enhancing lesions) since transplant[35]. Unfortunately, no trial have not reliably shown a halting of or reversal of disability from neurodegeneration, hence conventional progressive patients are likely to incur all the toxicity and none of the benefit of such treatment. The role of mesenchymal stem cells in transplant is still under study.

MS Treatment

First-Line Management of Relapsing-Remitting Multiple Sclerosis

-Interferon beta-1 alpha (Rebif®, Avonex®, Betaseron®, Extavia®)
-Glatiramer acetate (Copaxone®)
-Dimethyl Fumarate (Tecfidera®)
-Teriflunomide (Aubagio®)
-Ocrelizumab (Ocrevus®)
-Ofatumumab (Kesimpta®)

First-Line Management of Aggressive Inflammatory Pseudo-progression in Multiple Sclerosis

-definition of aggressive inflammatory pseudo-progression:
    -very large EDSS change/major changes on neurological exam in motor/brainstem/cerebellar categories. Typically patients move from fully ambulatory to significant limitation in ambulation in < 12 months with coincident gadolinium activity on MRI and objective exam improvement after trial of high dose steroids and ≤ 45 years of age
-no approved therapy, no consensus
-typically used agents include Mitoxantrone (Novantrone®), Cyclophosphamide (Cytoxan®)

Definition of Failure of First-Line Agents for Escalation Therapy

-relapse activity unchanged or worsened despite first-line agent
-a combination of mild-moderate relapse activity and new MRI (new T2/FLAIR and/or gadolinium (gd) enhancing lesions) activity with first-line agent
-rapid progression in absence of distinct relapse events as described above

Current Escalation Management of Relapsing-Remitting Multiple Sclerosis in Treatment Failure

In patients with evidence of failure, conventionally a switch to a **second-line** option includes:

-Fingolimod (Gilenya®)*
-Dimethyl Fumarate (Tecfidera®)*
-Natalizumab for a finite period of time (Tysabri®)*
-Alemtuzumab (Lemtrada®)*
-Ocrelizumab (Ocrevus®)**
-Ofatumumab (Kesimpta®)
-Cladribine (Mavenclad®)*

**only approved and covered for use in relapsing patients[36]*
***approved for both relapsing remitting MS and primary progressive MS in a special cohort*

Escalation treatment options in MS depend on the nature and severity of failure on first-line agents and associated comorbidities and pregnancy planning and other issues.

Risk factors for poor outcomes on first-line agents include:

- Incomplete recovery from relapses
- High relapse frequency in first 2-5 years from onset, short interval between initial relapses
- Reaching high EDSS in the first five years of disease (EDSS >3)
- Ongoing accumulation of T2/gd lesions, brain atrophy and other measures of neurodegeneration

Definitions of treatment failure in MS (modified from CanTOR guidelines 2020[37]):

Mild Failure

- Relapse rate may be better than prior to DMT, but still active (annualized relapse rate or annualized relapse rate (ARR) ~ 0.5-1) and coupled with mild activity on MRI (new T2/gd lesions)
- Near complete recovery from relapses

Moderate Failure

- Relapse rate unchanged from previous or worsening

- Incomplete relapse recovery with fixed FSS changes > 1 in motor/cerebellar/brainstem/sphincter/sensory domains, but EDSS still < 6.0

OR

- Milder relapse breakthrough but coupled with active MRI (T2/gd lesions)

Severe Failure

- Highly active relapse rate (ARR =>2)
- Marked residual disability from relapses, at least 0.5 point change in EDSS if 5.5 or => 2 point if EDSS ≤4.0
- Above coupled with active MRI (new T2/Gd lesions)

OR

- Rapid and severe progression in apparent absence of relapses in relatively young patient coupled with active MRI (gd lesions), but exam improved with trial of high dose steroids (suggesting inflammatory-based progression)

Note that transition to classic progressive disease is not currently considered "treatment failure". This many change in the coming years.

Selection Criteria For Autologous Hematopoietic Stem Cell Transplant In MS:

Inclusion Criteria

- MS by current McDonald criteria
- Age ≤ 45
- EDSS ≤ 6.0 based on observed ambulation assessment
- If EDSS = 6.0, it cannot be for a period > 12 months
- *Failure to respond to standard MS DMT or pseudoprogression (defined below).*
- Patients must be confirmed eligible after consultation with an MS neurologist with knowledge on AHSCT and escalation therapy
- All patients require approval of an MS neurologist with knowledge on AHSCT and escalation therapy and transplant hematologist. In the event of disagreement, an additional opinion will be sought
- Patients meet "failure" as per options 1 or 2 listed directly below

- *Failure to respond to standard MS DMT is defined as:*
  While adherent to a second-line DMT*:
  - One severe relapse or ≥ 2 moderate relapses in past 12 months regardless of MRI activity

  OR

  While adherent to a second-line DMT:
  - One or more moderate/severe relapses in past 12 months **AND**

- MRI evidence of new inflammatory disease within the same 12 month time period (characterized by ≥1 gadolinium enhancing lesions and/ or >2 new T2 lesions).

*Patients may be eligible at the discretion of the neurology and transplant team members if they have demonstrated evidence of severe indicators of failure on a first-line DMT (excluding interferons and glatiramer acetate) characterized by such features as high ARR, poor relapse-recovery and rapidly advancing EDSS secondary to relapses

*Special Circumstances for Users of Natalizumab***, Ocrelizumab, Ofatumumab, or Alemtuzumab*

- While fully adherent to a minimum of 12 months on Natalizumab or Ocrelizumab, or after two annual cycles of Alemtuzumab:
  - One moderate relapse AND MRI evidence of new inflammatory disease within the same 12 month time period in the form of any new gadolinium enhancing lesions or >2 new T2 lesions

    OR
  - ≥2 mild/moderate relapses over a 12 month period regardless of MRI activity
- If the patient has to stop Natalizumab or Alemtuzumab for adverse event-related reasons, the pre-treatment disease activity profile will be used to determine eligibility

*** Natalizumab before HCT poses the following problems: 1. MS flare due to immune reconstitution could occur if the interval between natalizumab discontinuation and stem cell mobilization was too long. This may not apply to patients whose MS is not controlled by the natalizumab. 2. JCV could cause PML if the interval between natalizumab discontinuation and stem cell mobilization was too short. This may be mitigated by checking JCV by PCR in CSF and proceeding with stem cell mobilization only if negative. 3. Natalizumab increases the number of CD34 cells in blood and marrow and changes the expression of some antigens on the CD34 cells in vivo and changes their function in vitro (eg, chemokine-induced migration).[45] It is unknown whether this persists after natalizumab discontinuation and, if yes, whether it has any impact on stem cell mobilization and HCT outcome. Until more knowledge has been obtained, our standard practice is to aim for the interval between the last dose of natalizumab and the infusion of cyclophosphamide for stem cell mobilization of 2-3 months, if JCV PCR in CSF is negative. If the interval needs to be longer because of JCV PCR positivity or for other reasons, bridging immunosuppressive therapy can be considered (eg, cyclophosphamide 750 mg/m2 iv monthly or rituximab 1 g iv once or twice 2 weeks apart).

.

- *Progression due to very active inflammatory disease (pseudoprogression):*
  - Rapid decline (<12 months) in EDSS (2 or more EDSS points within 12 months if EDSS < 5.0 or 1 or more EDSS points if EDSS => 5.0) with a cerebellar, brainstem, or pyramidal functional score of at least 3 points and impaired ambulation **AND**
  - MRI demonstrating two or more gadolinium enhancing lesions **AND**
  - Objective improvement in neurological exam with improvement in EDSS after trial of high dose steroids (as objectively determined by an MS neurologist)

Exclusion Criteria

- DMT failure in context of poor compliance/adherence (confirmation of dispensing by pharmacy is required)
- >2 courses of cladribine is a relative contraindication (concern of poor stem cell mobilization)
- Indwelling urinary catheter during the peri-transplant period (patients could make arrangements for intermittent catheterization during the high-risk period)
- Pregnancy, inability or unwillingness to use appropriate contraception
- Inability to provide informed consent for treatment
- Previous malignancy with the exception of non-melanoma skin cancer or carcinoma in situ.
- Active infection or significant organ dysfunction.
- In patients at risk, CD4 T cell count <100/microliter (HIV infection per se is not an exclusion).
- History of congenital immune deficiency
- Myelodysplasia/leukemia (marrow aspiration is required on all patients with CBC abnormality that could be due to myelodysplasia/leukemia and on all patients with history of myelotoxic drugs).
- Absence of support/caregiver during 4 months peri-transplant
- Inability to reside within the city of Calgary in the 30 days prior to and 100 days following transplant
- Natalizumab or another anti-lymphocyte antibody should ideally be discontinued 2 months before stem cell mobilization chemotherapy.

General Note Regarding Selection Criteria

Patients most likely to benefit from autoHCT include those of relatively younger age, with relatively short disease duration, a relapsing form of MS (although cases of disease inactivity/stabilization after autoHCT in patients with progressive MS have been described, this appears rare and thus not proposed here), accumulating disability but still ambulatory, and ongoing disease activity despite DMT.

HCT Details

Stem cell mobilization is achieved with cyclophosphamide, filgrastim and dexamethasone. Cyclophosphamide, 2500 mg/m^2 IV over 1 h, is given in BMT clinic. Antiemetics and hydration are given per our standard practice; Mesna, 2500 mg/m^2 IV, should be given in two to three divided doses, the first one concurrently with cyclophosphamide and the second (third) one 4h (8h) later. Filgrastim is started on day 7 and continued until apheresis per our standard practice (see chapter "Donor Management, Including Mobilization"). Dexamethasone, 2 mg QID PO on the days of filgrastim administration, is used to enhance stem cell mobilization and to prevent filgrastim-induced flare of MS activity.

Apheresis: The target CD34 cell yield is $5x10^6$/kg (~$5x10^6$/kg after CD34 cell enrichment). The minimum CD34 cell yield is $2x10^6$/kg (~$3x10^6$/kg after CD34 cell enrichment).

Graft processing: Both unmanipulated and CD34 cell-enriched grafts have been used. It is currently not known whether CD34 cell enrichment is necessary, but probably not (Table 1). EBMT currently recommends no CD34 selection, except in the context of a clinical trial[50], so we will follow that recommendation.

Conditioning: Several different regimens have been used (Table 1). Between 2014 and 2023 we used busulfan + cyclophosphamide + ATG (Ottawa regimen) (Appendix D). In 2024, we transitioned to cyclophosphamide + ATG. The reasons were:

- Multiple studies published in 2019-2024 showed similar efficacy to the Ottawa regimen (Table 1)
- The Ottawa regimen may be associated with a risk of potentially fatal liver veno-occlusive disease / sinusoidal obstruction syndrome (Atkins et al[35] and our experience in one patient (Appendix B)).

To avoid an unnecessarily large number of conditioning regimens that differ in minor details, we use the same regimen for MS as well as for systemic sclerosis (see chapter on Systemic Sclerosis, also Table 2 pasted here). Most of the centers that reported outcomes of the cyclophosphamide + ATG regimen used a slightly higher dose of ATG than our systemic sclerosis regimen (6 vs 4.5 mg/kg). However, this is probably negligible.

Table 1. Results of recent studies with ≥20 HSCT patients, at least 50% of whom had RRMS, and with NEDA** reported.

	Burt (US) 2009[38]	**Atkins** (Canada) 2016[35]	**Nash** (US) 2017[46]	**Moore** (Austr) 2018[47]	**Burt** (US) 2019[39]	**Jespersen** (Denmark) 2023[49]	**Silfverberg** (Sweden) 2024[48]	**Vaisvilas** (Lithuania) 2024[51]	**Kvistad** (Norway) 2024[52]	**Braun** (Germany) 2024[53]
No. of patients	21	24	24	35	52	32	174	31	29	20
% RRMS	100%	50%	100%	57%	100%	100%	100%	100%	100%	76%
Age (median)	33 y	34 y	36 y	37 y	35.6 y	~40 y	31 y	38 y	31 y (mean)	35 y (mean)
EDSS (median)	3.1	3.0 – 6.0	6.0	6.0	3.4	~4.0	3.5	6.0	2.9 (mean)	5.0 (mean)
Duration of MS (y, med)	5 y	6.5 y	10 y	7 y	5 y	4 y	3 y	8 y	5 y (mean)	6 y (mean)
Mobilization	Cy + GCSF	Cy + GCSF	GCSF + Pred	Cy + GCSF	Cy + GCSF	Cy + GCSF	Cy + GCSF	Cy + GSCF	Cy + GCSF	Cy + GCSF
CD34 selection	No	Yes	Yes	No	No	No	No	No?	No	No
Conditioning	Cy 200 + Alem 20 mg	Bu + Cy 200 + rATG 5 mg/kg	BEAM + rATG 5 mg/kg,	BEAM + hATG 40mg/kg	Cy 200 + rATG 6 mg/kg	Most Cy 200 + rATG 6 mg/kg	Most Cy 200 + rATG 6 mg/kg	Cy 200 + rATG 6.5 mg/kg	Cy 200 + rATG 6 mg/kg	BEAM + rATG 3.75mg/kg
Follow up (y)	3	7	5	3	5	3-4	5.5	4	6	9
TRM (by 1 y)	0%	4% (1 pt)	0%	0%	0%	0%	0%	0%	0%	0%
EDSS trend	Impr	Stabiliz	Impr	Impr	Impr	Stabiliz?	Impr	Impr	Stabiliz	Stabiliz
% pts with clinical relapse	24%	0%	13%	?	2% y1 8% y1-2 15% y1-5	23%	7%	29% at 2 y	17%	0% at 5 y
% pts with MRI progr	14%	0%	9%	?	?	7%	9%	10% at 2 y	21%	0% at 5 y
Progression-free survival*	77%	70%	91%	?	94%	?	97%? (5 pts progressed)	?	90%	~75% at 5y
Survival with NEDA**	62%	70%	69%	60%	78.5%	69%	73% at 5 y, 65% at 10 y	79% at 2 y, 54% at 5 7	69%	75% at 5 y, 55% at 10 y

Abbreviations: RRMS = relapsing remitting multiple sclerosis, rATG = rabbit ATG (Thymoglobulin), hATG = horse ATG, Alem = alemtuzumab, TBI = total body irradiation, Cy = cyclophosphamide, Bu = busulfan, Pred = prednisone, BM = busulfan + melphalan, BEAM = BCNU + etoposide + AraC + melphalan, TRM = transplant related mortality.

* Survival free of EDSS progression

** No Evidence of Disease Activity (NEDA), i.e., no EDSS progression, no clinical relapse, and no MRI activity

*** Prednisone 1 mg/kg/d x 10 days beginning one day before starting GCSF

Table 2. Transplant Conditioning/Infusion Regimen used in Calgary (since 2024):

Day	-6	-5	-4	-3	-2	-1	0
Cy*	50 mg/kg	50 mg/kg	50 mg/kg	50 mg/kg			
Rabbit ATG**				0.5 mg/kg	2.0 mg/kg	2.0 mg/kg	
Methyl-prednisolone				40 mg bid	40 mg bid	40 mg bid	X***
Stem cell infusion							X

* Cyclophosphamide (50 mg/kg ideal body weight in 250 mL D_5W infused over 2 h) with Mesna (50 mg/kg ideal body weight in 1 L NS over 24 h starting with each Cy dose), hydration (NS at 75 mL/h starting the night before the first Cy dose and continuing till 24 h post the last Cy dose) and antiemetics (ondansetron + dexamethasone [except on day -3, when methylprednisolone is given as ATG premedication] + aprepitant + prn dimenhydrinate + prn metoclopramide)
** Thymoglobulin (0.5-2.0 mg/kg in as low volume of NS as possible [0.5 mg/ml] infused over ≥4 h) with premedication (Methylprednisolone 1 mg/kg before each infusion + acetaminophen + diphenhydramine + meperidine prn)
*** Prednisone 0.25 mg/kg/d or equivalent methylprednisolone dose is given from day 0 to day 21, then tapered by day 37. This is to minimize the likelihood of fever (due to neutropenia, engraftment syndrome, or ATG-induced serum sickness) and its negative effect on neutrological status.

Infection prophylaxis posttransplant is more stringent than after autologous transplantation for hematologic malignancies. Anti-bacterial and fungal prophylaxis early posttransplant is given to avoid neutropenic fever, which could result in the worsening of neurological status. CMV and EBV monitoring and preemptive therapy is given because of severe lymphopenia produced by CD34 enrichment of the graft and by ATG. Specific measures:

- Valacyclovir 500 mg qd until VZV vaccination per our Standard Practice (see chapters “CMV/HSV/VZV/HHV6” and “Vaccination”)
- CMV and EBV PCR weekly from ~day 7 until 3 months posttransplant, and preemptive valganciclovir or rituximab per our Standard Practice (see chapters “CMV/HSV/VZV/HHV6” and “EBV/PTLD”)
- Levofloxacin 500 mg qd po or iv during neutropenia
- Fluconazole 400 mg qd po or iv from day 0 until 1 month posttransplant
- Pneumocystis/pneumococcal prophylaxis ideally with trimethoprim-sulfamethoxazole (80/400 mg qd po) from neutrophil engraftment until 12-24 months posttransplant per our Standard Practice (see chapter “Bacterial and Pneumocystis Prophylaxis”)
- Vaccinations per our Standard Practice (see chapter “Vaccination”)

References

1. *Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. N Engl J Med. 2000;343(13): 938-952.*
2. *Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol. 2006;5(10): 932-936.*
3. *Martinelli Boneschi F, Vacchi L, Rovaris M, Capra R, Comi G. Mitoxantrone for multiple sclerosis. Cochrane Database Syst Rev. 2013 May 31;5:CD002127.*
4. *Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG) Ann Neurol 1996;39(3):285-94.*
5. *PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998;352(9139):1498-504.*
6. *IFNB Multiple Sclerosis Study Group. Interferon -1b is effective in relapsing-remitting multiple sclerosis. I: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 655–661*
7. *Johnson KP, Brooks BR, Cohen JA, Ford CC Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45(7):1268-76.*
8. *Fox RJ, Miller DH, Phillips JT, Hutchinson M, Hardova E, Kita M et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087-97.*
9. *Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367(12):1098-107.*
10. *Bomprezzi R. Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: an overview. Ther Adv Neurol Disord 2015;8(1): 20-30.*
11. *O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365(14):1293-303.*
12. *Menon S, Shirani A, Zhao Y, Oger J, Traboulsee A, Freedman MS et al. Characterizing aggressive multiple sclerosis. J Neurol Neurosurg Psychiatry doi:10,1136/jnnp-2013-304951.*
13. *Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in relapsing multiple sclerosis. N Engl J Med 2017 Jan 19;376(3):221-234. doi: 10.1056/NEJMoa1601277. Epub 2016 Dec 21.*
14. *Hauser SL, Kappos L, Montalban X, Craveiro L, Chognot C, Hughes R, et al. Safety of ocrelizumab in patients with relapsing and primary progressive multiple sclerosis. Neurology 19(16) e1546-e1559. https://doi.org/10.1212/WNL.0000000000012700.*
15. *Kappos L, Traboulsee A, Li DKB, Bar-Or A, Barkhof F, Montalban X, et al. Ocrelizumab exposure in relapsing-remitting multiple sclerosis: 10-year analysis of the phase 2 randomized clinical trial and its extension. J Neurol 2023 Oct 31. doi: 10.1007/s00415-023-11943-4. Epub ahead of print.*
16. *Alvarez E, Longbrake EE, Rammohan KW, Stankiewicz J, Hersh CM. Secondary hypogammaglobulinemia in patients with multiple sclerosis on anti-CD20 therapy: Pathogenesis, risk of infection, and disease management. Mult Scler Relat Disord 2023 Nov;79:105009. doi: 10.1016/j.msard.2023.105009. Epub 2023 Sep 15.*
17. *Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med 2020; 383:546-557*
    DOI: 10.1056/NEJMoa1917246
18. *Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Lancet 2002;360(9350):2018-25.*
19. *Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354(9):899-910*
20. *Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med 2006;354(9):911-23.*
21. *Outteryck O, Ongagna JC, Brochet B, Rumbach L, Lebrun-Frenay C, Debouverie et al. A prospective observational post-marketing study of natalizumab-treated multiple sclerosis patients: clinical, radiological and biological features and adverse events. The BIONAT cohort. Eur J Neurol 2013 Jun 12. doi: 10.1111/ene.12204.*
22. *Schwab N, Scheinder-Hohendorf T, Melzer N,Cutter G, Wiendl H. Natalizumab-associated PML. Challenges with incidence, resulting risk, and risk stratification. Neurology 2017;;88: 1197–1205*
23. *Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. 2010;4;362(5):387-401.*

24. *Cohen JA, Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362(5):402-15.*
25. *https://mssociety.ca/managing-ms/treatments/medications/disease-modifying-therapies-dmts*
26. *Berger JR, Cree BA, Greenberg B, Hemmer B, Ward BJ, Dong VM, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. Neurology 2018;90:e1815-e1821.*
27. *Coles AJ. Alemtuzumab treatment of multiple sclerosis. Semin Neurol 2013;33(1):66-73.*
28. *Croteau D, Flowers C, Kulick CG, Brinker A, Kortepeter CM. Acute acalculous cholecystitis A new safety risk for patients with MS treated with alemtuzumab. Neurology. 2018;90(18): e1548-e1552.*
29. *https://www.fda.gov/Drugs/DrugSafety/ucm624247.html*
30. *Giovannoni G. Cladribine to Treat Relapsing Forms of Multiple Sclerosis. G Giovannoni, Neurotherapeutics. 2017 Oct; 14(4): 874–887.*
31. *Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):416-26.*
32. *Giovannoni G, Boyko A, Correale J, et al. Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: An ambispective study. Multiple Sclerosis Journal 2023;29(6):719-730. doi:10.1177/13524585231161494*
33. *Sacardi R, Di Gioia M, Bosi A. Haematopoietic stem cell transplantation for autoimmune disorders. Curr Opin in Hematol 2008;15:594-560.*
34. *Atkins HL, Freedman MS. Hematopoietic stem cell therapy for multiple sclerosis: top 10 lessons learned. Neurotherapeutics 2013;10(1):68-76.*
35. *Atkins HL, Allan D, Anstee G, Arnold DL, Bar-Or A, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet. 2016;388: 576-585.*
36. *https://www.ab.bluecross.ca/dbl/pdfs/dbl_sec2.pdf.*
37. *Freedman MS, Devonshire V, Duquette P, Giacomini PS, Giuliani F, Levin MC, Montalban X, Morrow SA, Oh J, Rotstein D, Yeh EA; Canadian MS Working Group. Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Can J Neurol Sci 2020 Jul;47(4):437-455. doi: 10.1017/cjn.2020.66. Epub 2020 Apr 6.*
38. *Burt RK, Loh Y, Cohen B, Stefosky D, Balabanov R, Katsamakis G, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: A phase I/II study. Lancet 2009; 8: 244–53.*
39. *Burt RK, Balabanov R, Burman J, Sharrack B, Snowden JA, Oliveira MC, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: A randomized clinical trial. JAMA 2019;321(2): 165-174.*
40. *Krasulová E, Trneny M, Kozák T, Vacková B, Pohlreich D, Kemlink D, et al. High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a single centre 10-year experience. Mult Scler. 2010;16(6): 685-93.*
41. *Fassas A, Kimiskidis VK, Sakellari I, Kapinas K, Anagnostopoulos A, Tsimourtou V, et al. Long-term results of stem cell transplantation for MS: a single-center experience. Neurology 2011; 76(12):1066-70.*
42. *Bowen JD, Kraft GH, Wundes A, Guan Q, Maravilla KR, Gooley TA, et al. Autologous hematopoietic cell transplantation following high-dose immunosuppressive therapy for advanced multiple sclerosis: long-term results. Bone Marrow Transplant. 2012;47(7): 946-51.*
43. *Mancardi GL, Sormani MP, Di Gioia M, Vuolo L, Gualandi F, Amato MP, et al. Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: the Italian multi-centre experience. Mult Scler 2012;18(6): 835-42.*
44. *Shevchenko JL, Kuznetsov AN, Ionova TI, Melnichenko VY, Fedorenko DA, Kartashov AV, et al. Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis. Exp Hematol 2012 Nov;40(11):892-8.*
45. *Jing D et al: CD49d blockade bynatalizumab in patients with multiple sclerosis affects steady-state hematopoiesis and mobilizes progenitors with a distinct phenotype and function. Bone Marrow Transplant 2010.*
46. *Nash RA et al: High-dose immunosuppressive therapy and autologus HCT for relapsing-remitting MS. Neurology 2017*
47. *Moore JJ et al: Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. J Neurol Neurosurg Psychiatry 2019*
48. *Silfverberg T et al: HSCT for treatment of RRMS in Sweden: an observational cohort study. J Neurol Neurosurg Psychiatry 2024*

49. *Jespersen F et al: Autologous HSCT of patient with aggressive RRMS: Danish natin-wide experience. Mult Scler Relat Disord 2023*
50. *Sharrack B et al: Autologous HSCT and other cellular therapy in MS and immune-meidated neurological diseases: updated guidelines and recommendations from the EBMT ADWP and JACIE. Bone Marrow Transplant 2020*
51. *Vaisvilas M et al: Autologous HSCT is superior to alemtuzumab in patient with highly active relapsing MS and severe disability. Multiple Sclerosis and Related Disorders 2023*
52. *Kvistad CE et al: Autologous HSCT for MS: Long-term follow-up data from Norway. Multiple Sclerosis Journal 2024*

Appendix A: Schedule of Tests and Evaluations

	Baseline/ Eligibility	Transplant Regimen		Post-Transplant Haematology Monitoring					Post-Transplant Neurological Monitoring									
		Mobilization start	**Conditioning start**															
Week	~ -12	~ -6	~ -1	4	6	8	10	12	26	52	78	104	130	156	182	208	234	260
Medical History	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EDSS Exam*	X								X	X	X	X	X	X	X	X	X	X
CBC	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry panel	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/PTT	X																	
Pregnancy test	X																	
PFTs	X																	
MUGA or Echocardiogram	X																	
CXR, EKG	X																	
Urinalysis	X																	
TSH	X									X		X		X		X		X
Ig levels for tetanus, hepatitis B, measles and rubella														X				
Vaccinations	X								X#			X##		X###				
HIV1 and HIV2	X																	
HSV/VZV/CMV/EBV****	X																	
Hepatitis A/B/C serology	X																	
Dental Consult	X																	
MRI brain +/- spinal cord ####	X									X		X		X		X		X
Fertility consult	X**																	
Bone marrow biopsy	X***																	

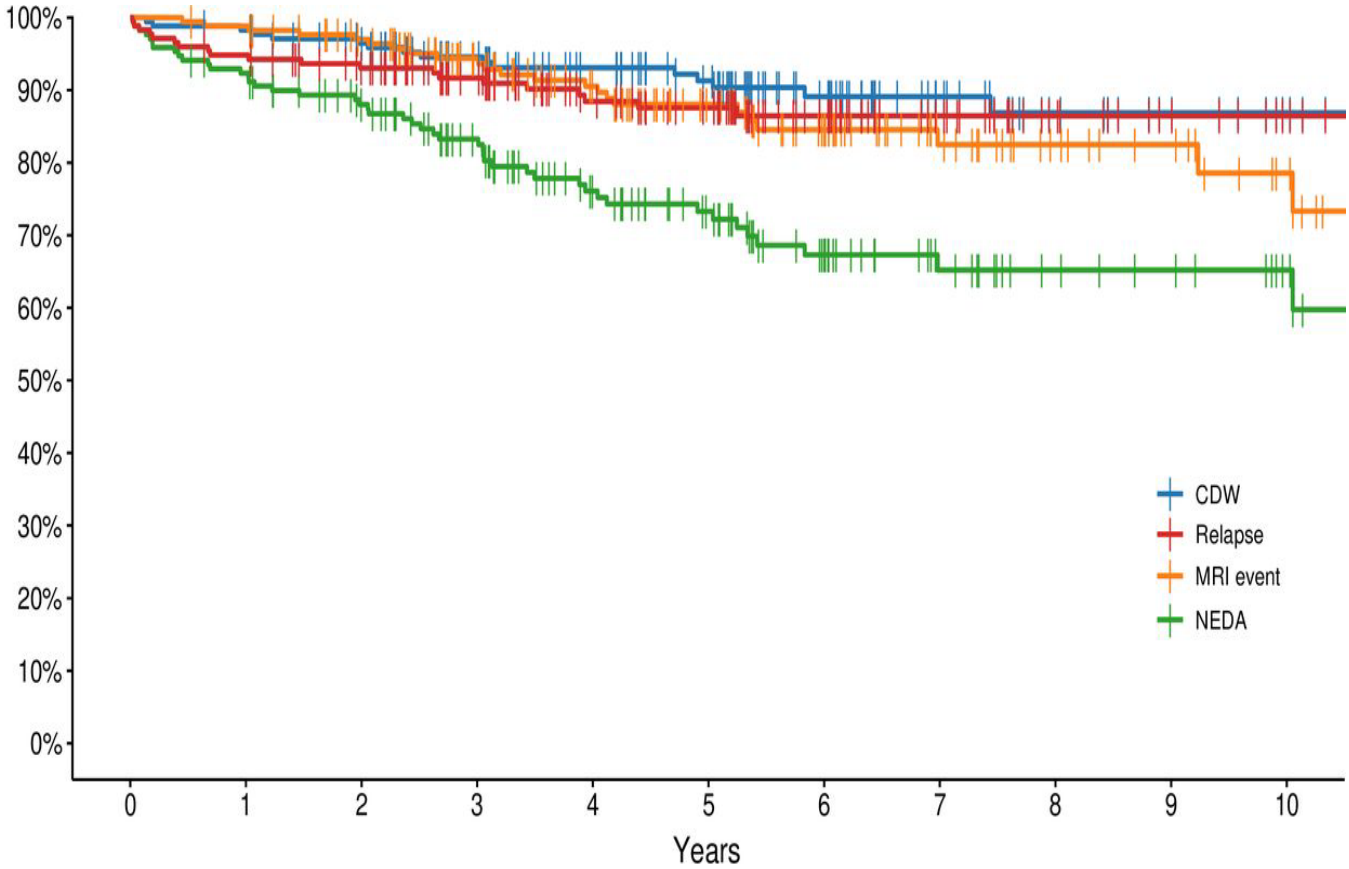
* EDSS = Extended disability status scale (0-10), done by a neurologist collaborating with the Calgary-based Alberta Blood and Marrow Transplant Program. During late posttransplant period, the EDSS may be estimated during a virtual visit or obtained from referring neurologist.
**Male patients will be offered sperm banking, female patients will be offered fertility clinic consult.
***Only if blood cell counts are abnormal.
**** Pretransplant, HSV, VZV, CMV and EBV IgG should be done once. Posttransplant, CMV and EBV PCR should be done weekly until 12 weeks.
# Referral to Public Health for non-live vaccines.
Referral to Public Health for live vaccines.
Referral to Public Health for boosters if specific Ig levels for vaccine-preventable diseases are low.
Arranged by Neurology

Appendix B: Calgary Experience as of January 2024

UPN	Year of auto HCT	EDSS pre HCT**	Mobilization	CD34 selection	Conditioning	Alive?	MS activity since HCT?*	Comment
986	2009		Cy+GCSF	No	Cy+Thymo	Y	Y since ~2011	Was on the verge of RRMS→SPMS at HCT
1052	2010		Cy+GCSF	No	Cy+Thymo	Y	Y since 2016	
1355	2014		Cy+GCSF	Yes	Bu+Cy+Thymo	Y	Y since 2017	Was on the verge of RRMS→SPMS at HCT
1604	2016	2.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
1616	2017	4.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
1842	2019	3.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
1913	2020	2.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
2166	2022	2.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
2237	2023	2.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
2300	2023	1.5	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	
2317	2023	3.0	Cy+GCSF	Yes	Bu+Cy+Thymo	Y	N	Moderate VOD/SOS***

* Relapse, progression, or new or enhancing MRI lesions
** EDSS (expanded disability status scale, 0-10, a higher score denotes greater disability)
*** Liver veno-occlusive disease/sinusoidal obstruction syndrome

Appendix C: Results of the largest retrospective study



Numbers at risk

	0	1	2	3	4	5	6	7	8	9	10
CDW	173	169	158	133	113	99	71	46	30	24	18
Relapse	174	164	152	128	103	91	66	44	29	22	16
MRI event	170	167	155	128	109	83	61	40	29	24	16
NEDA	170	155	136	111	85	69	48	31	22	19	13

Kaplan-Meier curves for the primary endpoint of no evidence of disease activity (NEDA), and for the secondary endpoints of freedom from MRI events, freedom from clinical relapse, and freedom from confirmed disability worsening (CDW), in the Swedish registry study (Silfverberg 2024).[48] This study included only patients with RRMS. There was no transplant-related mortality, but one patient died at >6 years of suicide related to substance abuse.

Appendix D: Ottawa conditioning, used in Calgary 2014-2023, then retired.

Day	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	+7
Busulfan* ~2.4 mg/kg/day IV	X	X	X	X								
Lorazepam 1 mg QID PO (seizure prophylaxis)	X	X	X	X	X							
Hydration**					X	X	X	X	X	X		
Cyclophosphamide** 50 mg/kg/day IV						X	X	X	X			
MESNA continuous infusion 50 mg/kg/day IV						X	X	X	X			
ATG*** (Thymoglobuline) (mg/kg/day)								0.5	2.0	2.0		
Methyl-prednisolone****								X	X	X	X	X
Stem cell infusion											X	
GCSF ~0.5 ug/kg/d from d7 till ANC>1/nl												X

* **Busulfan dosing is PK-adjusted**. First dose is 2.4 mg/kg IV at a constant rate of 80 mg/hr (160 ml/hr for busulfan at 0.5 mg/ml concentration). Blood (4 ml green top (heparinized) tube) for busulfan PK is collected at the end of the infusion and at 1, 3 , 5 and 7 h after the end of the infusion. Subsequent doses are adjusted to target overall busulfan AUC of <16000 µmol.min/L over four days. The last dose of busulfan should be given in the morning of day -7 to ensure >>24 h interval between busulfan and cyclophosphamide infusions.

** Cyclophosphamide 50 mg/kg/day is given IV over 1 hour in 500 cc of normal saline. If actual weight is < ideal weight, cyclophosphamide is given based on actual weight. If actual weight is > ideal weight, cyclophosphamide is given as adjusted weight. Adjusted weight = ideal weight + 0.25 x (actual weight minus ideal weight). Anti-emetics, as pre-medications for Cyclophosphamide, should be given per institutional policy and medical judgement. Hydration with Normal Saline, approximately 2 liters/m^2/day, should be started on day -6, and at least 6 hours before cyclophosphamide and continued until 24 hours after the last cyclophosphamide dose.

*** ATG (Thymoglobulin) 0.5 mg/kg is given IV on day -3 and 2.0 mg/kg IV on days -2 and -1 (no dose adjustment), over 4-6 hours each day. Pre-medicate with methylprednisolone 1.0 gram IV, acetaminophen 650 mg po and diphenhydramine 25 mg IV or PO 30 minutes before infusion. An in-line 0.22 um filter should be used for ATG administration.

**** Methylprednisolone or prednisone is given to minimize the likelihood of fever (due to ATG, neutropenia, or engraftment syndrome) and its negative effect on neurological status, according to the following schedule:
Day -3 to -1, 1 g IV as premedication for ATG
Day 0 to 3, 0.5 mg/kg/d,
Day 4 to 7, 0.4 mg/kg/d,
Day 8 to 11, 0.3 mg/kg/d,
Day 12 to 15, 0.2 mg/kg/d,
Day 16 to 19, 0.1 mg/kg/d, then discontinue

Autologous Hematopoietic Cell Transplant in Systemic Sclerosis (SSc): Alberta Protocol

Presented by: Jan Storek / Caylib Durand / Mo Osman

Summary

- Autologous HCT (HCT) for SSc is indicated if:
    - Age <65, ideally younger
    - <5 years from the first non-Raynaud symptom, ideally <1 year
    - Severe skin involvement (mRSS >20), or
    - Moderate skin involvement (mRSS 15-20) with mild to moderate Interstitial lung disease (FVC/DLCO 40-80%, ideally 60-80%. No hypoxia)
    - No moderate/severe PAH (mean PAP <30 mmHg by right heart catheterization)
    - No or minimal heart involvement (no significant cardiac fibrosis, no heart failure, myocarditis/pericarditis must be in remission).
    - If GAVE, needs to be successfully treated before HCT
- Allogeneic HCT should be considered only in patients with concurrent hematologic disease or under a clinical trial.
- CAR T cells only under a clinical trial.

Autologous HCT Indications/Contraindications by SSc Manifestation

- **Skin involvement**
    - Thickening (as defined as mRSS. See Appendix 1 Figure 2)
        - *Localized* cutaneous systemic sclerosis (morphea)
            - Not an indication for HCT due to good prognosis with standard therapies.
        - *Limited* cutaneous systemic sclerosis (hands/distal forearms (not extending beyond elbows and no truncal involvement)/face) / CREST syndrome (calcinosis of skin, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia)
            - Associated with anti-centromere antibody (ACA) (60%)
            - Not an indication for HCT at present due to better prognosis compared to diffuse cutaneous systemic sclerosis without HCT, and minimal data on HCT. However, may consider HCT if interstitial lung disease.
        - *Diffuse* cutaneous systemic sclerosis (dcSSc, involves also proximal skin) – clearcut indication for HCT if otherwise meets criteria
            - Associated with Scl-70 antibody (60%)
            - Indicated for HCT if moderate to severe (mRSS >20) or if associated with lung disease
    - Other skin manifestations (alone not an indication for HCT)

- Edema (early)
- Contractures (late)
- Pruritus
- Hyper/hypopigmentation ("salt-and-pepper")
- Loss of appendicular hair
- Ulcers
- Calcinosis

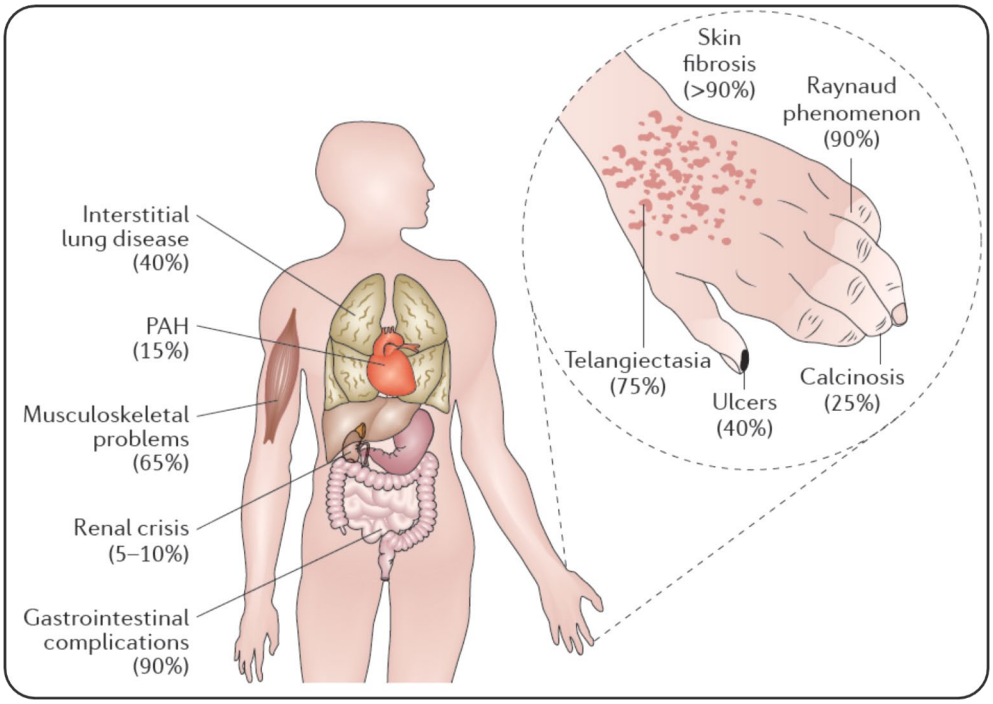


Figure 1. Manifestations of SSc (from A.Yannick et al: Nat Rev Dis Prim 2015)

- **Lung involvement**
  - Interstitial lung disease / fibrosing alveolitis
    - Indicated for HCT, particularly if rapidly progressing, but FVC and DLCO must be >40% predicted, ideally >60% predicted
  - Pulmonary artery hypertension is a contraindication to HCT
    - Absolute: RVSP >55 mmHg by echo or resting mean PAP >30 mmHg by RHC
    - Relative: RVSP 40-55 mmHg by echo or resting mean PAP 25-30 mmHg by RHC, or significant increase in PAP with fluid/exercise
  - Hypoxia requiring O_2 is a contraindication to HCT
  - Lung cancer (5-fold higher incidence compared to general population)
    - Contraindication to HCT
  - Smoking
    - Current smoking is a contraindication to HCT

- **Renal involvement**
    - Renal crisis is a contraindication to HCT
        - Renal crisis is characterized by hypertension, decreased GFR, non-heavy proteinuria, thrombotic microangiopathy
    - Renal failure due to any cause is a contraindication to HCT
    - Hypertension must be controlled before HCT considered, especially if due to renal crisis
- **Heart involvement**
    - Myocarditis and or cardiac fibrosis; myocardial ischemia; pericarditis/effusion
    - Absolute contraindications to HCT[1,2]:
        - LVEF <40%
        - D-sign or septal bounce on echo or MRI (sign of RV overload/failure or constrictive pericarditis)
        - Non-revascularized severe coronary artery disease
        - Uncontrolled severe arrhythmia
        - Pericardial Tamponade
        - Constrictive pericarditis
    - Relative contraindications to HCT:
        - LVEF 40-50%
        - Tricuspid annular plane systolic excursion (TAPSE) <18 mm on echo
        - Any sign of heart involvement with systemic sclerosis on MRI
        - No increase in cardiac output on RHC with exercise/fluid
    - The above cardiac contraindications may be less important with non-cardiotoxic conditioning[3,4]. However, long-term efficacy of AHCT using non-cardiotoxic conditioning is uncertain.
- **Gastrointestinal involvement**
    - Not a contraindication to HCT, unless severe or unless untreated Gastric Antral Venous Ectasia (GAVE)
    - Manifestations:
        - Esophagus: Esophageal dysmotility and incompetence of the LES leading to chronic esophagitis, stricture, Barrett's esophagus, pulmonary micro aspiration.
        - Stomach: GAVE ("watermelon stomach") that can lead to gastric ulcers and or anemia.
            - GAVE needs to be successfully treated (e.g., with Argon Plasma Coagulation) before HCT.
        - Colon: Diarrhea or constipation, bacterial overgrowth with malabsorption.
        - Anorectum: Fecal incontinence due to sphincter muscle damage, rectal prolapse.
- **Involvement of other organs (usually has no impact on whether AHCT is indicated):**
    - Systemic
        - Fatigue associated with pain similar to that described in patients with idiopathic fibromyalgia

        - Weakness, may or may not be associated with elevated CK. Important to assess for myositis overlap with systemic sclerosis (may be associated with worse outcomes)
        - Pain that can be directly or indirectly associated with active systemic sclerosis.
    - Vascular
        - Raynaud's phenomenon and associated digital ulcers. May also be assessed by nail fold capillaroscopy or nail fold video capillaroscopy.
        - Telangiectasia.
    - MSK/Joints
        - Myalgias and arthralgias with AM stiffness, due to inflammatory arthritis in addition to sclerodactyly and skin inflammation. Both can lead to fibrosis around tendons/periarticular soft tissue leading to tendon friction rubs, joint flexion contractures and decreased range of motion, which is more commonly associated with diffuse cutaneous SSc.
        - Inflammatory arthritis can be associated with systemic sclerosis directly but must also have workup for overlap with rheumatoid arthritis (CCP, RF and X rays).
    - Neuromuscular
        - Myositis
        - Peripheral neuropathy, including autonomic. Less evidence but might also be associated with medications for the treatment of systemic sclerosis.
        - CNS disease is rare
    - Genital
        - Erectile dysfunction, sexual dysfunction is common in both sexes.
        - Dyspareunia due to vaginal dryness/narrow introitus.

Pathogenesis

- Poorly known but thought to involve 3 main pathways: Inflammation, fibrosis and vasculopathy (Figure 2)
- Immune dysregulation (T and B lymphocytes), endothelial cell and fibroblast abnormalities
- Autoantibodies:
    - Antibodies may contribute to the pathogenesis of systemic sclerosis:
        - Anti-Scl-70 (anti-topoisomerase on fibroblast surface)[5]?
        - Anti-PDGFR with profibrotic activity[6]?
    - Whether autoantibodies persist after AHCT is controversial[7,8]

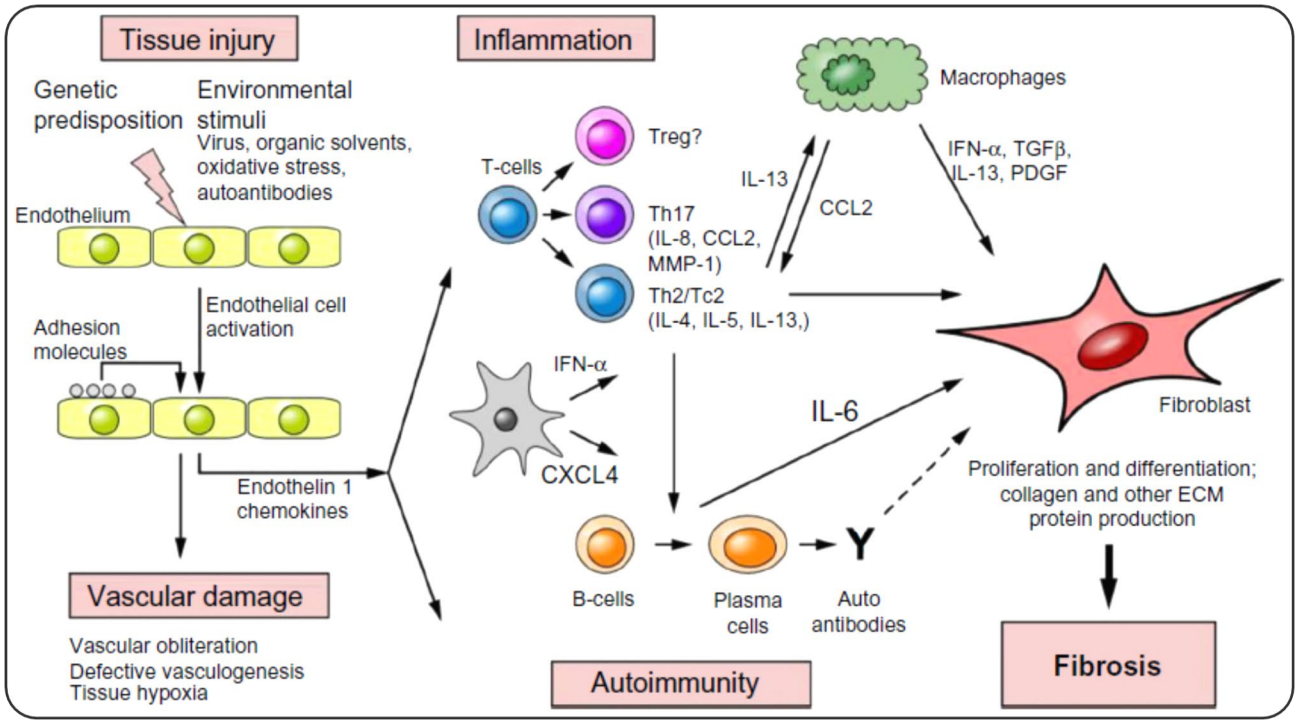


Figure 2: Proposed Pathophysiology of Systemic Sclerosis (from Fuschiotti P: Immunotargets Ther 2016).

Incidence of SSc

- 0.6 to 122/million/year; Median 12/million/year in North American studies[9]
- Trend toward increasing incidence
- Females > Males, particularly ≥1-para/gravida females
- Peak age 50-60 y

Prognosis without HCT

- Survival ~80% at 2 years, ~60% at 5 years, ~40% at 10 years per Altman et al[10]; consistent with more recent studies[11,12]
- Survival is particularly low with:
  - Diffuse cutaneous systemic sclerosis[13,14]
  - Heart, lung (ILD or PAH), or renal involvement (SRC)[10]
  - For diffuse cutaneous systemic sclerosis without or with only mild internal organ involvement, rapid Skin Thickness Progression Rate (STPR)[15]
    - Onset of skin thickening defined as the first time the patient's fingers became swollen and never again returned to normal
    - STPR = mRSS / time interval between the onset of skin thickening and the documented mRSS in years

        - STPR >45 associated with survival of 76% at 2 y (compared to ~86% with STPR ≤45 (p=.002)
        - Not validated for patients with >2 y interval between the onset of skin thickening and the documented mRSS

SSc Treatments Other than HCT

- Systemic immunosuppressive/antifibrotic/anti-cytokine agents
    - All studies retrospective or non-randomized prospective (thus dubious efficacy), except for cyclophosphamide, which was shown to have limited efficacy in randomized studies[16], and for MMF, which has efficacy similar to cyclophosphamide[17].
    - Cyclophosphamide
        - In a randomized study of oral Cy vs placebo for 1 y, the Cy group had a smaller decline of FVC (1% vs 2.6% predicted, p<.03)[18]. There was no difference at 2 years[19].
    - MMF (mycophenolate mofetil)
        - In a randomized study of MMF vs Cy, MMF was as efficacious as Cy, but Cy was more toxic[17].
    - Methotrexate
        - Corticosteroid (caveat: at high dose may induce renal crisis)
    - Rituximab (RTX)
        - Several case studies and series demonstrate efficacy of RTX in systemic sclerosis patients. Recently some RCT data particularly in patients with SSc-associated ILD (see RECITAL and EVER-ILD). Particularly for combination therapy.
    - IL-6 inhibitors (Tocilizumab/Actemra)
        - Minimal efficacy for ILD but shows mild improvement in skin fibrosis and particularly useful for overlapping inflammatory arthritis.
    - Antifibrotics (Nintedanib/OFEV)
        - SENSIS trial shows stabilization of FVC and has been approved for SARD-ILD in combination with immunosuppression.
    - Efficacy of established non-AHCT therapies is typically short-term, and long-term efficacy of newer non-AHCT therapies (combination therapies like rituximab+tocilizumab) is unknown.

- Organ/Symptom-based therapies
    - Pruritus – antihistamines, topical steroids, methotrexate.
    - Raynaud / digital ulcers – Ca channel blocker, avoiding cold environment, heated gloves, Raynaud's gel, nitro patches, PDE4 inhibitors like sildenafil.
    - Contractures – physiotherapy, occupational therapy, hot wax bathes.

- Renal crisis – ACE inhibitor, good blood pressure control, avoiding systemic steroids especially if RNA Pol3 autoantibodies are present.
  - These patients should never be given any type of steroid because of significant risk of scleroderma renal crisis. However, in case of HCT, we have been giving peri-ATG steroid, recommend with and ACE inhibitor.
- Esophageal dysmotility – proton pump inhibitor, antihistamines like famotidine in combination, gastric coating agents. Medications may need to be compounded because of poor bioavailability and absorption by GI complication of systemic sclerosis.
- Malabsorption/diarrhea due to bacterial overgrowth – antibiotics, dietary fiber.
- ILD – Oxygen, antifibrotics, immunosuppression, lung transplant.
- PAH – oxygen, diuretic, PAP lowering agents (macitentan, riociguat), lung transplantation.
- Arthritis – NSAID, hydroxychloroquine, methotrexate, leflunomide, sulfasalazine. Note that MMF does not work for controlling inflammatory arthritis.
- CHF – ACE inhibitor, implantable cardioverter-defibrillator

Autologous HCT (HCT)

Multiple non-randomized and 3 randomized studies of HCT for SSc are published (Appendix 1). From these studies it can be surmised that AHCT is superior compared to pre-2015 conventional therapy (e.g., oral or monthly IV cyclophosphamide) for the following indications:

- Indications
  - SSc involving skin + lungs, if FVC or DLCO 40-80% predicted or rapid decline of FVC (>10% over 12-18 months), particularly if patient never smoked, or
  - Systemic sclerosis without lung involvement, if mRSS >20 with high ESR/CRP or rapid skin thickness progression rate
  - Disease duration <5 years, ideally <1 year
    - Insufficient data for patients with longer disease duration[4]. With other autoimmune disease, duration appears to matter[20-23].
    - Pretreatment with systemic immunosuppressive drugs may not be a contraindication[24]
  - No pulmonary or cardiac contraindication as outlined above (under SSc Manifestations)
  - If GAVE, needs to be successfully treated before HCT
  - Age ≤65 years
    - Progression-free survival is worse with older age[25,26].
- Benefits
  - Survival benefit
  - Skin improvement (over years; greater improvement proximally than distally)
  - Lung stabilization or slight improvement

    - QOL improvement
- Risks
    - Early transplant-related mortality (TRM) (first 5 years) 5-10%
        - Organ failure, particularly heart and lung
        - Infections
    - Late toxicity
        - Myelodysplastic syndrome/Acute myeloid leukemia
        - Solid cancer (increased incidence with SSc alone)
        - Second autoimmune disease (e.g., thyroiditis, immune cytopenia)
- HCT Protocol
    - Optimal drugs/doses for stem cell mobilization and transplant conditioning are unknown. Intermediate intensity conditioning may be optimal[27], but fludarabine-based low intensity conditioning appears also efficacious[4]. Role of CD34 selection is uncertain[25,28].
    - Two protocols have been widely used. ASTIS protocol[29], with conditioning based on cyclophosphamide 200 mg/kg, is typically used in Europe. SCOT protocol[30], with conditioning based on cyclophosphamide 120 mg/kg + TBI 8 Gy, is typically used in the USA.
    - In Calgary, between 2016 and 2019, we used the ASTIS protocol, except we did not use graft CD34 cell enrichment due to its cost and controversial benefit. In 2020, we switched to the SCOT protocol as it appeared to be associated with lower incidence of SSc relapse/progression, and possibly lower transplant-related mortality and possibly lower incidence of a new autoimmune disease than the ASTIS protocol (ref[30] for SCOT, refs[29,31,32] for ASTIS). In 2021, a CIBMTR retrospective analysis was completed, which did not show a difference in overall survival (OS) or progression-free survival (PFS) between the ASTIS and SCOT-like protocol (Georges G et al: ACR 2021 Meeting, Abstract No. 1364). In summer 2022, a staff shortage substantially impacted our Radiation Physics department. Given that the TBI with lung and kidney shielding, used in the SCOT study, required a lot of staff resources and given the lack of evidence for the potential superiority of the SCOT over the ASTIS protocol, in October 2022 we switched back to the ASTIS protocol, including CD34 enrichment. The rationale for the CD34 enrichment was that by then there had been 4 studies, 3 of which showed at least a trend toward better outcomes with CD34 enrichment – Oliveira's retrospective EBMT study showing no benefit[28], Georges' retrospective CIBMTR study showing a trend toward improved PFS (Georges G et al: ACR 2021 Meeting, Abstract No. 1364), Ayano's small retrospective study from Japan showing a significantly improved PFS[33]. and Henes' prospective non-interventional EBMT study showing a better SSc response but insignificant impact on PFS[25]. It had also become clear by 2022 that CD34 enrichment together with ATG is likely associated with a high incidence of new autoimmune diseases after HCT and the need for ATG had been questioned

(reviewed in Levin et al[34]). Therefore, the protocol we started to use in October 2022 was a modified ASTIS protocol with a reduced dose of Thymoglobulin (4.5 instead of 7.5 mg/kg).

- A low intensity protocol using fludarabine, low dose cyclophosphamide, rabbit ATG, and rituximab conditioning has been evaluated in a pilot study of 28 patients[4]. Transplant-related mortality at one year was only 4% despite patients were included who would be conventionally considered transplant-ineligible (SSc duration >5 y, DLCO as low as 30%, O_2-dependent, mPAP >30 mmHg after fluid challenge, interventricular septal flattening/bounce, late Gd enhancement on CMR, pericardial effusion). Short-term efficacy (1 year) appeared to be at least as good as with ASTIS/SCOT regimens as only 1 patient (4%) relapsed by one year, and trends toward improved mRSS and FVC were observed. Long-term efficacy is unknown. We adopted this protocol in 2022 as an alternative for patients for whom the HCT would be relatively contraindicated by conventional criteria.

In Calgary, as of October 2022, we use primarily the modified ASTIS protocol:

Mobilization

Day	1	2	3	4	5	6	7	8	9	10	11	≥12	≥13
Cy*	2.5 g/m^2												
GCSF**							X	X	X	X	X	X	
Apheresis of MNCs***													X

* Cyclophosphamide (2.5 g/m^2 dose dissolved in 500 mL D_5W and infused over 2 h) with Mesna, hydration (500 mL NS over 1 h before each Cy infusion, and 500-1000 mL NS over 2-4 h after Cy infusion [500 mL over 2 h for <70 kg patient, 1000 mL over 4 h for ≥70 kg patient]) and antiemetics (granisetrone + dexamethasone + aprepitant + prn dimenhydrinate + prn metoclopramide + prn prochlorperazine). Mesna, 2500 mg/m^2 IV, should be given in two to three divided doses, the first one concurrently with cyclophosphamide and the second (third) one 4 h (8h) later. The dose of Cy (2.5 g/m^2) deviates from the ASTIS protocol, which used 4 g/m2. This is to keep it standard with our routine mobilization protocol – see SPM chapter on mobilization.
** 300-900 ug per dose depending on weight per SPM chapter on Mobilization; with prn codeine
*** Start when blood CD34 count is >20 x 10e6/L. Target to collect 8 x 10e6/kg CD34 cells. Perform CD34 selection using CliniMACS. Target 5 x 10e6/kg CD34 cells for infusion. Cryopreserve.

Conditioning

Day	-6	-5	-4	-3	-2	-1	0
Cy*	50 mg/kg	50 mg/kg	50 mg/kg	50 mg/kg			
Rabbit ATG**				0.5 mg/kg	2.0 mg/kg	2.0 mg/kg	
Methylprednisolone				40 mg bid	40 mg bid	40 mg bid	
Stem cell infusion							X

* Cyclophosphamide (50 mg/kg ideal body weight in 250 mL D_5W infused over 2 h) with Mesna (50 mg/kg ideal body weight in 1 L NS over 24 h starting with each Cy dose), hydration (NS at 75 mL/h starting the night before the first Cy dose and continuing till 24 h post the last Cy dose) and antiemetics (ondansetron + dexamethasone [except on day minus 3, when methylprednisolone is given as ATG premedication] + aprepitant + prn dimenhydrinate + prn metoclopramide)
** Thymoglobulin (0.5-2.0 mg/kg in as low volume of NS as possible [0.5 mg/ml] infused over ≥4 h) with premedication (Methylprednisolone 1 mg/kg before each infusion + acetaminophen + diphenhydramine + meperidine prn)

Alternatively (e.g., in patients not meeting conventional HCT eligibility criteria), Burt's low-intensity, fludarabine-based protocol can be used:

Mobilization

Day	1	2	3	4	5	6	7	8	9	10	11	≥12	≥13
Cy*	2.5 g/m^2												
GCSF**							X	X	X	X	X	X	
Apheresis of MNCs***													X

* Cyclophosphamide (2.5 g/m^2 dose dissolved in 500 mL D_5W and infused over 2 h) with Mesna, hydration (500 mL NS over 1 h before each Cy infusion, and 500-1000 mL NS over 2-4 h after Cy infusion [500 mL over 2 h for <70 kg patient, 1000 mL over 4 h for ≥70 kg patient]) and antiemetics (granisetrone + dexamethasone + aprepitant + prn dimenhydrinate + prn metoclopramide + prn prochlorperazine). Mesna, 2500 mg/m^2 IV, should be given in two to three divided doses, the first one concurrently with cyclophosphamide and the second (third) one 4 h (8h) later. The dose of Cy (2.5 g/m^2) deviates from the Burt protocol, which used 2 g/m^2. This is to keep it standard with our routine mobilization protocol – see SPM chapter on mobilization.
** 300-900 ug per dose depending on weight per SPM chapter on Mobilization; with prn codeine
*** Start when blood CD34 count is >20 x 10e6/L. Target to collect 5 x 10e6/kg CD34 cells. No product manipulation (no CD34 cell selection). Cryopreserve.

Conditioning

Day	-6	-5	-4	-3	-2	-1	0
Fludarabine		30 mg/m^2	30 mg/m^2	30 mg/m^2	30 mg/m^2		
Rabbit ATG**		0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	
Cy*					60 mg/kg		
Rituximab***	500 mg						
Methylprednisolone		40 mg bid	40 mg bid	40 mg bid	40 mg bid	40 mg bid	
Stem cell infusion							X

* Cyclophosphamide (60 mg/kg ideal body weight in 300 mL D_5W infused over 2 h) with Mesna (60 mg/kg ideal body weight in 1 L NS over 24 h starting with the Cy dose), hydration (NS at 75 mL/h starting the night before the Cy dose and continuing till 24 h after the dose) and antiemetics (ondansetron + aprepitant + prn dimenhydrinate + prn metoclopramide. As Cy is infused after ATG, the methylprednisolone given before ATG serves also as an antiemetic for Cy). On day -2, hydration (NS at 75 mL/h) should be held while infusing ATG to avoid fluid overload.
** Thymoglobulin (0.5-1.5 mg/kg in as low volume of NS as possible [0.5 mg/ml] infused over ≥4 h) with premedication (Methylprednisolone 1 mg/kg before each infusion + acetaminophen + diphenhydramine + meperidine prn)
*** Rituximab or a biosimilar. Premedications include acetaminophen + H1 antihistamine + H2 antihistamine + prn steroid/antihistamine/acetaminophen. Rituximab/biosimilar is non-formulary for SSc, so requires STEDT approval or the patient needs to pay (~$1500). The timing of rituximab deviates from the Burt protocol (day -6 instead of -5). The reason is the difficulty for our inpatient unit to administer fludarabine+ATG+rituximab in one day.

- Special management notes
  - Discontinue DMARDs (e.g., MMF, MTX, cyclophosphamide) 2-4 weeks before mobilization to maximize the likelihood of a high CD34 cell yield. This does not apply to prednisone. If a patient is on prednisone before mobilization, prednisone should be continued peri transplant and tapered by day 37 (as routine – see below). Patients who have been on prednisone long-term may need a slower posttransplant taper.

- Avoid rapid intravascular volume changes, particularly fluid overload, and electrolyte concentration extremes (could trigger CHF or arrhythmia due to subclinical/subechocardiographic myocardial fibrosis)[1,3]
- Avoid hypertension (could trigger renal crisis) – use lisinopril or enalapril

- Supportive care post-transplant
  - Steroids, apart from peri-ATG, are routinely <u>not</u> used.
    - History: In SCOT trial, prednisone was used at 0.5 mg/kg/d from day 6 to day 21, then tapered by day 37, to prevent engraftment syndrome and serum sickness. This was not done in ASTIS trial. We did not use steroids in our first 16 patients who received ASTIS-like conditioning. Neither engraftment syndrome requiring systemic steroids nor serum sickness occurred (per Storek memory, chart review not done). In 2020-2022, in 9 patients, we used SCOT-like conditioning and, to replicate SCOT completely, we included prednisone at 0.5 mg/kg/d from day 6 to day 21, taper by day 37. In 2022, we transitioned back to ASTIS-like conditioning but kept the prednisone, however, changed it to 0.25 mg/kg/d from day 0 to day 21, taper by day 37. Among 7 patients who received the ASTIS-like conditioning with prednisone in 2022-2024, 1 developed renal crisis on or before d35, which responded only partially to captopril and resulted in chronic renal insufficiency with creatinine ≥400 umol/L, and 1 patient developed an episode of what appeared to be a mild renal crisis on or before d49 (between ~d20 and d49), which responded near-completely to perindopril. At that point it was decided to abandon the routine use of steroids peri-transplant, except peri-ATG.
  - ACE inhibitor or ARB should be considered, particularly for patients with a cardiac problem or a history of renal crisis. Lisinopril, 10-20 mg qd from start of conditioning to day 60 and targeting systolic BP 90-110 mmHg, was a part of the SCOT protocol. Can be discontinued already around day 30 in patients who need a calcium channel blocker (e.g. nifedipine XL) or a phosphodiesterase-5 inhibitor (e.g., sildenafil) for Raynaud's/digital ulcers, as the combination with lisinopril could be associated with symptomatic hypotension.
  - GCSF from day 7 till engraftment per our SPM
  - Valacyclovir from start of conditioning till 1 day before first dose of VZV vaccine
  - Septra from engraftment till 1 y per our SPM, possibly extension to 2 y if CD4<200/ul at 1 y
  - Levofloxacin from day 0 till engraftment (risk of cardiac mortality with sepsis)
  - Fluconazole from day 1 till day 28 (risk of esophageal candidiasis)
  - EBV and CMV PCR weekly till day 100 (risk of PTLD, particularly with rabbit ATG) and preemptive therapy per SPM
  - Vaccination per the Vaccination chapter of our SPM

Allogeneic HCT (AlloHCT)

- Case reports suggest efficacy[35-37]
- The only case series is a CIBMTR registry study of 12 cases with follow up of surviving patients of at least 1 year[38]. Of the 12 patients, 6 died, and 6 are alive at 13-60 months posttransplant. SSc status at last follow up was not given. Thus, this report is not informative regarding efficacy but suggests that mortality after alloHCT may be substantial.
- AlloHCT should currently be considered only in patients with concurrent hematologic disease or under a clinical trial.

CAR T cells

- Case reports and small series of autologous or allogeneic CD19-directed CAR T cells suggest efficacy for skin tightness, Raynaud's, digital ulcers, interstitial lung disease, and myocardial fibrosis.[39,40] Toxicity (CRS, neurotoxicity, hematotoxicity) appears to be less frequent and less severe than in patients with B cell malignancies.
- Currently available only under clinical trials. As of January 2025, none is open in Alberta.

Pre-Transplant Tests/Appointments – see Table below

Tests/Appointments*	Rheumatologist to Arrange	Calgary BMT to Arrange
PFT, including 6MWT and O_2 sat by forehead probe if low by finger probe (Respirology or PFT lab)	Yes	
Chest CT (contiguous & high res), BAL if infection suspected	Yes	
VQ scan (Nuclear Medicine)	Yes	
ECG +/- Holter (if PVCs or history of palpitation/syncope/falling)	Yes	
Echocardiogram including strain	Yes	
Cardiac MRI including Gad	Yes	
Sperm bank or fertility gynecologist, if relevant	Yes	
Blood tests ○ Labs including CBC+diff, LFTs, Creatinine, Albumin, CRP, ANA, CK, TSH, NTproBNP, Troponin T (Troponin I if elevated CK), IgM, IgG, IgA ○ Malabsorption labs: Vitamin A, B12, C, E, folate, ionized Ca, P, Mg, iron studies (TIBC, transferrin saturation, ferritin) ○ Serology for HIV, HSV, VZV, CMV, EBV, HepB, HepC ○ Pregnancy test (pre-menopausal women only) ○ INR, PTT ○ Systemic sclerosis associated autoantibodies (“Systemic sclerosis Profile” at Mitogen Advanced Diagnostic Lab, use separate requisition)	Yes	
Urine tests (Urinalysis, urine albumin:creatinine ratio)	Yes	
SSc Rheumatologist (confirm Dx, mRSS, quantify contractures, NFCapillaroscopy, baseline for postAHCT decision of relapse, research skin biopsy if patient consents)	Yes	Yes (if not yet seen by Drs. Durand or Osman)
GI doc + EGD (GAVE, esophageal stricture or infection)	If Fe deficient	Yes
Esophageal manometry (Dr M. Woo)		Yes
Dentist, including X-rays	Encourage pt to see local dentist	Yes
RHC with exercise (Dr J.Howlett)		Yes
BMA including flow cytometry & cytogenetics (if MDS suspected)		Yes

* If done >3 months before AHCT, consider repeating, particularly PFT and Echo.
Blood and urine tests should be repeated pre-mobilization unless done within 1 month pre-mobilization.

Post-Transplant Tests/Appointments (at 6 months, and 1,2,3,4,5 years)

- Rheumatology appointment with Dr. Caylib Durand. This includes capillaroscopy and optionally research skin biopsy. Not needed for patients from Northern AB (taken care of by Dr. Mo Osman)
- GI appointment with Drs. Matt Woo or Dorothy Li (SHC). This includes optional research esophageal manometry
- Echocardiogram
- PFT: Spirometry, DLCO, 6MWT
- Chest CT – 1 year posttransplant only (for non-AB patients, this is just a recommendation)
- Oxygen saturation ideally by forehead probe, if <92%, then ABG
- Labs including CBC+diff, CRP, ANA, CK, TSH, NTproBNP, Troponin T (high sensitivity), IgM, IgG, IgA
- Urinalysis (random)
- Urine albumin:creatinine ratio (from spot urine), if unavailable, then protein:creatinine ratio
- Systemic sclerosis associated autoantibodies ("Systemic sclerosis Profile" at Mitogen Advanced Diagnostic Lab)
- Estradiol and anti-mullerian hormone (females <50-y-old), AM free testosterone (males), FSH and LH (both females <50-y-old and males) – 1 year posttransplant only
- CD4 T cell count – 1 year posttransplant only

How to Refer for HCT:

- For Alberta Connect Care users: Enter Ambulatory Referral to Blood and Marrow Transplant Team – Internal Referral – To department "CGY ACCC BMT COORDINATION".
- For non-Connect Care users, including patients from outside of Alberta: Fax referral letter to Calgary Blood and Marrow Transplant Program at 587-231-3994.
- Please refer all patients fitting the above criteria at the outset – not only after they have failed a therapy. In the three randomized studies, most patients received the HCT as first line therapy or after only a few months of immunosuppressive therapy.

References

1. Burt RK, Oliveira MC, Shah SJ, et al. Cardiac involvement and treatment-related mortality after non-myeloablative haemopoietic stem-cell transplantation with unselected autologous peripheral blood for patients with systemic sclerosis: a retrospective analysis. Lancet 2013;381:1116-24.
2. Farge D, Burt RK, Oliveira MC, et al. Cardiopulmonary assessment of patients with systemic sclerosis for hematopoietic stem cell transplantation: recommendations from the European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Party and collaborating partners. Bone Marrow Transplant 2017;52:1495-503.
3. Henes JC, Koetter I, Horger M, et al. Autologous stem cell transplantation with thiotepa-based conditioning in patients with systemic sclerosis and cardiac manifestations. Rheumatology (Oxford) 2014;53:919-22.
4. Burt RK, Han X, Quigley K, et al. Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: a pilot safety study that decreases neutropenic interval to 5 days. Bone Marrow Transplant 2021;56:50-9.
5. Henault J, Robitaille G, Senecal JL, Raymond Y. DNA topoisomerase I binding to fibroblasts induces monocyte adhesion and activation in the presence of anti-topoisomerase I autoantibodies from systemic sclerosis patients. Arthritis Rheum 2006;54:963-73.
6. Baroni SS, Santillo M, Bevilacqua F, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med 2006;354:2667-76.
7. Storek J, Zhao Z, Lin E, et al. Recovery from and consequences of severe iatrogenic lymphopenia (induced to treat autoimmune diseases). Clin Immunol 2004;113:285-98.
8. Tsukamoto H, Nagafuji K, Horiuchi T, et al. Analysis of immune reconstitution after autologous CD34+ stem/progenitor cell transplantation for systemic sclerosis: predominant reconstitution of Th1 CD4+ T cells. Rheumatology (Oxford) 2011;50:944-52.
9. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Seminars in arthritis and rheumatism 2008;37:223-35.
10. Altman RD, Medsger TA, Jr., Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 1991;34:403-13.
11. Mayes MD, Lacey JV, Jr., Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246-55.
12. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:2437-44.
13. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine 2002;81:139-53.
14. Scussel-Lonzetti L, Joyal F, Raynauld JP, et al. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine 2002;81:154-67.
15. Domsic RT, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger TA, Jr. Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. Ann Rheum Dis 2011;70:104-9.
16. Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. Arthritis research & therapy 2008;10:R124.
17. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708-19.
18. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-66.
19. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026-34.
20. Storek J, LeClercq SA, Aaron SL. Lack of sustained response of advanced dermatomyositis to autologous haematopoietic cell transplantation. Scandinavian journal of rheumatology 2013;42:421-2.
21. Atkins HL, Muraro PA, van Laar JM, Pavletic SZ. Autologous hematopoietic stem cell transplantation for autoimmune disease--is it now ready for prime time? Biol Blood Marrow Transplant 2012;18:S177-83.
22. Burt RK, Testori A, Craig R, Cohen B, Suffit R, Barr W. Hematopoietic stem cell transplantation for autoimmune diseases: what have we learned? Journal of autoimmunity 2008;30:116-20.

23. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2012;47:770-90.
24. Moore J, Englert H, Furlong T, Poon T, Milliken S, Ma D. Auto-HSCT induces sustained responses in severe systemic sclerosis patients failing pulse cyclophosphamide. Bone Marrow Transplant 2012;47:1486-7.
25. Henes J, Oliveira MC, Labopin M, et al. Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party. Haematologica 2021;106:375-83.
26. van Bijnen S, de Vries-Bouwstra J, van den Ende CH, et al. Predictive factors for treatment-related mortality and major adverse events after autologous haematopoietic stem cell transplantation for systemic sclerosis: results of a long-term follow-up multicentre study. Ann Rheum Dis 2020;79:1084-9.
27. Gratwohl A, Passweg J, Bocelli-Tyndall C, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases. Bone Marrow Transplant 2005;35:869-79.
28. Oliveira MC, Labopin M, Henes J, et al. Does ex vivo CD34+ positive selection influence outcome after autologous hematopoietic stem cell transplantation in systemic sclerosis patients? Bone Marrow Transplant 2016;51:501-5.
29. van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA 2014;311:2490-8.
30. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. N Engl J Med 2018;378:35-47.
31. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv 2017;1:2742-55.
32. Daikeler T, Labopin M, Di Gioia M, et al. Secondary autoimmune diseases occurring after HSCT for an autoimmune disease: a retrospective study of the EBMT Autoimmune Disease Working Party. Blood 2011;118:1693-8.
33. Ayano M, Tsukamoto H, Mitoma H, et al. CD34-selected versus unmanipulated autologous haematopoietic stem cell transplantation in the treatment of severe systemic sclerosis: a post hoc analysis of a phase I/II clinical trial conducted in Japan. Arthritis research & therapy 2019;21:30.
34. Levin D, Osman MS, Durand C, et al. Hematopoietic Cell Transplantation for Systemic Sclerosis-A Review. Cells 2022;11.
35. Khorshid O, Hosing C, Bibawi S, et al. Nonmyeloablative stem cell transplant in a patient with advanced systemic sclerosis and systemic lupus erythematosus. The Journal of rheumatology 2004;31:2513-6.
36. Nash RA, McSweeney PA, Nelson JL, et al. Allogeneic marrow transplantation in patients with severe systemic sclerosis: resolution of dermal fibrosis. Arthritis Rheum 2006;54:1982-6.
37. Loh Y, Oyama Y, Statkute L, et al. Non-myeloablative allogeneic hematopoietic stem cell transplantation for severe systemic sclerosis: graft-versus-autoimmunity without graft-versus-host disease? Bone Marrow Transplant 2007;39:435-7.
38. Pasquini MC, Voltarelli J, Atkins HL, et al. Transplantation for Autoimmune Diseases in North and South America: A Report of the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 2012.
39. Auth J, Muller F, Volkl S, et al. CD19-targeting CAR T-cell therapy in patients with diffuse systemic sclerosis: a case series. Lancet Rheumatol 2024.
40. Wang X, Wu X, Tan B, et al. Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis. Cell 2024;187:4890-904 e9.
41. Binks M, Passweg JR, Furst D, et al. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. Ann Rheum Dis 2001;60:577-84.
42. Farge D, Marolleau JP, Zohar S, et al. Autologous bone marrow transplantation in the treatment of refractory systemic sclerosis: early results from a French multicentre phase I-II study. Br J Haematol 2002;119:726-39.
43. Nash RA, McSweeney PA, Crofford LJ, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. Blood 2007;110:1388-96.
44. Oyama Y, Barr WG, Statkute L, et al. Autologous non-myeloablative hematopoietic stem cell transplantation in patients with systemic sclerosis. Bone Marrow Transplant 2007;40:549-55.
45. Vonk MC, Marjanovic Z, van den Hoogen FH, et al. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. Ann Rheum Dis 2008;67:98-104.

46. Burt RK, Shah SJ, Dill K, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet 2011;378:498-506.

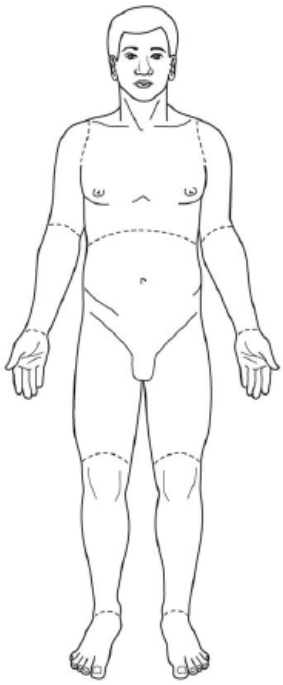
Appendix 1: Methods and Results of Studies of AHCT for SSc*

Study	N	Patient character-istics	HSC mobiliz-ation	Condition-ing (or control Rx)	CD34 selection	Med F/U (y)	TRM	Efficacy
Non-random-ized								
Binks M: Ann Rheum Dis 2001[41]	41	Age 41 (med) Dis.dur. ~2 y mRSS 29 FVC <70% in ½ pts	Cy 4 g/m^2 + GCSF (most pts)	Cy 150-200 mg/kg (most pts)	Yes (most pts)	1	17%	OS at 1 y 73% mRSS improved Lung function stable
Farge D: Brit J Haematol 2002[42]	11	Age 46 (med) Dis.dur. ~2 y mRSS 29 FVC 67%	Cy 4 g/m^2 + GCSF	Cy 200 mg/kg (most pts)	Yes	1 ½	9%	OS at 1 ½ y 64% mRSS improved QOL improved
Nash RA: Blood 2007[43]	34	Age 41 (med) Dis.dur. <4 y mRSS 30 FVC 72%	GCSF	Cy 120 mg/kg + TBI 8 Gy + Atgam 90 mg/kg	Yes	5	24%	OS at 5 y 64% PFS at 5 y 64% mRSS improved Lung function stable QOL improved
Oyama Y: Bone Marrow Transplant 2007[44]	10	Age 46 (med) Dis.dur. ~3 y mRSS 30 FVC ~70%	Cy 2 g/m^2 + GCSF	Cy 200 mg/kg + Thymoglob. 7.5 mg/kg	No	2	0%	OS at 2 y 90% PFS at 2 y 70% mRSS improved Lung function stable
Vonk MC: Ann Rheum Dis 2008[45]	26	Age 42 (med) Dis.dur. ~2 y mRSS 32 FVC 76%	Cy 4 g/m^2 + GCSF	Cy 200 mg/kg	Yes	5	4%	OS at 5 y 96% PFS at r y 64% mRSS improved Lung function stable
Tsukamoto H: Rheumatol 2011[8]	11	Age 52 (avg) Dis.dur. <5 y mRSS 22 FVC 65%	Cy 4 g/m^2 + GCSF	Cy 200 mg/kg	Yes	5	0%	OS at 3 y 91% mRSS improved FVC 65→78% DLCO stable ↓ Scl70, TNFa, TGFb
Random-ized								

Burt RK: Lancet 2011[46] (ASSIST)	10 vs 9 ctrls	Age 45 (med) Disease duration ~1 y Cy <6 IV doses mRSS ~23 FVC ~65%	Cy 2 g/m^2 + GCSF	Cy 200 mg/kg + Thymoglob. 6.5 mg/kg (w M-pred 1 g x 4) ***vs*** Cy 1 g/m^2 monthly x 6	No	1	0% vs 0%	OS @ 1 y 100% vs 100% Evaluations at BL and at 1 y: mRSS 28→15 vs 19→22 FVC 62→74% vs 67→61% QOL (SF36 total score) 39→56% vs 50→40% (all differences between groups significant, except for OS)
Van Laar: JAMA 2014[29] (ASTIS)	79 vs 77 cntls **	Age 44 (avg) Disease duration ~1 y Cy <5 g IV total mRSS 25 (avg) FVC 81% (avg)	Cy 4 g/m^2 + GCSF	Cy 200 mg/kg + Thymoglob. 7.5 mg/kg (w M-pred 1 mg/kg x3) ***vs*** Cy 750 mg/m^2 monthly x 12	Yes	6**	10% vs 0%	OS @ 4y 86% vs 76% EFS @ 4y 81% vs 74% (event = death or irreversible organ failure) Changes from BL to 2 y: mRSS decrease, 20 vs 9 FVC increase, 5 vs -1% QOL (SF36 physical score) increase, 10 vs 4 (all significant)
Sullivan: NEJM 2018[30] (SCOT)	36 vs 39 cntls	Age 18-69 Disease Duration ≤5 y Cy up to 4-6 mo mRSS 30 (avg) FVC 74% (avg)	GCSF	Cy 120 mg/kg + TBI 8 Gy + Atgam 90 mg/kg ***vs*** Cy 750 mg/m^2 monthly x12	Yes	>5	3% vs 0%	OS @ 4 ½ y 91% vs 77% EFS @ 4 ½ y 79% vs 50% (event = death or renal/cardiac/pulmonary failure) (all significant)

* Only studies with ≥10 patients are shown.
** Only 71 vs 57 patients completed treatment, and 8 controls received HCT at ≥2 y. The analyses under Efficacy are intention-to-treat analyses.
Abbreviations: Dis.dur., disease duration; med, median; mRSS, modified Rodnan skin score; FVC, forced vital capacity; Cy, cyclophosphamide; GCSF, granulocyte colony stimulating factor (filgrastim); HCT, hematopoietic cell transplantation; F/U, follow up; TRM, transplant related mortality; TBI, total body irradiation; Thymoglob., Thymoglobulin; M-pred, methylprednisolone; pts, patients; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; QOL, quality of life; TNFα, tumor necrosis factor alpha; TGFβ, transforming growth factor beta; BL, baseline;

Appendix 2: Modified Rodnan Skin Score (mRSS)



	Right				Left			
Fingers	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Hands	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Forearms	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Upper Arms	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Face			0 ☐	1 ☐	2 ☐	3 ☐		
Anterior Chest			0 ☐	1 ☐	2 ☐	3 ☐		
Abdomen			0 ☐	1 ☐	2 ☐	3 ☐		
Thighs	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Legs	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Feet	0 ☐	1 ☐	2 ☐	3 ☐	0 ☐	1 ☐	2 ☐	3 ☐
Column Totals								
Total:								
Key:	*0 – No Thickening*		*1 – Mild Thickening*		*2 – Moderate Thickening*		*3 – Severe Thickening*	
Notes:								

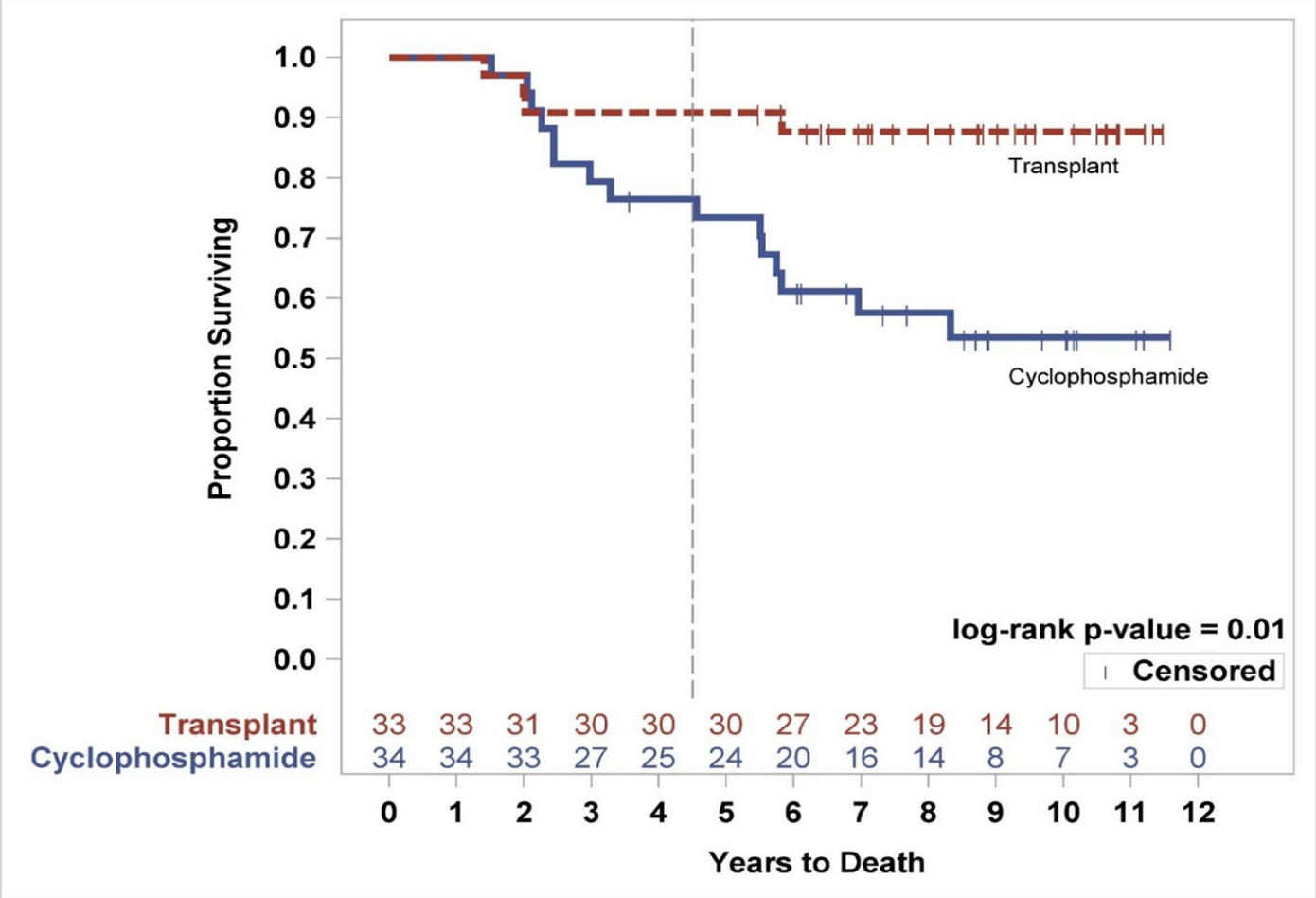
Uninvolved skin = 0, Mild thickening = 1, Moderate thickening = 2, Severe thickening (cannot pinch) = 3. mRSS is the total of points from the above locations (max 51). From Klippel JH: Rheumatology, Mosby 2000.

The total score is out of 51. Ideally the skin scores are evaluated by an experienced Rheumatologist familiar with systemic sclerosis. Tethering is not scored as a 3 but should be noted. Scores are a reflection of the total average for the area of skin tested and not maximum scores as this can be misleading with patches of skin being overrepresented. Care must also be given to lower extremity evaluation because of complications from edema and other comorbidities.

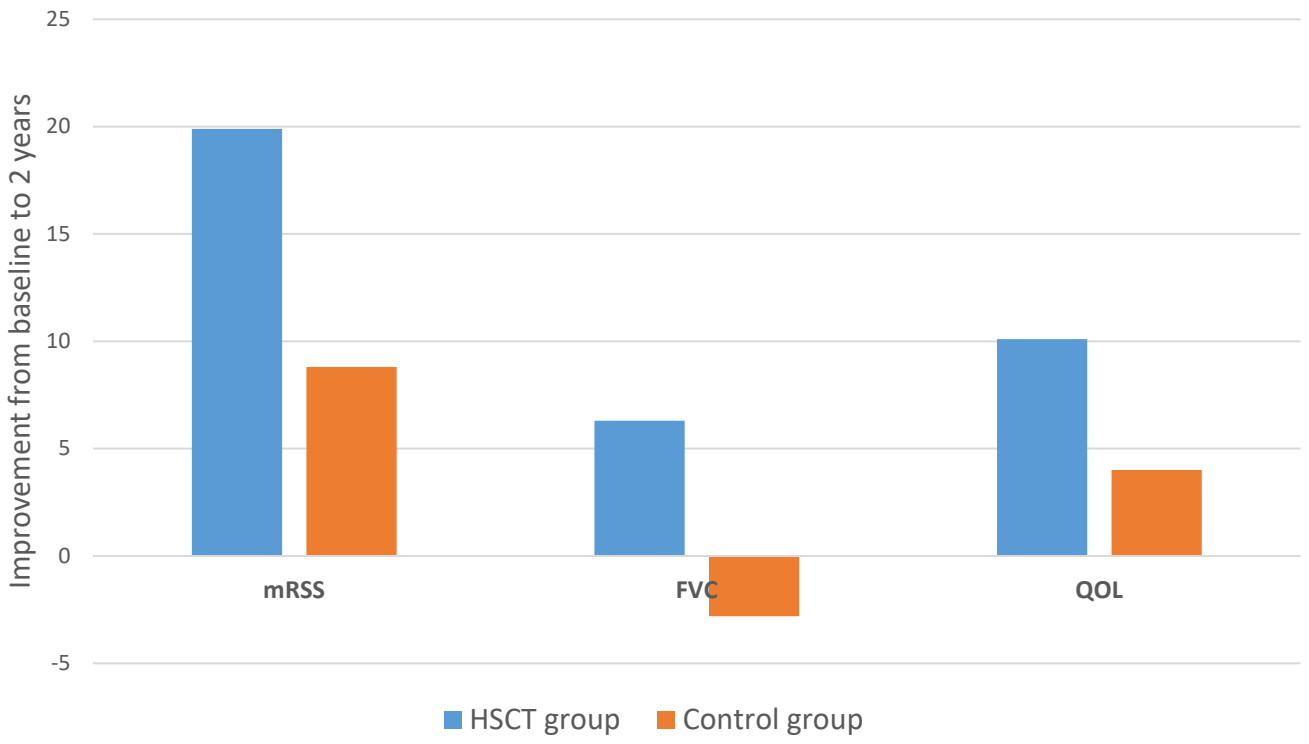
mRSS		
0	**Fine wrinkles in skin** **No skin thickness when rolling skin**	
1	**Appreciable skin thickness but still able to make skin fold between 2 fingers** **Still able to demonstrate fine wrinkles**	
2	**Appreciable skin thickness with difficulty in making skin folds** **No fine wrinkles**	
3*	**Appreciable skin thickness with inability to make skin folds between 2 fingers** **Don't count tethering and atrophy! mRSS=0**	

*No not count scores for tethering or atrophy.

Appendix 3: Survival, mRSS, FVC, and Quality of Life in Randomized Studies of HCT versus conventional therapy (cyclophosphamide).



Overall survival in SSc patients randomized to hematopoietic stem cell transplantation (HSCT) vs 1 year of cyclophosphamide (control). Long-term follow up data on patients from the SCOT study.[31] Presented at American College of Rheumatology 2018 annual meeting by Sullivan KM et al - Abstract 1820.



Modified Rodnan Skin Score (mRSS), forced vital capacity (FVC), and quality of life (QOL) in the ASTIS study. Between baseline and 2 years after start of treatment, mRSS dropped by mean 20 points in the patients randomized to HSCT (hematopoietic stem cell transplantation) vs 9 points in the control patients randomized to 1 year of cyclophosphamide ($p<0.001$). FVC improved by +6 vs -3 percentage points ($p=0.004$), and quality of life (QOL) assessed by Short Form 36 Physical Component improved by 10 vs 4 points ($p=0.01$).[29]

Appendix 4: Information for Patients

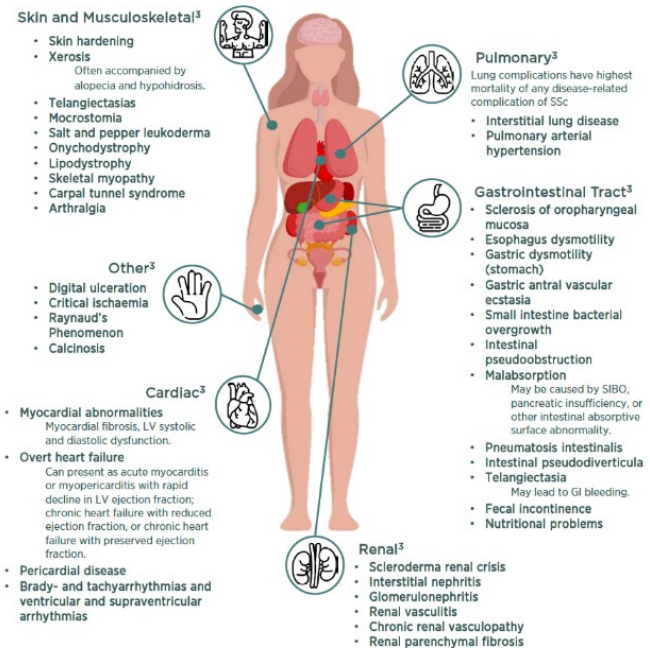
Understanding Systemic Sclerosis and Autologous Hematopoietic Cell Transplantation in Alberta

What is Systemic Sclerosis:

Systemic sclerosis (SSc) is a multi-organ, autoimmune, connective tissue disease. It is relatively rare, with the prevalence in Canada among the highest in the world (44/100000). Patients with SSc live an average of 20 years shorter than the general population, and while SSc is 8-9 times more common in women, outcomes in men are significantly worse. There are different types of SSc with one third of all patients with SSc develop the most severe form called diffuse cutaneous systemic sclerosis (dcSSc). Skin tightness or fibrosis is a marker of disease severity and severe skin tightness or fibrosis is a hallmark of dcSSc that has a much higher level of disability and increased risk of death compared to patients with limited cutaneous SSc (lcSSc). Most often SSc is treated with medications that suppress the immune system (e.g., MMF (CellCept)), but they have limited success in the long term management of rapidly progressive dcSSc.

LeRoy and Medsger Classification Criteria[5,11]

Criteria	dcSSc	lcSSc	Sine SSc
Systemic involvement	X	X	X
Proximal cutaneous changes	X		
Distal cutaneous changes	X	X	
Raynaud's phenomenon	X	X	X
SSc-type nail-fold capillary pattern	X	X	X
SSc selective autoantibodies	X	X	X



Autologous hematopoietic cell transplant (abbreviated as AutoHCT or HCT) is offered in Alberta for the treatment of dcSSc.

What is autologous HCT?

First, your blood-forming stem cells are collected. Next, you receive high dose immunosuppressive chemotherapy that is thought to kill the cells causing SSc. Next, the previously collected stem cells are reintroduced into your body. The stem cells make your immunity against bugs recover faster than if you receive chemotherapy without the stem cells. In the last decade, three randomized trials of HCT (ASSIST, ASTIS and SCOT) were published. Despite differences between patient populations and HCT techniques, all trials demonstrated superiority over conventional medical therapies for dcSSc. One of the most important outcomes for transplant is improved chance of survival. It can also result in less skin

tightness/thickenining/fibrosis along with improvement in other disease outcomes. However, AutoHCT is not for all patients with a summary of eligibility below.

Alberta AutoHCT Program Eligibility:

Age:	Age up to 65. Younger patients typically do better.
Disease Onset:	Less than 5 years from first non-Raynaud symptom.
Type of Disease:	Diffuse systemic sclerosis, severe skin disease (mRSS>20) or less severe skin if lungs involved.
Restrictions:	No features of heart failure or pulmonary hypertension (higher risk of death).
	Only mild or moderate interstitial lung disease (FVC 40-80%, ideally 60-80%).
	No untreated watermelon stomach (risk of bleeding).

Establishing Expectations for AutoHCT:
Rapidly progressive dcSSc has increased risk of death and disability but there are risks associated with AutoHCT as well. First and most important is that there is the risk of transplant-related death of up to 10%, usually due to lung or heart failure with or without an infection. This risk is usually within the first several months post-transplant and is overall still lower than the risk of death associated in the long run with SSc (not treated with AutoHCT). It is also important to understand that it is likely that the AutoHCT will not completely reverse all clinical features of SSc, especially well established fibrosis of the skin or other internal organs. The overall goal is to improve survival and to stop systemic sclerosis progression. Any reversal of other symptoms is hoped for but not always obtained.

If you are offered HCT, there is a net benefit compared to conventional medical therapy.
There are also other potential risks including a relapse where your disease could return. There is a risk of infection especially within the first 100 days of transplantation. There are possible risks of developing a new (unrelated) autoimmune disease (approximately 10% chance). There may be an increased risk of cancer of any organ, but this is not known for sure. There is a possibility of infertility or premature menopause because of the chemotherapy. This list covers most but not all potential complications of AutoHCT. It is important for each patient to weigh the benefits and risks for transplant before deciding to continue.

What to expect for the AutoHCT evaluation:
Typically, by the point of seeing the transplant team the patient has been seen and diagnosed by a Rheumatologist with dcSSc and then referred to a Rheumatologist with a focus in systemic sclerosis. The systemic sclerosis specialist then refers to the transplant team for further workup and evaluation. For the AutoHCT evaluation you will meet a Rheumatologist and Hematologist associated with the transplant program.

Multiple tests will be arranged for, including blood/urine tests, pulmonary function test, chest imaging like CAT scan, echocardiogram, cardiac MRI, right heart catheterization, endoscopy of esophagus and stomach.

Your evaluation may also require you to meet with other specialists depending on the organ systems involved but usually include:

- Hematologist, Rheumatologist, Gastroenterologist, Cardiologist, Dentist.

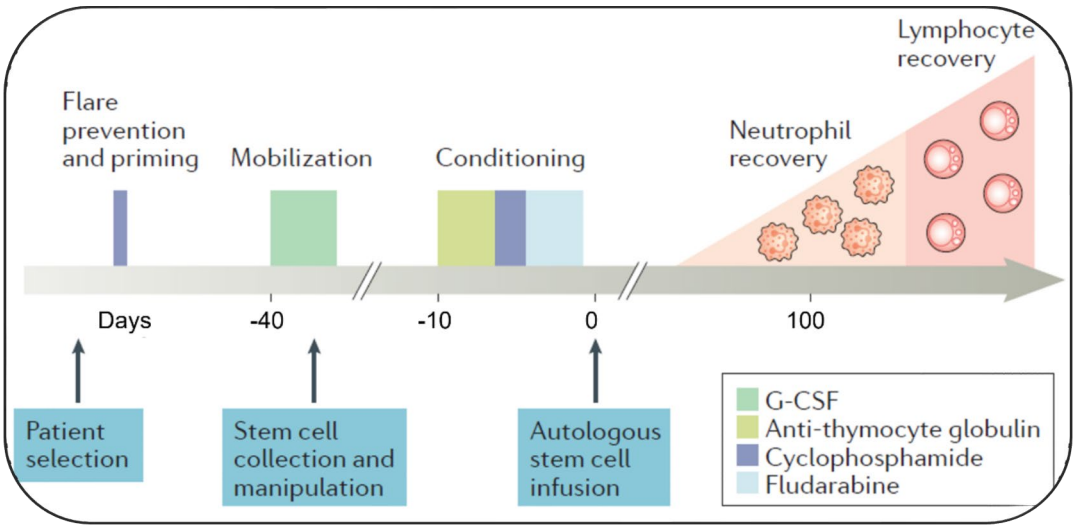
It may also include (less likely):

- Respirologist, Nephrologist, Dermatologist, Fertility specialist.

After the work up and meetings are completed, the transplant team will decide if there are reasons the transplant should not be considered. If cleared for transplant and you have decided to proceed then the transplant is arranged (usually within 3 months of starting the referral, assuming most of the pretransplant tests have been completed before the referral).

What to expect during HSCT:

Most likely you will be on immunosuppression medications or medications designed to control the immune system before the transplant. These will need to be stopped before starting the transplant. You will then have your blood-forming stem cells mobilized and collected (outpatient process in Calgary that takes 2-3 weeks), then be admitted to the Arthur Child Comprehensive Cancer Centre in Calgary to get the conditioning chemotherapy and get treatment for the early toxicities of the chemotherapy. Your admission length will vary based on how well you tolerate the transplant, typically one month, sometimes longer. The process is graphically shown in the figure below:



What Happens After AutoHCT:

At 2-3 months post-transplant you will return home, assuming no significant complications. You will be immunocompromised meaning you will be at increased risk of infection. It will take 1-2

years before your immune system has recovered to normal. You will need to repeat your childhood vaccinations. You will need regular follow up with your primary Rheumatologist and will need to see the Calgary transplant team of specialists at 6 months, 1 year, and then yearly for up to 5 years following your transplant. You will also have yearly investigations and blood work to do to monitor your progress and to watch for complications or relapse.

In case of transplant success, you will be off all immunosuppressive medications. However, there might still be a need for other medications to manage esophageal or intestinal symptoms, Raynaud's, or other organ symptoms which may be lifelong.
In case of transplant success, work or school can be typically started at 6-12 months post-HCT.

Patients from outside Calgary or out of Province patients:

1. Calgary, Alberta is the AutoHCT program for SSc for Western Canada.
2. Your local Rheumatologist will need to refer you to the transplant team for evaluation and transplantation.
3. If accepted you will need to be in Calgary for about 4 months for pretransplant care, the transplant, and posttransplant care.
4. You will need to travel back to Calgary for long-term follow up appointments as not all centers have the specialists needed for the transplant evaluations. It is also important to centralize most of the data collection for the transplant and systemic sclerosis evaluations. You will still follow up with your local Rheumatologist for regular visits. Patients from the Edmonton and surrounding area will follow up for the yearly Rheumatology appointment in Edmonton with Dr Mo Osman but will still need to see the Hematologist in Calgary.
5. After 2-5 years, or if your SSc has relapsed, you will be discharged from the program to follow up with your local Rheumatologist.
6. Important Social and Financial Considerations:
    a. A caregiver (a relative or a friend) is required to stay with the patient in Calgary for a minimum of one month after hospital discharge. Ideally the caregiver should stay with the patient in Calgary for a total of 4 months (1-2 months pre-transplant and 2-3 months post-HCT)
    b. Despite the inpatient and outpatient medical care, including inpatient medications, are fully covered, there are important out-of-pocket expenses for patients who live >1 h car ride from Calgary. Here are the estimates:
        i. Accommodation in Calgary at $1000-2000/month x 4 months = $4000-8000
        ii. In-Calgary transportation at $1000 (if accommodation is not within walking distance from Arthur Child Comprehensive Cancer Centre)
        iii. Co-pays for outpatient medications: $500-3000, assuming 80% is paid by patient's insurance. If patient is on provincial disability benefits, the drugs should be fully covered
        iv. Transportation from home to Calgary and back. Sometimes covered by a charity (e.g., Hope Air)

v. Other Expenses that should be considered are meals in Calgary. Meals for caregiver should also be considered. If caregiver has to take a leave from work, s/he can apply for Caregiver Benefits (55% of wage to a max of ~$600/week in Alberta)
vi. Total of the out-of-pocket expenses: $5,500-12,000 plus the Other Expenses, plus transportation from home to Calgary and back.

Transplantation for Germ Cell Tumours

Presented by: Doug Stewart
Updated by: Robert Puckrin

Summary

- High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is indicated in second- or third line therapy (i.e. as therapy for 1st or 2nd relapse) for patients with advanced germ cell tumor. Patients in first relapse who are likely to be cured with conventional dose chemotherapy (CDCT) alone such as TIP include those with low International Prognostic Factor Study Group (IPFSG) scores and those with gonadal or retroperitoneal primary site who have achieved a CR or a marker-negative PR lasting >6 months prior to their first relapse. However, patients in first relapse who are unlikely to be cured with CDCT alone should be considered for HDCT as part of initial salvage therapy, including those with higher IPFSG scores, incomplete response to first-line cisplatin-based therapy, primary platinum refractory disease, or relapse 6 months or less after achieving a marker-negative PR. For patients treated with CDCT in the initial salvage setting, HDCT remains an option in the third-line setting, should subsequent relapses occur. Patients with a late relapse >2 years after completing initial chemotherapy or growing teratoma syndrome typically have chemoresistant disease and are prioritized for surgical resection.
- Stem cell mobilization at our center has typically been performed using the second cycle of salvage bridging chemotherapy (e.g. TIP: paclitaxel 175 mg/m2 d1, ifosfamide 1.67g/m2 d1-3, cisplatin 33 mg/m2 d1-3, G-CSF 5-10mcg/kg/d starting day 9, and apheresis scheduled days 14-16). Other strategies include mobilization using GCSF alone and then proceeding directly to HDCT, or mobilization using 1-2 cycles of TI (paclitaxel and ifosfamide) chemotherapy. Of note, demonstrating a response to CDCT is not necessarily required since HDCT can still achieve durable remissions in a subset of patients with platinum-refractory disease.
- Standard HDCT conditioning for GCT involves tandem transplants using 2 cycles of high-dose Carboplatin 700 mg/m2/d plus Etoposide 750 mg/m2/d, both given d-5,-4,-3 before ASCT. A minimum of 1-2 million CD34+ cells/kg is required for each cycle of HDCT. The second cycle of HDCT is given after recovery of granulocyte and platelet counts, unless there was a grade 4 nonhematologic toxic effect or no response to the first course. In general, the time between day 0 ASCT#1 and day 0 ASCT#2 is only 4-5 weeks.

Background

Germ cell tumors (GCTs) account for less than 1% of all cancers; however, they represent the most common malignancy in young men between the ages of 15 and 35 years. Approximately 70% of patients with advanced disease are cured with conventional-dose, platinum-based chemotherapy. For patients with advanced disease the current standard first-line therapy is 3-4 cycles of cisplatin, etoposide and bleomycin (BEP). There is no role for high-dose chemotherapy (HDCT) and

autologous stem cell transplantation (ASCT) in the first-line treatment of patients with germ cell tumours[1]. Patients who do not achieve long-term remission with initial chemotherapy are still often curable with second- and even third-line treatment strategies. Options include cisplatin and ifosfamide with either paclitaxel (TIP) or vinblastine (VIP) with durable complete response (CR) rates of up to 63% in phase II trials in well-selected patients. Another salvage approach is the use of HDCT and ASCT which has demonstrated long-term remissions primarily in single-arm and retrospective studies.

Stem Cell Transplantation in GCT

In 2007, Indiana University published a large retrospective evaluation of their experience using high dose carboplatin and etoposide in 184 consecutive patients[2]. Most patients (73%) were treated in the initial salvage setting. The high-dose regimen consisted of two cycles of 700 mg/m2 of carboplatin plus 750 mg/m2 of etoposide, both given intravenously 5, 4, and 3 days before ASCT. Four-year PFS was 63% for the study cohort. In a 2017 update of 364 consecutive patients with GCT who progressed after cisplatin-based chemotherapy and received HDCT, the 2-year PFS was 60% and 2-year OS was 66% (Figure 1)[3]. Patients with late relapse of GCT >2 years after previous therapy were excluded. In a multivariable analysis, factors associated with disease progression included use of HDCT as third-line or later therapy, platinum-refractory disease (defined as tumor progression within 4 weeks of cisplatin-based chemotherapy), mediastinal primary tumor site, nonseminoma histology, intermediate- or poor-risk IGCCCG disease at the time of GCT diagnosis, and human chorionic gonadotropin >1,000 mIU/mL at initiation of HDCT. However, durable remissions were still reported in 20-40% of patients with these high-risk features (Table 1). There were 9 (2.5%) treatment-related deaths and 5 (1.3%) patients developed therapy-related leukemia.

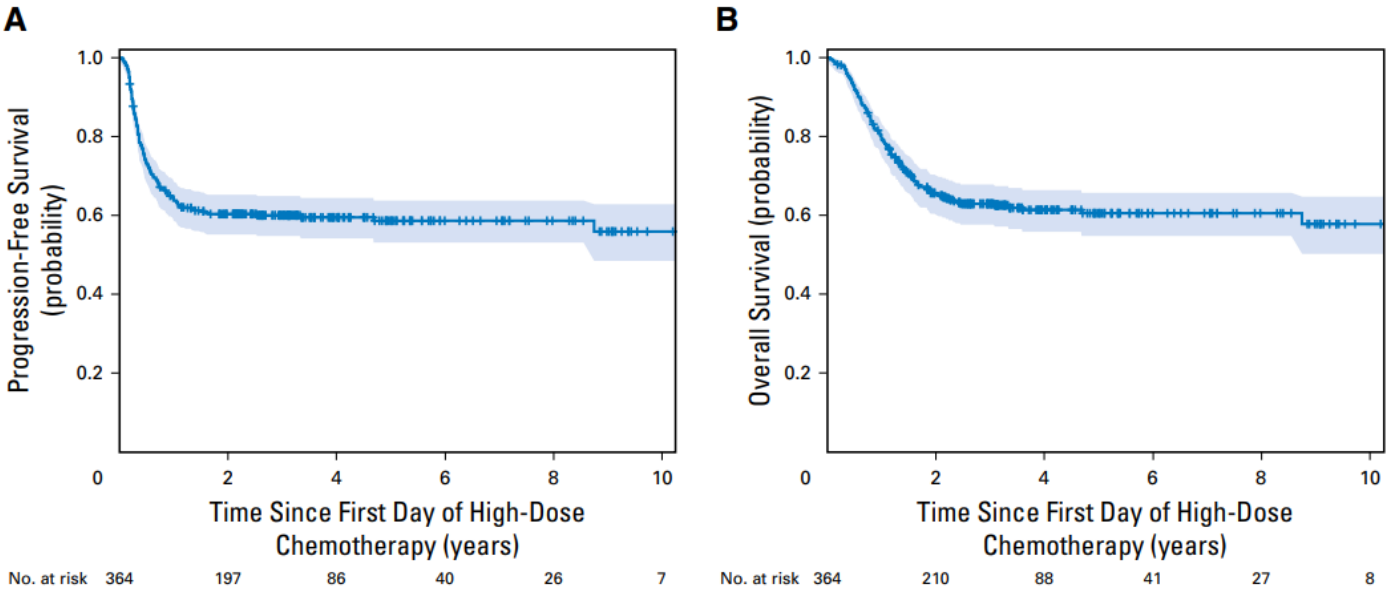


Figure 1: Outcomes of HDCT for relapsed GCT at Indiana University

Variable (no. of patients)	2-year PFS, %	*P**
High-dose chemotherapy		0.03
Second line (303)	63	
Third line or later (61)	49	
Platinum sensitivity		<0.001
Sensitive (242)	75	
Refractory (122)	33	
Location of primary tumour		<0.001
Testis/RP (344)	63	
Mediastinum (20)	23	
Tumour histology		<0.001
Seminoma (79)	90	
Nonseminoma (285)	52	
Initial IGCCCG risk		<0.001
Good (151)	82	
Intermediate (39)	58	
Poor (174)	43	
Serum AFP, ng/mL		
< 1,000 (336)	62	0.05
≥ 1,000 (28)	42	
Serum hCG, mIU/mL		
< 1,000 (274)	69	<0.001
≥ 1,000 (90)	37	
Age (continuous variable)	NA	0.44

Table 1: Outcomes of HDCT in different subgroups of patients with relapsed GCT at Indiana University

HDCT vs CDCT for relapsed GCT

The IT-94 randomized Phase III trial compared HDCT to conventional dose chemotherapy (CDCT) in the salvage setting[4]. This multicenter international study enrolled 280 patients from 43 institutions in 11 countries. The trial compared the efficacy of four cycles of CDCT using etoposide/ifosfamide/cisplatin (VIP)/VeIP versus three cycles of the same CDCT followed by one cycle of HDCT using carboplatin (200–550 mg/m2), etoposide (1800 mg/m2) and cyclophosphamide (200 mg/kg) followed by autologous stem cell rescue. Although no survival benefit was observed for HDCT, the interpretation of the trial is limited by the fact that it lacked sufficient statistical power, patients refractory to first-line platinum-containing chemotherapy were excluded, and that only one cycle of HDCT was provided while those studies which reported an advantage of HDCT over historical results with CDCT included two or more HDCT cycles.

Data from a large multicenter, international retrospective analysis of initial salvage chemotherapy in approximately 1600 subjects were reported in 2011[5]. Approximately equal numbers of patients were treated with CDCT and HDCT. Overall, PFS and OS were found to be superior for patients treated with HDCT as compared with CDCT. On multivariable analysis, important prognostic factors were

identified that allowed patient stratification into five well-defined prognostic categories. Within these prognostic categories, PFS and OS remained superior for HDCT in each class with the exception of OS in the low-risk group. Despite the lack of randomized evidence, retrospective studies such as these support the consensus in international guidelines that HDCT is an effective second-line or third-line therapy for patients with relapsed metastatic GCT[6-8]. The ongoing Alliance 031102/EORTC 1407 (TIGER) trial is randomizing patients with relapsed GCT to HDCT versus conventional TIP chemotherapy and is expected to provide a definitive answer to the role for HDCT in GCT.

The optimal treatment approach for patients with relapsed metastatic GCT likely varies in accordance with underlying risk factors. Retrospective data suggests that patients with low-risk IPFSG scores may achieve comparable survival rates with CDCT versus HDCT[5]. Indeed, patients with gonadal or retroperitoneal primary site, who have achieved a CR or a marker-negative PR lasting >6 months prior to their first relapse, frequently achieve durable remissions with TIP. For patients treated with CDCT in the initial salvage setting, HDCT remains an option in the third-line setting, should subsequent relapses occur[3]. Conversely, patients with higher IPFSG score and those with incomplete response to first-line cisplatin-based therapy, primary platinum refractory disease, or who relapse 6 months or less after achieving a marker-negative PR, are usually considered for second-line HDCT. Although patients with primary mediastinal NSGCT or very high risk IPFSG scores experience less favorable outcomes with HDCT, the available evidence still supports the consideration of HDCT in these high-risk groups given that durable responses can be achieved in >20-30%[3, 5]. Patients with brain metastases may still benefit from high-dose carboplatin/etoposide conditioning, although surgery and/or radiation may first be required for symptomatic or hemorrhagic brain metastases[9]. In contrast, patients relapsing >2 years after first-line therapy and those with growing teratoma syndrome tend to be chemoresistant and should be prioritized for surgical approaches instead[6].

Stem cell mobilization

Demonstrating a response to CDCT is not necessarily required prior to HDCT in relapsed GCT, since HDCT can still achieve durable remissions in a subset of patients with platinum-refractory disease[3]. At Indiana University, patients with relapsed GCT typically undergo stem cell mobilization using G-CSF and then proceed directly to HDCT[3]. Bridging chemotherapy is not typically administered for patients with platinum-refractory disease, whereas an optional 1-2 cycles of bridging VIP is considered for patients with platinum-sensitive disease to control symptoms before HDCT. Due to the frequently urgent need for treatment and the resource and logistical constraints at our center, stem cell mobilization has typically been performed using the second cycle of bridging chemotherapy (e.g., TIP: paclitaxel 175 mg/m2 d1, ifosfamide 1.67g/m2 d1-3, cisplatin 33 mg/m2 d1-3), with G-CSF 5-10mcg/kg/d starting day 9 and apheresis scheduled days 14-16. However, difficulties with stem cell mobilization have been observed using TIP[10]. An alternative approach utilized at MSKCC and in the TIGER trial is to collect stem cells using 1-2 cycles of bridging TI chemotherapy and then proceeding to HDCT (paclitaxel 200 mg/m2 d1, ifosfamide 2g/m2 d2-4, GCSF 10mcg/kg from d4 until adequate

collection or neutrophil recovery, apheresis on days 11-14). A second cycle of TI may be used to mobilize additional stem cells if needed. Of note, as few as >1-2x10^6/kg CD34+ stem cells may be sufficient for each cycle of HDCT in GCT[11].

Sequential HDCT Cycles vs Single HDCT/ASCT for GCT

German investigators reported the results of a randomized trial that was designed to answer the question of whether multiple sequential HDCT cycles are superior to a single HDCT cycle[12]. Between November 1999 and November 2004, 211 patients with relapsed or refractory GCT were randomly assigned to treatment with either one cycle of conventional-dose VIP plus three additional cycles of high-dose carboplatin 1,500 mg/m2 and etoposide 1,500 mg/m2 (CE) over 3 days. Treatment in arm B involved three identical conventional dose cycles of VIP plus one additional cycle of high-dose carboplatin 2,200 mg/m2, etoposide 1,800 mg/m2, and cyclophosphamide 6,400 mg/m2 (CEC) given over 4 days. The investigators found no statistically significant differences in event-free survival (EFS), progression-free survival (PFS) or OS between the two groups. Toxicity was more severe within the single high-dose CECy arm with 16% treatment-related deaths as compared with 4% in the sequential high-dose CE arm, which led to the premature closure of the trial and a nonsignificant trend toward improvement in OS for the sequential arm. The final conclusion of the study is that 2-3 sequential high-dose cycles remain the standard of care when HDCT is used with curative intent during the treatment of GCT. Restaging tumor markers +/- imaging should be performed after cycle 1 of HDCT to document a response. Patients not responding to the first cycle of HDCT are unlikely to benefit from a second cycle and should be considered for surgical resection or palliative intent standard chemotherapy instead[13].

Prognostic Models

Lorch and colleagues presented the results of a large retrospective international multicenter analysis conducted by the International Prognostic Factor Study Group to identify prognostic groups for initial salvage therapy independent of regimen intensity[5]. This is the largest series ever reported and included approximately 2000 patients from 38 centers throughout 14 countries in Europe and North America. Seven factors were found to be significant for PFS on multivariate analysis including and overall scores were divided into five groups (Table 2). This is widely considered the standard predictive model in the relapsed/refractory setting.

Table 2. Prognostic models: international prognostic factor study group score

Factors		Points	
Primary site	Gonadal	0	
	Retroperitoneal	1	
	Mediastinal (NSGCT)	3	
Response to first-line therapy	CR/PR-	0	
	PR+/SD	1	
	PD	2	
Progression-free interval after first-line therapy	> 3 months	0	
	≤ 3 months	1	
Serum hCG level	≤ 1000 IU/l	0	
	>1000 IU/l	1	
Serum AFP level	Normal	0	
	≤1000 ng/ml	1	
	> 1000 mg/ml	2	
Liver, bone or brain metastases	Absent	0	
	Present	1	
Add points for preliminary score (0-10); regroup into category score: (0):0; (1-2): 1; (3-4): 2; (5 or more): 3 add histology points as below to category score to determine final risk category			
Histology	Seminoma	-1	
	NSGCT/mixed	0	
Stratification	Points	2-year PFS (%)	3-year OS (%)
Very low risk	-1	75	77
Low risk	0	51	66
Intermediate risk	1	40	58
High risk	2	26	27
Very high risk	3	6	6

AFP: α-feto protein; CR: Complete response; DFS: Disease-free survival; FFS: Failure-free survival; hCG: Human chorionic gonadotropin; NSGCT: Nonseminomatous germ cell tumour; OS: overall survival; PD: progression of disease; PFS: progression-free survival; PR-: partial response with negative markers; PR+: partial response with positive markers; SD: stable disease.

Alberta Results

In a study of 43 patients with median age 28 (range 19-56) who received single (n=18) or tandem (n=25) HDCT and ASCT for relapsed metastatic GCT in Alberta between 2000-2018, 2-year PFS was 44% and OS was 65%.

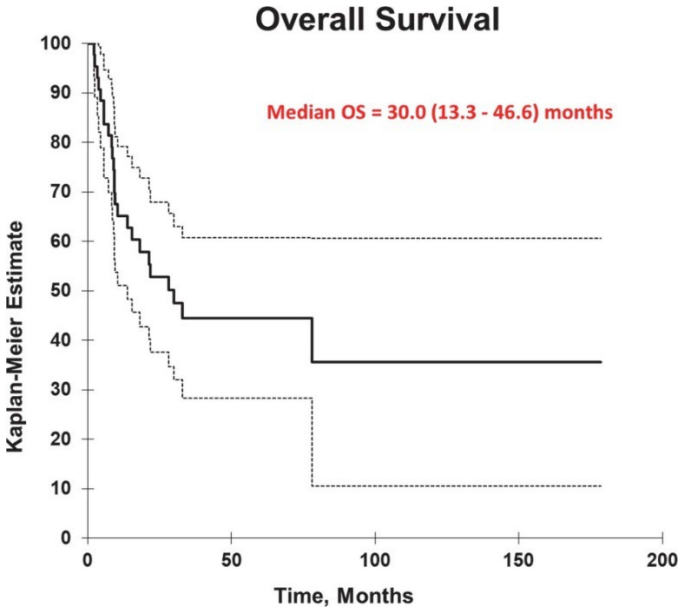


Figure 2: Overall survival after HDCT for GCT in Alberta

References

1. *Motzer RJ, Nichols CJ, Margolin KA, Bacik J, Richardson PG, Vogelzang NJ, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol. 2007;25(3):247-56.*
2. *Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007;357(4):340-8.*
3. *Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-Dose Chemotherapy and Autologous Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience. J Clin Oncol. 2017;35(10):1096-102.*
4. *Pico JL, Rosti G, Kramar A, Wandt H, Koza V, Salvioni R, et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol. 2005;16(7):1152-9.*
5. *Lorch A, Bascoul-Mollevi C, Kramar A, Einhorn L, Necchi A, Massard C, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. J Clin Oncol. 2011;29(16):2178-84.*
6. *Gilligan T, Lin DW, Aggarwal R, Chism D, Cost N, Derweesh IH, et al. Testicular Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(12):1529-54.*
7. *Hamilton RJ, Canil C, Shrem NS, Kuhathaas K, Jiang MD, Chung P, et al. Canadian Urological Association consensus guideline: Management of testicular germ cell cancer. Can Urol Assoc J. 2022;16(6):155-73.*
8. *Oldenburg J, Berney DM, Bokemeyer C, Climent MA, Daugaard G, Gietema JA, et al. Testicular seminoma and non-seminoma: ESMO-EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(4):362-75.*
9. *Kalra M, Adra N, Hanna N, Abonour R, Einhorn LH. High-dose chemotherapy plus peripheral blood stem cell transplantation for patients with relapsed germ cell tumors and active brain metastases. Cancer. 2020;126(6):1202-7.*
10. *Rick O, Bokemeyer C, Beyer J, Hartmann JT, Schwella N, Kingreen D, et al. Salvage treatment with paclitaxel, ifosfamide, and cisplatin plus high-dose carboplatin, etoposide, and thiotepa followed by autologous stem-cell rescue in patients with relapsed or refractory germ cell cancer. J Clin Oncol. 2001;19(1):81-8.*
11. *Chovanec M, Adra N, Abu Zaid M, Abonour R, Einhorn L. High-dose chemotherapy for relapsed testicular germ cell tumours. Nat Rev Urol. 2023;20(4):217-25.*
12. *Lorch A, Kleinhans A, Kramar A, Kollmannsberger CK, Hartmann JT, Bokemeyer C, et al. Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. J Clin Oncol. 2012;30(8):800-5.*
13. *Al-Ezzi EM, Zahralliyali A, Hansen AR, Hamilton RJ, Crump M, Kuruvilla J, et al. The Use of Salvage Chemotherapy for Patients with Relapsed Testicular Germ Cell Tumor (GCT) in Canada: A National Survey. Curr Oncol. 2023;30(7):6166-76.*

Complications

Graft-vs-Host Disease

Presented by: Jan Storek

Summary

- **Prophylaxis**
  - For matched sib or unrelated donor HCT, standard GVHD prophylaxis consists of
    - Antithymocyte globulin (ATG, Thymoglobulin) 4.5 mg/kg,
    - Cyclosporine A (CSA) starting with 2.5 mg/kg IV bid on day -1, targeting trough levels of 200-400 ug/L until day 56, and tapering to zero by day 84, and
    - Methotrexate (MTX) on day 1, 3, 6 and 11.
  - For haploidentical donor HCT, standard GVHD prophylaxis consists of
    - Posttransplant Cyclophosphamide (PTCy), 50 mg/kg on d +3 and 50 mg/kg on d +4,
    - Tacrolimus starting with 0.06 mg/kg on day +5, targeting trough levels of 5-15 ug/L until day 56, and tapering to zero by d 84, and
    - Mycophenolate mofetil (MMF) on d +5 through +35
- **Diagnosis** is made clinically, with the help of ancillary test like LFT, Histology, Schirmer's, or PFT
  - **Acute vs Chronic GVHD**:
    - If only skin/GI/liver manifestations of GVHD (see Common signs in Appendix 1) without a diagnostic sign of cGVHD (at any time since HCT), it is aGVHD.
    - If skin/GI/liver/eye/mouth/lung/genital manifestations of GVHD with a diagnostic sign of cGVHD (at any time since HCT), it is cGVHD.
- **Grading**
  - aGVHD is graded per 1994 Consensus criteria
    - Grade 1 = Maculopapular rash covering <50% BSA
    - Grade 2-4 = Maculopapular rash covering >50% BSA or gut or liver involvement
  - cGVHD is scored per 2017 NIH criteria
    - Mild = Max 2 organs involved to a mild degree, lungs not involved
    - Moderate-Severe = 3+ organs involved to a mild degree, or any organ involved to moderate or severe degree, or lungs involved (even to a mild degree)
- **Therapy (initial)**
  - Grade 1 aGVHD or Mild cGVHD are treated topically or with observation only
  - Grade 2-4 aGVHD is treated with prednisone 2–2.5 mg/kg/d or equivalent. If response, taper over 2-3 months.
  - Moderate-Severe cGVHD is treated with prednisone 1 mg/kg/d or equivalent. If response, taper over 6-9 months.
  - For patients developing GVHD on a calcineurin inhibitor (CNI), the CNI is continued. For patients off CNI, CNI may be added to the steroid.

- **Next Line Therapy**
  - Indications for moving from initial to next line therapy:
    - For aGVHD, worsening after 3-5 days, no improvement after 5-7 days, incomplete response after >28 days, or inability to taper methylprednisolone to <0.5 mg/kg/d or prednisone to <0.6 mg/kg/d
    - For cGVHD, worsening after 1-2 weeks, no improvement after 4-8 weeks of prednisone >0.5 mg/kg/d, or two failed attempts at prednisone taper necessitating prednisone dose increase to >0.25 mg/kg/d
  - First choice next line therapy: Ruxolitinib 10 mg bid orally
  - Second choice/subsequent next line therapy for aGVHD is undefined. Extracorporeal photopheresis (ECP) or sirolimus can be tried. Palliation should be considered.
  - Second choice/subsequent next line therapy for cGVHD may include ECP, sirolimus, imatinib, rituximab, or ibrutinib.
  - Clinical trial is always the preferred option as results with any next line therapy have been suboptimal.

Background

Despite over 50 years of experience with allogeneic stem cell transplantation, aGVHD remains the main cause of death of patients in remission after this treatment, and cGVHD is associated with not only mortality, but mainly poor quality of life long-term. Risk factors may include HLA disparity, transplantation from an unrelated donor, female-to-male transplants, parity of female donor, recipient or donor age, peripheral blood stem cells (PBSC) vs marrow, or seropositivity for/reactivation of some herpes viruses. In Alberta, per analysis of HCT recipients from HLA matched sibling donors (MSD) or 7-8/8 HLA matched unrelated donors (URD) whose GVHD prophylaxis consisted of ATG, CSA, and MTX, the only risk factor for aGVHD was non-MSD and CMV D-R+ serostatus (donor negative, recipient positive), and the only possible risk factor for cGVHD was sex combination other than male donor with male recipient[1].

The main target organs for aGVHD are the skin, the liver, and the gut. Clinical features range from localized erythematous skin rash to bullae and moist desquamation. Acute liver injury manifestation ranges from mildly abnormal liver enzymes (predominantly cholestatic) to severe hyperbilirubinemia. Gut injury manifestations range from nausea, vomiting, and diarrhea to severe abdominal pain and ileus. Chronic GVHD may involve virtually any organ, most frequently the skin, the gut, the liver, the eyes, the mouth, the lungs, and genitalia. Details on clinical manifestations are in Appendix 1.

Prophylaxis of GVHD

Our standard GVHD prophylaxis is

- ATG + CSA + MTX for MSD and URD HCT[1], and
- PTCy + Tacrolimus + MMF for haploidentical HCT. The PTCy+Tacro+MMF prophylaxis can also be used for MSD or URD HCT if a patient cannot tolerate ATG (eg, severe infusional reaction to the first dose) or MTX (eg, effusions)[2, (De Jong CN et al: randomized study of PTCy+CSA vs MMF+CSA presented at ASH 2019)].

Other GVHD prophylaxes, used at other centers or evaluated in research, include

- CNI (CSA or Tacrolimus) + antimetabolite (MTX or MMF)
  - Time-honored GVHD prophylaxis for MSD and URD HCT, used since 1980's, may still be the "gold standard" if paired with marrow graft (60% cGRFS and 84% OS in US BMT CTN 1301, not inferior to PTCy with marrow graft or CD34 selected PBSCs (https://www.hematologyandoncology.net/supplements/highlights-in-graft-vs-host-disease-from-the-2021-transplantation-cellular-therapy-tct-meetings-of-the-astct-and-the-cibmtr/).
    - The reason we prefer to combine CNI and antimetabolite with ATG in the MDS/URD setting is that with peripheral blood stem cell (PBSC) graft the addition of ATG results in lower incidences of aGVHD and cGVHD without negatively impacting relapse, which improves cGRFS (moderate-severe chronic GVHD- and relapse-free survival) and possibly also OS[3,4]. The reason we combine CNI and antimetabolite with PTCy in the haploidentical setting is that in the 1980's haploidentical HCT with CNI + antimetabolite had dismal outcomes and outcomes became acceptable only when PTCy was added, initially by the Johns Hopkins group and more recently by most centers in N.America and Europe. In China, ATG in combination with CNI + antimetabolite is frequently used for haploidentical HCT with good outcomes[5-8]. We might adopt it for haploidentical HCT in the future, if a randomized study shows superiority of the ATG-based vs the PTCy-based GVHD prophylaxis.
    - Re choice of CNI, there is no difference between CSA and tacrolimus in terms of OS. CSA may be associated with more grade 2-4 aGVHD but possibly less relapse and may be less nephrotoxic[9-12].
    - Re choice of antimetabolite, there is no difference between MTX and MMF in terms of OS. MTX may be associated with less grade 2-4 or 3-4 aGVHD but greater toxicity (e.g., stomatitis)[13-16].
- Sirolimus + CNI + MTX or MMF
  - Has been evaluated only in the setting of nonmyeloablative HCT, where it was superior to CNI+MMF[17]. We do not use it as busulfan followed by sirolimus can result in a high incidence of liver venoocclusive disease/sinusoid obstruction syndrome[18] or microangiopathic hemolysis[19].

- CD34 cell enriched graft, without any posttransplant immunosuppressive therapy (IST)
  - Associated with a high mortality due to infections and possibly relapse (retrospectively reviewed by Montoro et al[20], prospectively studied in US BMT CTN 1301 (https://www.hematologyandoncology.net/supplements/highlights-in-graft-vs-host-disease-from-the-2021-transplantation-cellular-therapy-tct-meetings-of-the-astct-and-the-cibmtr/). More studies are needed to determine whether this disadvantage is outweighed by the advantage of reducing aGVHD and cGVHD.
- Naïve T cell-depleted graft
  - Promising given low mortality due to infections and low incidence of cGVHD[21], but more studies are needed to determine whether this advantage may be outweighed by increased incidence of relapse.
- Alpha/beta T cell-depleted graft, with or without B cell depletion
  - Promising in pediatric HCT[22], more studies are needed in adult HCT.
- PTCy + ATG + CNI
  - Promising in matched URD setting[23], but more definitive studies are needed.

ATG + CSA + MTX details

Drug	Dose	Days	Route
Cyclosporine*	2.5 mg/kg every 12 h IV	-1 until oral feasible, then PO** every 12 h until day +56, then taper to zero by day +84	IV, PO
Methotrexate	15 mg/m^2	Day +1	IV
	10 mg/m^2	Day +3	IV
	10 mg/m^2	Day +6	IV
	10 mg/m^2	Day +11	IV
Thymoglobulin	0.5 mg/kg	Day -2	IV
	2 mg/kg	Day -1	IV
	2 mg/kg	Day 0***	IV

* Adjust dose to maintain trough plasma level 200 – 400 µg/L

** Convert IV dose resulting in therapeutic trough levels to PO dose by multiplying the IV dose 2.5-times.

*** If day 0 is postponed by one day from the originally planned day 0 (e.g., because PBSCs are collected over two days instead of one day), the last dose of ATG is infused on the planned day 0, i.e., true day -1.

Methotrexate Administration and Adjustment Guidelines

The first dose of methotrexate is given on day +1, at least 24 hours following infusion of stem cell product. Dosage adjustments will be made for renal and hepatic function, and for patients with severe mucositis or known fluid collections (pleural effusions or ascites). Dosage reductions between categories are additive: The final dosage reduction is the sum of dosage reductions for renal or hepatic dysfunction, mucositis, and fluid collections (below).

Dosage adjustment for hepatic dysfunction*

Direct Bilirubin (micromoles/litre)	% Dose Reduction
< 34	0
34-50	25
51-100	50
> 100	100

* Hyperbilirubinemia purely due to CSA (negative abdominal ultrasound, no infection such as bacteremia) is not a reason for dose reduction

Dosage adjustment for renal dysfunction

Creatinine Clearance (mL/minute)	% Dose reduction
>50	0
40-50	50
<40	100

Mucositis. Methotrexate should be completely withheld in the presence of severe mucositis defined as impending airway compromise. If no impending airway compromise, no reduction is needed.

Fluid collection. If clinically-significant fluid collections are present they should be drained. If they can be successfully drained, reduce methotrexate by 25%. If they cannot be drained, methotrexate should be withheld.

Folinic acid 5 mg IV q 6 h is given 24 hours after each dose of methotrexate, and continued until 12 h before the next dose of methotrexate or, in case of the last dose, until ANC>0.5/nL.

PTCy + Tacrolimua + MMF details

Drug	Dose	Days	Route
Cyclophosphamide	50 mg/kg (actual, >30% -> AIBW)	+3, +4	IV, in ½ L in NS
Tacrolimus	0.06 mg/kg (ideal) bid	+5 until +56/84*	PO**
MMF	1 g bid PO	+5 until +35	PO or IV
MESNA	12.5 mg/kg qid (actual/AIBW)	+3, +4	IV

Abbreviations: AIBW = adjusted ideal body weight; NS = normal saline; IV = intravenous; PO = per oral; QID = 4 times a day.
* Target trough plasma level of 5-15 ug/L until day 56, then taper to zero by day 84.
** If patient cannot take PO, convert to IV, dividing the PO dose by 3.

Alternative if CNI, MTX, or MMF is not tolerated

Up until 2022, our guideline recommended to switch a patient not tolerating CSA to prednisone at the doses given below (next paragraph). A retrospective review of local data in 2022 showed that patients who prematurely discontinued CNI due to intolerance and were switched to corticosteroid prophylaxis had increased risks of grade II-IV and grade III-IV acute GVHD and GVHD-related NRM compared to those who received continuous CNI prophylaxis (Puckrin et al, submitted). Thus, in 2022 the guideline was changed to the following:

CNI prophylaxis should be continued whenever possible – the medical team should tolerate mild/moderate renal dysfunction. A less favored option is to target lower cyclosporine trough levels. This option should ideally be avoided between day 15 and 28, as targeting 200-400 appears important between day 15 and 28 whereas lower target may be acceptable before day 15 or after day 28[24]. For those with severe toxicities which necessitate discontinuation of CNI, we now recommend combining MMF (1g BID until day +84) with corticosteroids according to the following schedule:

- Days 7-14 methylprednisolone 0.5 mg/kg IV
- Days 15-29 methylprednisolone 1 mg/kg IV
- Days 30-45 prednisone 0.5 mg/kg
- Days 45-60 prednisone 0.25 mg/kg
- Days 61-84 prednisone taper to zero

Patients planned to get CNI + MMF who cannot tolerate MMF may instead receive a corticosteroid until day 35 at 50% above doses in addition to continuing the CNI. Similar approach can be considered for patients for whom total MTX dose needs to be reduced to <50%.

Therapeutic Monitoring and Dosing of CNI

Cyclosporine A (CSA) trough plasma level target for GVHD prophylaxis is 200-400 ug/L until day 56, then taper to zero by day 84, providing there is no evidence of GVHD. For non-malignant indications (e.g., aplastic anemia), CSA taper is initiated on day 180.

CSA Neoral® for oral use is available as a capsule (10mg, 25mg, 50mg, 100mg) and as an oral solution (100mg/ml). CSA Sandimmune® is for IV use. Initial dose is 2.5mg/kg IV q12h or 6.25mg/kg PO q12h if starting on day -1. This dosing typically results in levels higher than 400 ug/L, which requires subsequent dose reduction. If CSA is started later (eg, after day 84 for new onset grade 2-4 aGVHD or moderate-severe cGVHD), 2.0-2.5 mg/kg PO typically results within three days in the therapeutic level of 200-400 ug/L.

Conversion of IV to oral requires a 2.5 to 3-fold increase in dosage.

The following algorithms can be utilized in guiding dose adjustment:

CSA level	Adjustment
<200 ug/L	Increase by 25%
200-400 ug/L	No change
350-400 ug/L	Consider decreasing by 25% if level trending upwards
400-450 ug/L	Decrease by 25%
>450 ug/L	Hold 1-2 doses, decrease by 25-50%

Inpatient, trough levels are drawn three times a week. If infused intravenously, CSA blood specimen should not be drawn from the same line used for administration. Outpatient, levels are drawn weekly, at a minimum. Consider repeating levels after 2-4 doses after a dose adjustment or the initiation/discontinuation of an interacting medication. For cGVHD, once maintenance dose is established for patients on long term CSA, frequency of trough level collection may be decreased to a monthly or as needed basis. In addition to monitoring drug levels, regular monitoring should also include blood pressure, CBC, serum electrolytes (Mg, K), renal function, hepatic function, and CMV and EBV PCR. Lower than the above recommended target levels may be used in case of renal or hepatic impairment, except for pure hyperbilirubinemia due to CSA.

CSA is a substrate and inhibitor of CYP3A4 and P-glycoprotein. Additional monitoring and dose adjustment may be required when starting or stopping drugs that inhibit or induce CYP3A4. Renal function should be closely monitored with co-administration of drugs that might exhibit additive/synergistic nephrotoxicity with CSA.

Patients are reminded to take CSA consistently with or without food to minimize variability. Capsules should be kept in the foil packaging until dose is ready to be taken. Patients are asked to leave capsules open to the air for no more than 15 minutes if needed to tolerate CSA's characteristic smell. Oral solution should be diluted in a glass container. Plastic and styrofoam containers should not be used. Orange juice and apple juice are recommended diluents by the manufacturer. Chocolate milk has also been used. Grapefruit and pomegranate juice should be avoided due to their interaction with the CYP450 system. The provided syringe can be wiped clean, but not washed as it may result in dose variation.

Tacrolimus trough plasma level target for GVHD prophylaxis/treatment is 5-15 ug/L. Routine taper (in the absence of GVHD) is the same as for CSA, i.e., from day 56 with the goal of reaching zero by day 84.

Tacrolimus (Prograf®) is available for oral use as an immediate release capsule (0.5mg, 1mg or 5mg) and for IV use. A 1mg/ml oral suspension can also be compounded. Advagraf® extended release capsules are not recommended for HCT setting. Initial dose of Prograf is 0.03 mg/kg/d IV as a continuous infusion or 0.06 mg/kg/day PO q12h if starting on day -1 or in the first several days after

HCT. This dosing typically results in levels higher than 15 ug/L, which requires subsequent dose reduction. If tacrolimus is started later (eg, after day 84 for new onset grade 2-4 aGVHD or moderate-severe cGVHD), 0.02 mg/kg IBW PO q12h typically results within three days in the therapeutic level of 5-15 ug/L.

Conversion of IV to oral requires a 2.5-4 fold increase in dosage.

The following algorithm can be utilized in guiding dose adjustment:

$$\text{New dose} = \frac{(\text{current dose})(\text{target whole blood level})}{(\text{current whole blood level})}$$

As for CSA, tacrolimus blood specimens should not be drawn from the same line used for tacrolimus administration. Levels are drawn three times a week inpatient and at least once weekly outpatient, less frequently after stable levels in case of cGVHD. Consider repeating levels after 2-4 doses after a dose adjustment or the initiation/discontinuation of an interacting medication. In addition to monitoring the levels, regular monitoring should also include blood pressure, blood glucose, CBC, serum electrolytes (Mg, K), renal and hepatic function, and CMV and EBV PCR. Lower than the above recommended target levels may be used in case of renal or hepatic impairment.

Tacrolimus is a substrate of CYP3A4 and p-glycoprotein. Additional monitoring and dose adjustment may be required when starting or stopping drugs that inhibit or induce CYP3A4. Renal function should be closely monitored with co-administration of drugs that might exhibit additive/synergistic nephrotoxicity with tacrolimus.

Patients are reminded to take tacrolimus consistently with or without food to minimize variability. Grapefruit and pomegranate should be avoided due to their interaction with the CYP450 system.

Grading of aGVHD

For aGVHD grading, we use the 1994 Consensus Conference grading system.[25] To determine the overall grade of aGVHD, organ stages need to be determined first:

Organ Staging of aGVHD

Organ Stage	Skin	Liver	Gut
0	No rash	Total bilirubin < 34 umol/L	No diarrhea
1	Maculopapular rash <25% body surface area	Total bilirubin 34 to 50	Diarrhea 500 – 1000 mL/day or nausea with positive UGI biopsy
2	Maculopapular rash 25 – 50% body surface area	Total bilirubin 51 to 100	Diarrhea 1000 – 1500 mL/day
3	Maculopapular rash > 50% body surface area	Total bilirubin 101 to 250	Diarrhea 1500 – 2000 mL/day
4	Generalized exfoliative, ulcerative, or bullous dermatitis	Total bilirubin ≥250	Diarrhea >2000 mL/day or severe abdominal pain or ileus

Grading of aGVHD (determination of overall grade based on organ stages)

	Stage				
Grade	**Skin**		**Liver**		**Gut**
0	0	And	0	And	0
I	1-2	And	0	And	0
II	3	Or	1	Or	1
III	0-3	And	2 - 3	Or	2 – 4
IV	4	Or	4		any

Frequency of aGVHD grading: At initial diagnosis, at worsening, and generally once a week in the first 3 months postHCT.

Grading ("Scoring") of cGVHD

For cGVHD scoring, we use the 2014 NIH scoring system[26]:

Organ Scores of cGVHD:

	Score 0	Score 1	Score 2	Score 3
SKIN	No symptoms	<19% BSA with disease signs but NO sclerotic features	19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	>50% BSA OR deep sclerotic features "hidebound" (not able to pinch) OR impaired mobility, ulceration, or severe pruritis
MOUTH	No symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs with partial limitation of oral intake	Severe symptoms with disease signs on examination with major limitation of oral intake
EYES	No symptoms	Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 times daily) OR asymptomatic signs of keratoconjunctivitis sicca	Moderate dry eye symptoms partially affecting ADL (requiring drops >3 times daily or puntal plugs) WITHOUT vision impairment	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms) OR loss of vision caused by keratoconjunctivitis sicca
GI TRACT	No symptoms	Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	Symptoms associated with mild to moderate weight loss (5-15%)	Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs OR esophageal dilation
LIVER	Normal LFT	Bilirubin (total) normal ALT 180-300 U/L ALP ≥429 U/L	Bilirubin24-72 umol/L ALT >300 U/L	Bilirubin >72 umol/L
LUNGS	No symptoms FEV1 >80%	Mild symptoms (shortness of breath after climbing 1 flight of steps), or FEV1 60-79%	Moderate symptoms (shortness of breath after walking on flat ground), or FEV1 40-59%	Severe symptoms (shortness of breath at rest requiring O_2), or FEV1 ≤39%
JOINTS & FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fascitis, moderate decreased range of motion AND mild to moderate limitation of ADL	Contractures WITH significant decrease of range of motion AND significant limitation of ADL (unable to tie shoes, button shirt, dress self)
GENITAL TRACT*	No symptoms/signs	Mild signs*	Moderate signs*	Severe signs*

**** Genital signs:***

Female genitalia:

1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosus.
2) Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds.
3) Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia:

1) Mild: lichen planus-like feature;
2) Moderate: lichen sclerosus-like feature or moderate erythema;
3) Severe: phimosis or urethral/meatal scarring.

Global Score of cGVHD:

Mild cGVHD:

- **≤2 organs involved with max organ score 1, plus lung score 0**

Moderate cGVHD:

- **≥3 organs involved with max score 1, or**
- **≥1 organ (not lung) with a score of 2, or**
- **Lung score 1**

Severe cGVHD:

- **≥1 organ with a score of 3, or**
- **Lung score 2 or 3**

Frequency of cGVHD scoring: At initial diagnosis, at worsening, and at least every 3 months in the first year postHCT.

Treatment of GVHD (initial)

For grade 1 aGVHD and mild cGVHD, we use a topical corticosteroid (e.g., betamethasone 0.1% cream bid). Observation-only is also reasonable. For a list of topical/ancillary therapies, see Appendix 2.

For grade 2-4 aGVHD and moderate-severe cGVHD, systemic corticosteroids remain the cornerstone of treatment. An exception may be sirolimus for aGVHD[27], which should not be used in patients conditioned with busulfan[18,19]. Only ≤50% patients have a sustained complete or substantial partial response to a corticosteroid. Steroid-refractory or steroid-dependent patients usually have poor outcomes.

Dosing of systemic corticosteroids for initial therapy of grade 2-4 aGVHD and moderate-severe cGVHD has been derived from expert opinions. For aGVHD, we use 2.0-2.5 mg/kg/d prednisone (or equivalent), tapered over 2-3 months. For cGVHD, we use 1.0 mg/kg/d, tapered over 6-9 months.

Attempts of lowering the initial dose of prednisone for grade 2-4 aGVHD have been associated with unexciting results. Per a randomized study of starting with 1 vs 2 mg/kg/d, the primary endpoint of lowering the cumulative prednisone dose by >33% was not reached as many patients who started with 1 mg/kg/d needed incrementation to 2 mg/kg/d[28]. However, this may not apply to grade 2a aGVHD.

Grade 2a aGVHD is defined as biopsy-confirmed UGI GVHD (nausea/vomiting/anorexia) with or without mild LGI GVHD (diarrhea <1 L/d), rash <50% BSA, and no hepatic involvement. It can be treated with 1 mg/kg/d prednisone + oral beclomethasone dipropionate 1 mg qid, with or without budesonide 3 mg bid (recommended if diarrhea)[29,30]. If no response in 10 days, increase prednisone to 2.0-2.5 mg/kg. If response in 10 days, taper prednisone over one week.

Adding an immunosuppressive drug to a steroid has been unsuccessful both for aGVHD and cGVHD[31-35], except possibly for a CNI. The questionable benefit of adding a CNI to a steroid for first line treatment of cGVHD is based on expert opinions[36] and one randomized study of CSA+prednisone vs prednisone alone[37] which showed prednisone-sparing effect of the addition of CSA to prednisone, associated with a lower incidence of avascular necrosis, but no impact on cGVHD-related outcomes or OS. In a small study, tacrolimus had a 39% response rate in steroid-refractory patients[38]. In practice, many patients are already on CNI for prophylaxis. For the patients who are no longer on CNI, in Alberta we use the addition of CNI to prednisone optionally.

Next-Line Treatment of GVHD (Steroid-Refractory/Dependent)

Favorable outcomes following next-line (post-steroid) therapy have been infrequent with any therapy. Studies of next-line therapy suffer from small patient numbers, short-term follow up, lack of control arm, or cross-over design which makes the evaluation of impact on OS impossible. Thus, whether any additional treatment of steroid-refractory/dependent GVHD has a lasting benefit with acceptable toxicity has not been rigorously determined.

Only patients who failed systemic steroids should proceed to next-line therapy. Failure of systemic steroids has had multiple definitions. We use the EBMT-NIH-CIBMTR Task Force definition,[39] modified to a minor degree in REACH 2 and 3 trials[40,41], i.e.,

- For aGVHD, worsening after 3-5 days, no improvement after 5-7 days, incomplete response after >28 days, or inability to taper methylprednisolone to <0.5 mg/kg/d (prednisone to <0.6 mg/kg/d)
- For cGVHD, worsening after 1-2 weeks, no improvement after 4-8 weeks of prednisone >0.5 mg/kg/d, or two failed attempts at prednisone taper necessitating prednisone dose increase to >0.25 mg/kg/d

Ruxolitinib (Jak1/2 inhibitor) is our first-choice as it is the only post-steroid failure therapy clearly shown to be efficacious in randomized studies (REACH2 for aGVHD, REACH3 for cGVHD)[40,41].

However, the efficacy has been modest. Moreover, it is not known whether ruxolitinib improves OS, as both REACH1 and 2 had a cross-over design. In both studies, about one third of patients randomized to the control arm crossed over to ruxolitinib

In REACH2, ruxolitinib, 10 mg bid orally, was superior to standard care (other IST) for steroid-refractory grade 2-4 aGVHD. In this trial, 309 patients ≥12 years old were randomly assigned (1:1) to ruxolitinib versus the investigator's choice of therapy (mostly ECP). At day 28, ruxolitinib achieved superior rates of overall response (PR+CR) (62% vs 39%) and CR (34% vs 19%). Superiority of ruxolitinib was maintained at day 56 (40% vs 22% overall response). Treatment was discontinued in 72% patients receiving ruxolitinib and in 85% of patients in the control group; most discontinuation was due to lack of efficacy. The most common grade ≥3 toxicity with ruxolitinib was thrombocytopenia, and anemia, and possibly infections, particularly CMV. Despite impact of ruxolitinib on OS could not be evaluated due to the cross-over design, it is notable that 18-month OS was only ~40% in both arms (Table S6 of the published study[40]).

In REACH3, ruxolitinib, 10 mg bid orally, was superior to standard care (other IST) for steroid-refractory/dependent moderate-severe cGVHD. A total of 329 patients ≥12 years old were randomly assigned (1:1) to ruxolitinib versus the investigator's choice of therapy (mostly ECP). At 6 months, ruxolitinib achieved superior rates of overall response (50% vs 26%) and CR (7% vs 3%). Treatment was discontinued in 50% patients receiving ruxolitinib and in 74% of patients in the control group; most discontinuation was due to lack of efficacy. The most common grade ≥3 toxicity with ruxolitinib was thrombocytopenia, neutropenia, and anemia. Despite impact of ruxolitinib on OS could not be evaluated due to the cross-over design, it is notable that 12-month OS was 81% in the ruxolitinib arm and 84% in the control arm.

Dose reduction to 5 mg bid or 5 mg qd is required for cytopenias or renal or hepatic impairment.

For patients who have a response, ruxolitinib may be tapered gradually after 2 months (in aGVHD) or after 6 mo (in cGVHD). It is important that ruxolitinib is tapered gradually rather than discontinued abruptly or reduced rapidly, because a "withdrawal syndrome" that resembles systemic inflammatory response syndrome may be seen when ruxolitinib is discontinued in myelofibrosis.

Previous published experience (pre-REACH1/2) was limited to a retrospective study of 95 SR GvHD (acute or chronic) patients from 19 centres[42]. The dose in most patients was 5-10 mg bid, and the study showed an overall response rate of 81% with 46% complete remissions. Median time to response was 1.5 weeks. GVHD flared in only 7% of patients during steroid taper. The 6-month survival estimate was 79%, and the safety profile was favorable. Side effects included cytopenias and CMV reactivation. Our local experience with ruxolitinib for SR aGVHD in 2016-2020 includes 16 patients, with 5 CR, 6 PR/stable and 5 refractory (all GI). Local data for cGVHD has not been collected.

Extracorporeal Photopheresis.
For aGVHD, ECP has been evaluated only in retrospective studies.[43] In the largest one (n=128),[44] 77% patients achieved PR or CR. A higher response rate was noted for grade 2 (compared to 3-4) aGVHD. The response rates appear to be the best for skin-only aGVHD.[43] In Alberta, we have not been able to reproduce the relatively high response rate in published studies.

For cGVHD, ECP has been evaluated in 3 prospective studies. In the largest one (n=83), 44% patients achieved PR or CR. In another prospective study, the response rate was only 31% for skin disease and variable for other organs.[45] In a randomized study of 100 patients that was focused on patients with skin cGVHD, cutaneous PR or CR at 3 months was achieved in 40% ECP patients vs 10% controls (p=.002) and extracutaneous PR or CR was noted in 30% ECP patients vs 7% controls (p=.04).

Toxicity is low, virtually only CVC-associated infections and thrombosis.

Because of the relatively low toxicity and because, apart from ruxolitinib, ECP is the only next line therapy with efficacy documented in a randomized, albeit small, study, ECP is a good choice treatment added to or used instead of ruxolitinib, except when precluded by logistics (eg, patient lives too far from Calgary). Recommended schedule is 3x a week, alternatively Monday through Friday (daily) every other week. If no clinical benefit within 3 months (for cGVHD, earlier for aGVHD), discontinue ECP. If clinical benefit, attempt to taper, unless tapering other drugs is a higher priority.

Sirolimus.
For aGVHD, in a prospective phase 2 study in steroid-refractory (n=31) or intolerant (n=3) patients, PR+CR was achieved in 76% patients.[46] Similar response rate (86%) was described in a small retrospective study (n=22).[47]

For cGVHD, 38 of 47 (81%) patients experienced PR or CR in a retrospective study.[48]

Major side effects are hyperlipidemia, headache, poor wound healing, renal dysfunction, edema, cytopenias and hemolytic-uremic syndrome. Hemolytic-uremic syndrome is particularly problematic in patients treated concurrently with CNI. Sirolimus should not be used in the first 1-2 months after transplant if busulfan was used for conditioning and methotrexate was used for aGVHD prophylaxis, due to the high incidence of VOD/SOS and possibly also HUS.[18,19]

Initial dosing is 1-2 mg/day. The initial dose of sirolimus must be significantly reduced in patients concomitantly treated with azole or macrolide antibiotics.

Target therapeutic trough level is 5-15 ng/mL. The following algorithm can be utilized in guiding dose adjustment:

$$\text{New dose} = \frac{(\text{current dose})(\text{target whole blood level})}{(\text{current whole blood level})}$$

Sirolimus trough levels are initially drawn once weekly. Levels should be drawn 7 days after a dose adjustment or the initiation/discontinuation of an interacting medication. Once maintenance dose is established, frequency of trough level determination may decrease to a monthly or as needed basis. In addition to monitoring drug levels, regular monitoring should also include blood pressure, lipid panel, CBC, and renal function.

Sirolimus is a substrate of CYP3A4 and p-glycoprotein. Additional monitoring and dose adjustment may be required when starting or stopping drugs that inhibit or induce CYP3A4. When starting an azole, sirolimus dose should be preemptively halved. Analogously, when stopping an azole, sirolimus dose should be preemptively doubled.

Patients are reminded to take sirolimus consistently with or without food to minimize variability. The oral solution should be diluted with 60 ml of water or orange juice in a glass or plastic cup. Grapefruit and pomegranate juice should be avoided due to their interaction with the CYP450 system.

An advantage of ECP and sirolimus for Albertan patients is that no special approval (eg, STEDT) is needed.

The agents listed below have shown some promise only for cGVHD (not aGVHD) and require a special approval (eg, STEDT).

Rituximab*:* Objective responses of cGVHD were initially reported in more than 70% of patients, mainly with cutaneous and musculoskeletal manifestations[43]. True response rate in steroid-dependent/refractory patients is probably on the order of 50% (30% CR, 20% PR)[49]. Usual therapeutic scheme consist of 4 courses of rituximab at a dose of 375 mg/m^2, but significantly lower doses may be equally effective[50]. Side effects include infusion reactions, mild hypogammaglobulinemia and late neutropenia.

Imatinib*:* Small prospective studies, using imatinib at a dose of 100-400 mg/day, indicate response rate at 6 months between 50% and 80% of patients with cutaneous, eye, lung, and gastrointestinal cGVHD[43,51]. Myelosuppression, fluid retention and dyspnea are the most common side effects.

Ibrutinib*:* Ibrutinib, a BTK inhibitor, at 420 mg qd orally, was studied in 42 patients[52,53]. Five patients were not evaluable for response due to early discontinuation. Responses occurred in 29 (67%) of the 37 evaluable patients (9 CR, 19 PR), and were associated with meaningful steroid dose reduction. Sustained responses of >/=20, >/=32, and >/=44 weeks were seen in 20 (69%), 18 (62%), and 16 (55%) of the 29 responders, respectively. Death occurred in 9/42 (21%) patients, 2 due to relapse, 2 due to an infection, 3 due to GVHD, 2 unknown. Dose reductions were reported for 13 (31%) patients, mostly due to fatigue. Other side effects included nausea, diarrhea, muscle spasms, and bruising.

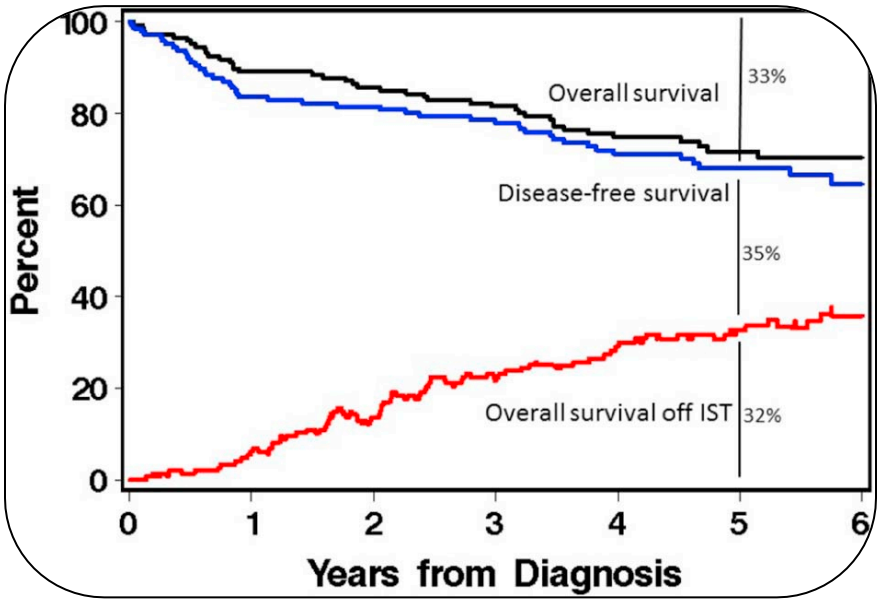
Mycophenolate Mofetil *(MMF):* In case series, the response rates to MMF is reported between 40% and 75%[43]. Side effects, including cytopenias, gastrointestinal discomfort and diarrhea, may require dose reduction or discontinuation. MMF can induce histopathologic changes of the GI tract mucosa which mimic intestinal GVHD[54]. A doubt on MMF efficacy has been shed by a randomized study of initial cGVHD with MMF+prednisone vs MMF alone, in which case MMF was not effective[35].

Infection Prophylaxis

Patients with chronic GVHD are immunosuppressed and their treatment with IST makes their immunosuppression even more severe. As these patients are at an increased risk of opportunistic infections, adequate surveillance and prophylaxis is necessary (see sections on infection prophylaxis).

Prognosis of Chronic GVHD

The prognosis continues to be poor. In a FHCRC study of 250 patients with moderate-severe cGVHD with median follow up >5 years, at 5 years since cGVHD diagnosis about 1/3 patients were dead, 1/3 patients alive and on systemic immunosuppressive therapy (IST), and 1/3 patients alive and off IST (Figure below).[55]



References

1. Ousia S, Kalra A, Williamson TS, et al. Hematopoietic cell transplant outcomes after myeloablative conditioning with fludarabine, busulfan, low-dose total body irradiation, and rabbit antithymocyte globulin. Clin Transplant 2020:e14018.
2. Bolanos-Meade J, Reshef R, Fraser R, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). Lancet Haematol 2019;6:e132-e43.
3. Walker I, Panzarella T, Couban S, et al. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. Lancet Oncol 2016.
4. Walker I, Panzarella T, Couban S, et al. Addition of anti-thymocyte globulin to standard graft-versus-host disease prophylaxis versus standard treatment alone in patients with haematological malignancies undergoing transplantation from unrelated donors: final analysis of a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol 2020;7:e100-e11.
5. Chang YJ, Wang Y, Mo XD, et al. Optimal dose of rabbit thymoglobulin in conditioning regimens for unmanipulated, haploidentical, hematopoietic stem cell transplantation: Long-term outcomes of a prospective randomized trial. Cancer 2017;123:2881-92.
6. Lin R, Wang Y, Huang F, et al. Two dose levels of rabbit antithymocyte globulin as graft-versus-host disease prophylaxis in haploidentical stem cell transplantation: a multicenter randomized study. BMC Med 2019;17:156.
7. Wang Y, Fu HX, Liu DH, et al. Influence of two different doses of antithymocyte globulin in patients with standard-risk disease following haploidentical transplantation: a randomized trial. Bone Marrow Transplant 2014;49:426-33.
8. Wang Y, Wu DP, Liu QF, et al. Low-dose post-transplant cyclophosphamide and anti-thymocyte globulin as an effective strategy for GVHD prevention in haploidentical patients. J Hematol Oncol 2019;12:88.
9. Hiraoka A, Ohashi Y, Okamoto S, et al. Phase III study comparing tacrolimus (FK506) with cyclosporine for graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28:181-5.
10. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood 2000;96:2062-8.
11. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. Blood 1998;92:2303-14.
12. Kanda Y, Kobayashi T, Mori T, et al. A randomized controlled trial of cyclosporine and tacrolimus with strict control of blood concentrations after unrelated bone marrow transplantation. Bone Marrow Transplant 2016;51:103-9.
13. Kharfan-Dabaja M, Mhaskar R, Reljic T, et al. Mycophenolate mofetil versus methotrexate for prevention of graft-versus-host disease in people receiving allogeneic hematopoietic stem cell transplantation. The Cochrane database of systematic reviews 2014:CD010280.
14. Chhabra S, Liu Y, Hemmer MT, et al. Comparative Analysis of Calcineurin Inhibitor-Based Methotrexate and Mycophenolate Mofetil-Containing Regimens for Prevention of Graft-versus-Host Disease after Reduced-Intensity Conditioning Allogeneic Transplantation. Biol Blood Marrow Transplant 2019;25:73-85.
15. Perkins J, Field T, Kim J, et al. A randomized phase II trial comparing tacrolimus and mycophenolate mofetil to tacrolimus and methotrexate for acute graft-versus-host disease prophylaxis. Biol Blood Marrow Transplant 2010;16:937-47.
16. Hamilton BK, Rybicki L, Dean R, et al. Cyclosporine in combination with mycophenolate mofetil versus methotrexate for graft versus host disease prevention in myeloablative HLA-identical sibling donor allogeneic hematopoietic cell transplantation. Am J Hematol 2015;90:144-8.
17. Sandmaier BM, Kornblit B, Storer BE, et al. Addition of sirolimus to standard cyclosporine plus mycophenolate mofetil-based graft-versus-host disease prophylaxis for patients after unrelated non-myeloablative haemopoietic stem cell transplantation: a multicentre, randomised, phase 3 trial. Lancet Haematol 2019;6:e409-e18.
18. Lewis C, Kim HT, Roeker LE, et al. Incidence, Predictors, and Outcomes of Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome after Reduced-Intensity Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 2020;26:529-39.

19. Rodriguez R, Nakamura R, Palmer JM, et al. A phase II pilot study of tacrolimus/sirolimus GVHD prophylaxis for sibling donor hematopoietic stem cell transplantation using 3 conditioning regimens. Blood 2010;115:1098-105.
20. Montoro J, Ceberio I, Hilden P, et al. Ex Vivo T Cell-Depleted Hematopoietic Stem Cell Transplantation for Adult Patients with Acute Myelogenous Leukemia in First and Second Remission: Long-Term Disease-Free Survival with a Significantly Reduced Risk of Graft-versus-Host Disease. Biol Blood Marrow Transplant 2020;26:323-32.
21. Bleakley M, Heimfeld S, Loeb KR, et al. Outcomes of acute leukemia patients transplanted with naive T cell-depleted stem cell grafts. J Clin Invest 2015;125:2677-89.
22. Locatelli F, Merli P, Pagliara D, et al. Outcome of children with acute leukemia given HLA-haploidentical HSCT after alphabeta T-cell and B-cell depletion. Blood 2017;130:677-85.
23. Salas MQ, Prem S, Atenafu EG, et al. Dual T-cell depletion with ATG and PTCy for peripheral blood reduced intensity conditioning allo-HSCT results in very low rates of GVHD. Bone Marrow Transplant 2020;55:1773-83.
24. Kwan ACF, Blosser N, Ghosh S, et al. Toward optimization of cyclosporine concentration target to prevent acute graft-versus-host disease following myeloablative allogeneic stem cell transplant. Clin Transplant 2022;36:e14732.
25. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995;15:825-8.
26. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389-401 e1.
27. Pidala J, Hamadani M, Dawson P, et al. Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. Blood 2020;135:97-107.
28. Mielcarek M, Furlong T, Storer BE, et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. Haematologica 2015;100:842-8.
29. McDonald GB, Bouvier M, Hockenbery DM, et al. Oral beclomethasone dipropionate for treatment of intestinal graft-versus-host disease: a randomized, controlled trial. Gastroenterology 1998;115:28-35.
30. Hockenbery DM, Cruickshank S, Rodell TC, et al. A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. Blood 2007;109:4557-63.
31. Alousi AM, Weisdorf DJ, Logan BR, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood 2009;114:511-7.
32. Bolanos-Meade J, Logan BR, Alousi AM, et al. Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. Blood 2014;124:3221-7; quiz 335.
33. Incyte Announces Results of Phase 3 Study of Itacitinib in Patients with Treatment-Naïve Acute Graft-Versus-Host Disease. 2020. (Accessed October 11, 2021, 2021, at https://www.businesswire.com/news/home/20200102005480/en/Incyte-Announces-Results-Phase-3-Study-Itacitinib#:~:text=Incyte%20Announces%20Results%20of%20Phase%203%20Study%20of,or%20non-relapse%20mortality%20compared%20to%20placebo%20plus%20corticosteroids.)
34. Couriel DR, Saliba R, de Lima M, et al. A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. Biol Blood Marrow Transplant 2009;15:1555-62.
35. Martin PJ, Storer BE, Rowley SD, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. Blood 2009;113:5074-82.
36. Wolff D, Gerbitz A, Ayuk F, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. Biol Blood Marrow Transplant 2010;16:1611-28.
37. Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. Blood 2002;100:48-51.
38. Kanamaru A, Takemoto Y, Kakishita E, et al. FK506 treatment of graft-versus-host disease developing or exacerbating during prophylaxis and therapy with cyclosporin and/or other immunosuppressants. Japanese FK506 BMT Study Group. Bone Marrow Transplant 1995;15:885-9.
39. Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant 2018;53:1401-15.
40. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. N Engl J Med 2020;382:1800-10.
41. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. N Engl J Med 2021;385:228-38.
42. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 2015;29:2062-8.

43. Shapiro RM, Antin JH. Therapeutic options for steroid-refractory acute and chronic GVHD: an evolving landscape. Expert review of hematology 2020;13:519-32.
44. Das-Gupta E, Greinix H, Jacobs R, et al. Extracorporeal photopheresis as second-line treatment for acute graft-versus-host disease: impact on six-month freedom from treatment failure. Haematologica 2014;99:1746-52.
45. Greinix HT, van Besien K, Elmaagacli AH, et al. Progressive improvement in cutaneous and extracutaneous chronic graft-versus-host disease after a 24-week course of extracorporeal photopheresis--results of a crossover randomized study. Biol Blood Marrow Transplant 2011;17:1775-82.
46. Hoda D, Pidala J, Salgado-Vila N, et al. Sirolimus for treatment of steroid-refractory acute graft-versus-host disease. Bone Marrow Transplant 2010;45:1347-51.
47. Ghez D, Rubio MT, Maillard N, et al. Rapamycin for refractory acute graft-versus-host disease. Transplantation 2009;88:1081-7.
48. Jurado M, Vallejo C, Perez-Simon JA, et al. Sirolimus as part of immunosuppressive therapy for refractory chronic graft-versus-host disease. Biol Blood Marrow Transplant 2007;13:701-6.
49. Klobuch S, Weber D, Holler B, et al. Long-term follow-up of rituximab in treatment of chronic graft-versus-host disease-single center experience. Ann Hematol 2019;98:2399-405.
50. Teshima T, Nagafuji K, Henzan H, et al. Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. Int J Hematol 2009;90:253-60.
51. Majhail NS, Schiffer CA, Weisdorf DJ. Improvement of pulmonary function with imatinib mesylate in bronchiolitis obliterans following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2006;12:789-91.
52. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017;130:2243-50.
53. Waller EK, Miklos D, Cutler C, et al. Ibrutinib for Chronic Graft-versus-Host Disease After Failure of Prior Therapy: 1-Year Update of a Phase 1b/2 Study. Biol Blood Marrow Transplant 2019;25:2002-7.
54. Krejci M, Doubek M, Buchler T, Brychtova Y, Vorlicek J, Mayer J. Mycophenolate mofetil for the treatment of acute and chronic steroid-refractory graft-versus-host disease. Ann Hematol 2005;84:681-5.
55. Lee SJ, Nguyen TD, Onstad L, et al. Success of Immunosuppressive Treatments in Patients with Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant 2018;24:555-62.

Appendix 1: Signs and Symptoms of Chronic GVHD, including Common Signs/Symptoms for both Acute and Chronic GVHD (which are attributed to aGVHD unless a diagnostic symptom/sign of cGVHD)*

Organ/ Site	Diagnostic (sufficient to establish the diagnosis of cGVHD)	Distinctive (seen in cGVHD but insufficient alone to establish a diagnosis)	Other Features	Common (seen with both aGVHD and cGVHD)
Skin (see photos below)	• Poikiloderma • Scleroderma / morphea • Lichen sclerosus (morphea with overlying hypopigmented, finely wrinkled skin) • Lichen planus	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypo-pigmentation • Hyper-pigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle • Onycholysis • Pterygium unguis • Nail loss (usually symmetric)		
Scalp & body hair		• New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) • Premature gray hair	
Mouth	• Lichen planus	• Xerostomia • Mucocele • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
Eyes	• New dry/gritty/painful eyes with Schirmer's test ≤5 mm, • Keratoconjunctivitis sicca by slit lamp	• New onset of dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctuate keratopathy	• Photophobia • Periorbital hyper-pigmentation • Blepharitis (erythema of the eyelids with edema)	
Genitalia	• Lichen planus or sclerosus • Vaginal scarring/stenosis or clitoral/labial agglutination • Phimosis or urethal/meatus scarring or stenosis	• Erosions • Fissures • Ulcers		

Organ/ Site	Diagnostic (sufficient to establish the diagnosis of cGVHD)	Distinctive (seen in cGVHD but insufficient alone to establish a diagnosis)	Other Features	Common (seen with both aGVHD and cGVHD)
GI Tract	• Esophageal web • Strictures/stenosis in the upper- to mid-third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea/Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children)
Liver				• T.bilirubin or ALT or ALP >2 times UNL
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (BOS)** - diagnostic only if at least one distinctive manifestation of cGVHD in another organ	• Air trapping / bronchiectasis on CT	• Cryptogenic organizing pneumonitis • Restrictive lung disease	
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to sclerosis	• Myositis or polymyositis (diagnostic if biopsy-confirmed)	• Edema • Muscle cramps • Arthralgia or arthritis	
Hemato-poietic and immune			• Thrombocyto-penia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulin-emia • Auto-antibodies (AIHA, ITP)	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

Abbreviations: GVHD=graft-versus-host disease; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BOOP=bronchiolitis obliterans-organizing pneumonia; PFTs=pulmonary function tests; AIHA=autoimmune hemolytic anemia; ITP=idiopathic thrombocytopenic purpura.

** Adapted from Jagasia et al: BBMT 2015 (The 2014 Diagnosis and Staging Working Group Report)*

*** BOS is defined as all of the following 4 criteria:*

1. FEV1/FVC < 0.7

2. *FEV1 <75% predicted (even post salbutamol/albuterol), or ≥10% decline over less than 2 years (even post salbutamol)*
3. *Absence of infection*
4. *Evidence of air trapping by CT or by PFT (RV >120% predicted). Small airway thickening or bronchiectasis by CT is acceptable if no air trapping.*

Explanations of uncommon terms for mucocutaneous cGVHD

Lichen planus: A skin eruption characterized in its most typical form by pruritic polygonal purple papules. These small flat-topped papules may show a white lacy network on their surface, Wickham's striae. The oral changes are characteristically erythema with a reticulate lacy pattern on the buccal mucosa. Erosions may also be present. The entire oral cavity may be involved, as can the genitalia of men and women.

Poikiloderma: A dermatosis characterized by variegated cutaneous pigmentation, atrophy, and teleangiectasia.

Morphea: Morphea is a localized sclerosis of the skin. Early lesions typically show evidence of inflammation. A white firm plaque appears at the inflammatory site, surrounded by remaining inflammation. This plaque, over time, spreads peripherally and may become depressed. Telangiectatic vessels may be seen as well as hyperpigmentation.

Appendix 2. Ancillary Therapy for Chronic GVHD

Organ/Site	Prevention	Treatment
Skin & Appendages	• photoprotection • surveillance for malignancy	• Emollients (Glaxal Base) Corticosteroids (betamethasone valerate 0.1% cream/ointment *Betaderm, Celestoderm*, hydrocortisone 1% - for face) antipruritic agents (diphenhydramine 25-50 mg po every 6-8 hours, hydroxyzine 25 mg po TID - QID) • Erosions/ulcerations – microbiologic cultures • Topical antimicrobials (mupirocin/*Bactroban*) • Protective films or other dressings • Wound-care specialist consultation

Mouth & Oral Cavity	• Good oral/dental hygiene
	• Routine dental cleaning
	• Surveillance for infection and malignancy
	• Fluoride (*Prevident* rinse; prescribed by dentist when there is oral dryness)
		• High-potency corticosteroids: betamethasone sodium phosphate 5mg/mL solution (*Betnesol enema*) 5-10 mL swish + spit QID, dexamethasone 0.5mg/5mL compounded solution 5 mL swish + spit QID, fluocinonide 0.05% gel
		• Calcineurin inhibitors: cyclosporine 100 mg/mL solution swish + spit, tacrolimus 0.1% ointment
		• Therapy of oral dryness:
		  ○ artificial saliva / lubricants (*Moi-stir, Oralbalance, Biotene*)
		  ○ salt water / baking soda or *Club soda* rinses
		  ○ pilocarpine 5-10mg po TID

Eyes	• Photoprotection • Surveillance for infection, cataract and increased intraocular pressure	• Artificial tears (*Refresh tears*; bottle or individual – preservative-free, *Bion tears* –one time use, *Systane*), thicker formulations (*Celluvisc, Genteal Gel*), artificial tears ointment (*Lacrilube*, qhs) • Corticosteroids: Prednisone 1% ophthalmic solution – *Pred Forte* • Calcineurin inhibitors: cyclosporin, ophthalmic emulsion 0.05% (*Restasis*), prescribed by ophthalmologist • Pilocarpine 5-10mg po TID
Vulva & Vagina	• Surveillance for estrogen deficiency, infection (HSV, HPV, yeast, bacteria), malignancy	• Water-based lubricants (*KY jelly, Astroglide, Replens*) • Topical estrogens (*Premarin* - vaginal cream, *Vagifem* - vaginal tablet) • Corticosteroids: betamethasone – cream or enema • Dilatators • Surgery for extensive synechiae/obliteration • Early gynaecological consultation

GI tract & liver	• Surveillance for infection (viral, fungal)	• Dietary modification
		• Corticosteroids:
		  ○ upper GI – beclomethasone dipropionate oral solution 1mg/mL; 1mL po QID
		  ○ lower GI – budenoside 3 mg po TID
		• Enzyme supplementation: pancreolipase (*Cotazym, Pancrease MT, Creon, Ultrase, Viokase*)
		• GI reflux management
		• Esophageal dilatation
		• Ursodeoxycholic acid (if pruritus due to cholestasis)

Organ/Site	Prevention	Treatment
Lungs	• Surveillance for infection (PJP, viral, fungal, bacterial)	• inhaled corticosteroids: budenoside (*Pulmicort*), fluticasone (*Flovent*) • SABA: salbutamol (*Ventolin*) • LABA: formoterol (*Oxeze*), salmeterol (*Serevent*) • Combo: formoterol + budesonide (*Symbicort*), salmeterol + fluticasone (*Advair*) • Anticholinergics: tiotropium (*Spiriva*)
Musculo-skeletal	• Surveillance for decreased range of motion • Bone densitometry • Calcium supplementation • Vitamin D supplementation	• Physical therapy • Treatment of osteoporosis, if present

Appendix 3. Summary of aGVHD grading, diagnosis of cGVHD (at least one diagnostic sign present), and cGVHD scoring

aGVHD organ stage	1	2	3	4
Skin	<25% BSA	25-50%	>50% BSA	Bullae
Gut	0.5-1 L/d or N/V	1-1.5 L/d	1.5-2 L/d	>2 L/d or pain/ileus
Liver	Bili 34-50	Bili 51-100	Bili 100-250	Bili >250
aGVHD overall grade	**1**	**2**	**3**	**4**
	Skin 1-2	Skin 3 or Gut 1 or Liver 1	Gut 2-4 or Liver 2-3	Skin 4 or Liver 4

Diagnostic signs of cGVHD	
Skin /fascia	Poikiloderma, lichen, morphea/sclerosis/ fasciitis/contractures
Mouth	Lichen
Eyes	New dry/gritty/painful eyes with Schirmer ≤5 mm, keratoconjunctivitis sicca by slit lamp
Genital	Lichen, ♀: vaginal scarring/stenosis, clitoral/labial agglutination, ♂: phimosis, urethral scarring/stenosis
GI	Esophageal web/stenosis
Lungs	Bronchiolitis obliterans diagnosed by biopsy or CT+PFTs

cGVHD organ score	1	2	3
Skin/fascia	BSA <19%, no sclerosis	19-50%, sclerosis but able to pinch, ↓ROM a/w mild impact on ADL	>50%, unable to pinch, ulcer, ↓ROM a/w severe impact on ADL
Mouth	Mild symptoms	Some oral intake limitation	Major oral intake limitation
Eyes	Mild dryness	Some impact on ADL, no vision loss	Major impact on ADL, vision loss
Genital	Lichen planus (♂♀), Vulvar erythema	Vulvar erosions or fissures (♀), Lichen sclerosus ♂	Adhesions, dense sclerosis (♀), Phimosis (♂)
GI	Symptoms with <5% wt loss	Symptoms with 5-15% wt loss	>15% wt loss, esophag.dilation, suppl.feeding, diarrhea imp. ADL
Liver	Bili normal ALT 180-300 ALP ≥429	Bili 24-72 ALT >300	Bili >72
Lungs	FEV1 60-79%, DOE 1 flight up	FEV1 40-59%, DOE flat surface	FEV1 <40%, SOB at rest, O_2
cGVHD global score	**Mild (1)**	**Moderate (2)**	**Severe (3)**
	1-2 organs w max score 1, no lung	All in between (including lung score 1)	Score 3 in any organ, or lung score 2-3

CMV, VZV, HSV, HHV6

Presented by: Jan Storek

Summary

CMV (cytomegalovirus) Disease Prevention in alloHCT

- *Monitoring and Preemptive therapy*:
  - Plasma CMV DNA by Q-PCR weekly until d100, then monthly until 1 year postHCT.
  - If CMV DNAemia >25,000 IU/mL plasma, treat preemptively with induction valganciclovir, 900 mg bid, until DNAemia has dropped, but for at least one week.
  - Continue valganciclovir at maintenance dose of 900 mg qd until DNAemia <5,000 IU/mL twice, but for at least 2 weeks.
- *Primary prophylaxis with Letermovir* should be used only in seropositive patients with seronegative donor (D-R+). Cord blood is considered D-.
  - Monitoring and preemptive valgancilovir should be used as above, except:
  - Extend weekly DNAemia monitoring until 2-3 months post letermovir discontinuation.
- *Blood products*: Use leukodepleted and irradiated blood products.
- *Donor selection for HCT*: Prefer a CMV serostatus-matched donor. This is of minor importance, except if ATG is used for GVHD prophylaxis in a seropositive patient undergoing alloHCT for a lymphoid malignancy – in this scenario choosing a seropositive donor is of major importance.

VZV (Varicella Zoster Virus) and HSV (Herpes Simplex Virus) Disease Prevention in allo and autoHCT

- Valacyclovir, 500 mg qd, from start of conditioning until 1 day before the first dose of a live VZV vaccine (alloHCT) or until 1 month after the second dose of a non-live VZV vaccine (autoHCT).
- For *allogeneic* HCT recipients, VZV vaccination with a live vaccine should start at 2 years posttransplant or later. The later start is for patients on prolonged therapy with immunosuppressive drugs – wait until ≥3 mo after discontinuation of immunosuppressive therapy (systemic and topical) and no cGVHD activity.
- For *autologous* HCT recipients, VZV vaccination with a non-live vaccine (Shingrix) should start at 6 months posttransplant or later. The later start is for patients on prolonged maintenance immunosuppressive therapy – wait until ≥6 mo after discontinuation of a lymphodepleting antibody like rituximab.
- For CAR T cell recipients, management is currently identical to that of allogeneic HCT recipients.
- See Vaccination chapter for details.

HHV6 (Human Herpes Virus 6) Disease Prevention: None.

Cytomegalovirus (CMV)

Epidemiology: Incidences of CMV Reactivation / CMV Disease

- **Seronegative donor → Seronegative patient (D-R-)**
  - 70% / 35% with non-CMV safe transfusions (from random donors and not leukodepleted).
  - <2% / <2% with CMV safe transfusions.
    - In Alberta, 0% CMV reactivation needing preemptive Rx / 0% CMV disease[1].

- **Seropositive donor → Seronegative patient (D+R-)**
  - 70% / 35% with non-CMV safe transfusions.
  - 15% / 5% with CMV safe transfusions, before ganciclovir.
  - 10-15% / <3% with CMV safe transfusions, since ganciclovir.
    - In Alberta, 10% CMV reactivation needing preemptive Rx / 1% CMV disease[1].

- **Seropositive donor → Seropos pt (D+R+), and Seroneg donor → Seropos pt (D-R+)**
  - 70% / 35% before ganciclovir.
  - 70% / <2%-20% since ganciclovir.
    - In Alberta:
      - For MSD/URD with ATG-based GVHD prophylaxis:
        - In D+R+, 31% CMV reactivation needing preempt Rx / 4% CMV disease[1].
        - In D-R+, 64% CMV reactivation needing preempt Rx / 11% CMV disease[1].
          - With letermovir, 8/8 (50%) reactiv w preempt / 2/16 (12%) CMV dis.
        - Survival lower in D-R+ than D+R+ patients with lymphoid malignancies (Fig. 1), due at least in part to a higher grade 3-4 aGVHD incidence in D-R+ patients[2].
      - For Haplos with PTCy/MMF-based GVHD prophylaxis (Storek, unpubl, 2023):
        - In D+R+, 16/25 (64%) CMV reactive→preempt Rx / 2/25 CMV dis (non-fatal).
        - In D-R+,
          - Without letermovir, 5/6 CMV reactiv→preempt / 2/6 CMV disease.
          - With letermovir, 3/5 CMV reactiv→preempt / 0/5 CMV disease.

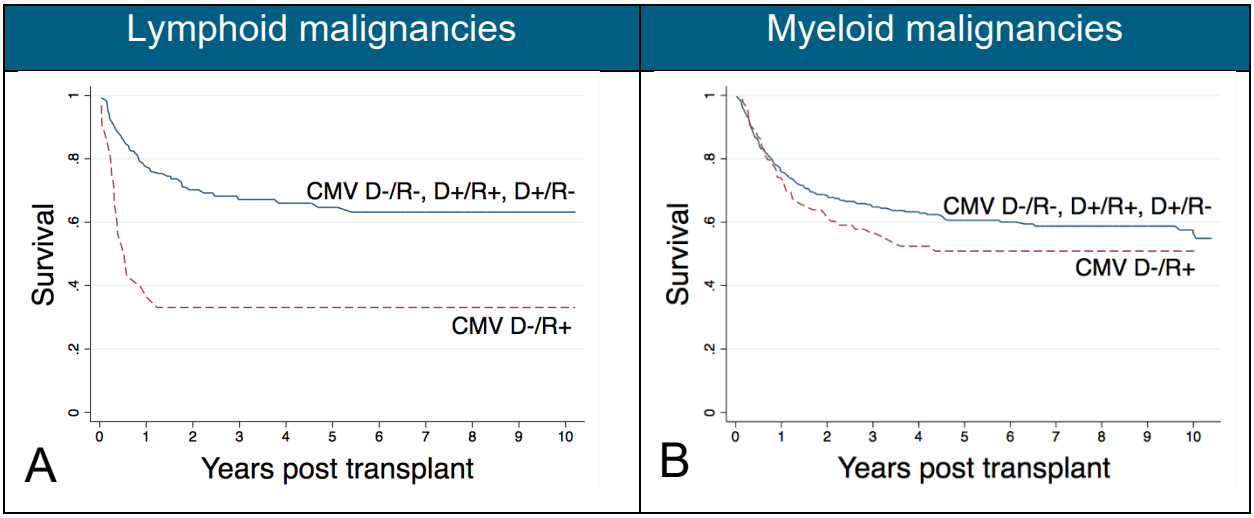


Figure 1. Impact of CMV serostatus on overall survival in patients with lymphoid malignancies (A) and patients with myeloid malignancies (B). In multivariate analysis, the differences were significant in patients with lymphoid malignancies (p=.001) but not myeloid malignancies (p=0.23).

- **Autologous seropositive patient**
  - 50% reactivation / ≤2% disease
- **Syngeneic seropositive patient**
  - 50% reactivation / 0% disease
- **Healthy individuals**
  - 50% - 80% are infected, <5% reactivate (poorly studied), 0% develop CMV disease.

Risk factors for CMV reactivation and disease:

- Seropositivity of recipient particularly if donor seronegative or cord blood
- T cell depletion, particularly ex vivo
- GVHD / immunosuppressive drugs
- Haploidentical HCT using PTCy+MMF+CNI

Clinical manifestations of CMV disease:

- Frequent: Gastroenteritis, Pneumonia
- Less frequent: Retinitis, Encephalitis, Hepatitis, Marrow suppression

Prevention of CMV Disease

Transfusions, and Hematopoietic Cell Donor Selection

- All blood products collected in Canada are leuko-depleted at the time of collection (CMV safe). Moreover, blood products for HCT recipients are routinely irradiated prior to transfusion.
- CMV seronegative HCT donor is preferred for CMV seronegative recipient.[3] However, the difference in survival of seropositive patients receiving grafts from seropositive vs negative donors is minor, if any[1,4].
- CMV seropositive HCT donor is preferred for CMV seropositive recipient[1,3,5,6].
    - Survival difference (between HCT from seropositive vs seronegative donors) in the setting of ATG-based GVHD prophylyaxis is marked in patients with lymphoid malignancies (HR=3.1, p=0.001) whereas minor, if any, in patients with myeloid malignancies (HR=1.2, p=0.23) (Fig. 1)[2].
    - The survival difference is virtually zero in the setting of haploidentical HCT with posttransplant cyclophosphamide based GVHD prophylaxis[7].
    - In patients with lymphoid malignancies and ATG-based GVHD prophylaxis, if an HLA matched but CMV seronegative sibling donor is available and no HLA matched and CMV seropositive sibling donor is available, search for an HLA matched and CMV seropositive unrelated donor is recommended[1].
- Recipient CMV serostatus should ideally be determined before blood product transfusions, particularly platelet or plasma transfusions or IVIG. If CMV IgG is transferred from a CMV seropositive blood donor to a CMV seronegative recipient, the recipient may become falsely CMV seropositive[8].

Antiviral Prophylaxis or Preemptive Therapy?

- Prophylaxis with val/ganciclovir, foscarnet, brincidofovir, or maribavir decreased the incidence of CMV disease modestly or not at all (if yes, then only during the period of taking the drug) and had no impact on OS due to poor risk:benefit ratio[9,10].
- Prophylaxis with high dose val/acyclovir
    - May be effective and safe,[11,12] but randomized studies do not exist.
- Prophylaxis with anti-CMV T cells
    - Efficacious and safe, but too costly.
    - Donor-derived anti-CMV T cells cannot be used in D-R+ patients who would most benefit from the prophylaxis.
    - Prophylaxis with 3rd party anti-CMV T cells is less efficacious, more data is needed to determine whether the benefit is worth the cost.
- Preemptive Therapy with val/ganciclovir
    - Never evaluated in a randomized study against no prophylaxis/no preemptive Rx.

        - In a randomized study of ganciclovir prophylaxis till d100 vs preemptive Rx[13], CMV disease incidence was similar, toxicity was worse with preemptive Rx (fungal infections, neurotoxicity, no difference in neutropenia), OS was similar.
    - Nevertheless, preemptive Rx has become popular based on single-arm studies showing less CMV disease than expected with no prophylaxis, not more CMV disease than with prophylaxis, and improved safety compared to prophylaxis.
- Prophylaxis with letermovir + pre-emptive therapy with val/ganciclovir
    - Safe but efficacy is limited – ~halfing of % patients with clinically significant (cs) CMV infection (CMV DNAemia requiring preemptive therapy or CMV disease)[14,15].
    - Pros:
        - Potential reduction of incidence/duration of val/ganciclovir-induced toxicity like neutropenia.
            - This may not be substantial with our preemptive strategy, as in 2012-2022, 256 of 850 alloHCT recipients needed preemptive therapy which lasted only median 27 days (too short to cause clinically significant neutropenia), and only 53 of the 256 recipients needed ≥1 additional preemptive therapy course (Storek, unpublished).
        - Survival benefit?
            - Shown only in a meta-analysis of retrospective studies, and not in a subgroup meta-analysis of US-based studies.[16] Not shown in a randomized study, albeit there was a trend toward improved OS.[15] The lack of clear-cut improvement of OS may have been related to a high incidence of csCMV infection after letermovir discontinuation (after d100).
                - A subsequent randomized study comparing letermovir until d100 vs until d200 did not show any survival benefit (not even a trend – OS 92% vs 92% in patients who took letermovir in the first 100 days and started letermovir vs placebo on ~d100)[17] Interestingly, csCMV infection incidence was similar in both arms, except in the "until d200" arm most csCMV infections occurred after d200 whereas in the "until d100" arm most csCMV infections occurred between d100 and d200.
            - No survival benefit shown in the largest study so far (Japanese registry study of >6,000 patients)[18].
            - In a large single center study (Lille, N=316), there was a trend toward OS benefit in high-risk but not in low-risk patients[19].
        - GVHD incidence/severity reduction?
            - So far theoretical. Practically reported in only one retrospective study for cGVHD (but not for aGVHD)[20], despite there have been >40 studies comparing letermovir to no letermovir.

        - Non-CMV infection incidence/severity reduction? (as CMV seropositivity/infection is a/w [predisposes to?] non-CMV infections, e.g., Covid[21])
            - So far only theoretical.
    - Cons:
        - Cost ($>20,000 for 3 months)
            - Inpatients require STEDT approval.
            - Outpatients are usually covered 70-80% by their insurance.
                - The 20-30% copayment may be too much, but co-pay assistant cards are available.
        - No impact on the incidence of CMV disease[15].
        - No activity against HSV and VZV, so val/acyclovir needed in addition to letermovir.
        - CMV DNAemia monitoring with preemptive VGCV needed in addition to letermovir.
        - CMV reactivation after end of prophylaxis[22,23] – extended weekly DNAemia monitoring needed (until 2-3 mo post letermovir discontinuation)
- Alberta approach:
    - Preemptive therapy with val/ganciclovir is currently the CMV disease prevention strategy of choice in Alberta.
    - Letermovir prophylaxis (primary), together with CMV DNAemia monitoring and preemptive val/ganciclovir, should be considered in D-R+ patients.
        - Rationale
            - D-R+ serostatus is the most important risk factor for csCMV infection and for mortality (clear-cut in pts with lymphoid malignancies, trend in patients with myeloid malignancies) in most AB patients (MSD/URD, ATG-based GVHD prophylaxis)[1,2] and probably also in Haplo setting with PTCy/MMF-based GVHD prophylaxis (Storek, unpublished), so these patients deserve to be offered the potential benefit of letermovir, albeit the benefit is uncertain.
            - For patients other than D-R+, the above uncertain pros do not outweigh the cons.
        - Financial implications should be clarified / discussed with the patient.
        - Weekly CMV DNAemia monitoring should be extended until 2-3 months post letermovir discontinuation.

Alberta Preemptive val/ganciclovir approach - Details

- CMV DNA monitoring in plasma from day 0 to day 100 weekly, then monthly to 1 year posttransplant.
- Monitor all patients (including CMV seronegative patients with seronegative donors, as there is a small chance that the CMV IgG test result is falsely negative).
- If 5,000-25,000 IU/mL, repeat DNAemia in 3-7 days.
- If >25,000 IU/mL, start preemptive treatment with ganciclovir or valganciclovir.
    - In 1999-2007 we used a threshold of 10-20 pp65 antigen positive cells per slide (containing ~200,000 granulocytes) and found it to be satisfactory (~2.8% cumulative incidence of CMV disease and no CMV pneumonia in D+R+ patients (ATG-conditioned)). Between 2007 and 2012, we used a ProvLab in-house real time PCR assay and a threshold of 50,000 genome copies/mL plasma, which corresponded to the previous pp65 antigenemia threshold. Since 2012, we have used commercial real time PCR assay (RealStar, Altona) and a threshold of 25,000 IU/mL plasma, which corresponded to the previous in-house real time PCR threshold.
- Induction with valganciclovir 900 mg p.o. BID (or ganciclovir 5 mg/kg IV BID) for at least one week. Continue induction until a down-going trend of CMV DNAemia, then switch to maintenance (QD). For example, if ganciclovir induction was started for 80,000 IU/mL, switch to maintenance after <80,000 IU/mL.
    - If DNAemia has not declined after 2-3 weeks of induction, suspect ganciclovir resistance.
- Maintenance with valganciclovir 900 mg p.o. QD (or ganciclovir 5 mg/kg IV QD) for at least 2 weeks.
    - Treat until <5,000 IU/mL at least twice, but treat for a total of at least 3 weeks (e.g., at least one week of induction and at least 2 weeks of maintenance).
    - Prolonged maintenance/secondary prophylaxis with VGCV can be considered for patients at high risk of recurrent CMV disease (e.g., active GVHD AND history of ≥2 episodes of csCMV infection).
        - Letermovir may be considered for the prolonged maintenance/secondary prophylaxis instead of val/ganciclovir, however, only if CMV DNAemia has become undetectable, as otherwise there is a high likelihood of developing letermovir resistance[24].
            - Secondary prophylaxis with letermovir is not covered by STEDT or Alberta Blue Cross (except possibly within 100 days postHCT).
- Both ganciclovir and valganciclovir doses need to be adjusted in renal insufficiency.
- If ANC<1.0/nL, give filgrastim. If ANC has not increased to >1.0/nL within 3 days, switch ganciclovir to foscarnet.
- If preemptive treatment is given between 3 and 12 months posttransplant, check CMV DNAemia weekly. Resume monthly monitoring after DNAemia has been undetectable at least twice.

Alberta Letermovir primary prophylaxis – Details

- Use only in high-risk patients (typically only D-R+).
  - Clarify financial implications with patient before starting. Some patients may choose not to start.
- Start on day 9 (the median start in Marty's randomized study[15]).
- Dose: 480 mg qd when off CSA, 240 mg qd orally when on CSA
  - No dose reduction with tacrolimus.
- Continue until day 84 (the median in Marty's randomized study was d82).
  - No survival benefit of extending letermovir to d200 shown in a randomized study[17].
- Stop letermovir when starting pre-emptive therapy or therapy with val/ganciclovir.
  - Restarting after val/ganciclovir discontinuation is not recommended. There is a lack of data whether letermovir restarting is of any value.
- CMV DNAemia monitoring weekly should be extended until 2-3 months post letermovir discontinuation!

Diagnosis and Therapy of CMV Disease

Diagnosis of CMV disease

- Diagnosis of CMV Enteritis requires histological or immunohistochemical evidence. PCR positivity alone is not sufficient for diagnosis.
- Diagnosis of CMV Pneumonia in the past required positive viral culture of BAL. Viral cultures were discontinued in 2015 and replaced with PCR. PCR has an excellent negative predictive value (>99%) but a poor positive predictive value (cannot distinguish CMV pneumonia from pulmonary CMV shedding). Data on BALs with concurrent viral culture and PCR were analyzed by Dr.R.Tellier of ProvLab in 2015, showing:

Viral load range (IU/mL)	Neg (0 to <150)	150 to 10^3	10^3 to 10^4	10^4 to 10^5	$>10^5$
% viral culture positive (pos/total)	0.33% (1/306)	6% (2/33)	27% (6/22)	40% (4/10)	100% (4/4)

  - Based on this data and the fact that pulmonary CMV shedding predisposes to CMV pneumonia, the diagnostic and therapeutic algorithm is as follows:
    - If CMV $>10^3$ IU/ml BAL, CMV pneumonia is possible/proven. Treat as CMV disease (below).

- If CMV between 150 (detection limit) and 10^3 IU/ml BAL, CMV pneumonia is unlikely. Treat the CMV shedding with 1 week induction and 1-2 weeks maintenance.
- If CMV undetectable, CMV pneumonia is ruled out.
- If transbronchial lung biopsy was done at the time of the BAL and is positive for CMV pneumonia by histology or immunohistology, treat as proven CMV pneumonia.

Therapy of CMV disease

- Induction with ganciclovir 5mg/kg IV twice daily, or Foscarnet 90 mg/kg IV twice daily, for 2-3 weeks. Followed by maintenance ganciclovir/valganciclovir/foscarnet for 3-4 weeks.
- For CMV pneumonia, add IVIG 500 mg/kg every other day for 2 weeks.

Herpes Simplex Virus (HSV) & Varicella Zoster Virus (VZV)

Background

Epidemiology:

HSV.

- ~70% adults infected.
- ~70% adult HCT recipients shed HSV post transplant (typically in the first month) and ~70% of the shedders developed HSV disease in pre-acyclovir era.
- <5% pts shed HSV and <<5% pts develop HSV disease post-transplant per literature since acyclovir prophylaxis.
    - In Alberta, in adult alloHCT recipients transplanted in 2012-2022 (acyclovir priphylaxis era), in the first posttransplant year, 74/854 (9%) developed HSV disease (Storek, unpubl).
        - 38 pts (4%) mild oro/gential
        - 27 pts (3%) severe oro/genital (requiring or extending peritransplant hospitalization)
        - 9 pts (1%) internal organ, all required/extended hospitalization
            - 3 esophagitis
            - 3 enteritis
            - 1 encephalitis
            - 2 pneumonias, both fatal, thus total fatal HSV disease incidence 0.2% (2/854)

VZV.

- >90% adults infected.
- 10-50% adult HCT recipients develop VZV disease (typically at 3-9 months post-transplant) without acyclovir prophylaxis.
- Similar cumulative VZV disease incidence with acyclovir prophylaxis, however, the time of onset shifted to after acyclovir discontinuation.

Risk factors: Seropositivity of recipient, GVHD / immunosuppressive drugs (this may not be a risk factor for any VZV disease, but it probably is a risk factor for severe VZV disease[2]).

Clinical manifestations of HSV disease: Painful mucocutaneous lesions of oropharynx/genitalia, internal organs may be involved, (e.g., lungs, GI tract, liver, CNS).

Clinical manifestations of VZV disease:

- Shingles (typically with reactivation) → neuralgia
- Chickenpox (typically with primary infection)
- Internal organs may be involved, e.g., lungs, GI tract, liver, CNS
    - Visceral VZV disease may be rapidly progressing and fatal

Prevention of HSV and VZV Disease

HSV Prevention/Prophylaxis with Valacyclovir:

- Accepted until 1-month post-transplant.
- Controversial until 3 months post-transplant – possibly useful for HSV seropositive recipients with HSV seronegative donors, as these patients may develop late HSV disease.
- Irrelevant for patients on VZV prophylaxis, who get valacyclovir anyway.

VZV Prevention/Prophylaxis with Valacyclovir:

- Use valacyclovir (VCV) followed by VZV vaccination.
    - In alloHCT, VCV for 2 years (longer if on immunosuppressive therapy) followed by two doses of a live VZV vaccine was effective for zoster incidence reduction and near-elimination of post-herpetic neuralgia (Appendix A)[25].
        - In Alberta, the timing of the start of the vaccination is at 2 years posttransplant or later.
        - The later start is for patients on prolonged therapy with immunosuppressive drugs – wait until ≥3 mo after discontinuation of immunosuppressive therapy (systemic and topical) and no cGVHD activity.
    - In autoHCT, VCV for up to 6 months together with two doses of a non-live vaccine composed of recombinant glycoprotein E with an adjuvant (Shingrix) starting at 2 months posttransplant was effective for zoster incidence reduction and substantially reduced post-herpetic neuralgia[26].
        - In Alberta, the timing of the start of the vaccination is at 6 months posttransplant (to coincide with the start of other vaccines) or later.

- The later start is recommended for patients on prolonged maintenance immunosuppressive therapy – wait until ≥6 mo after discontinuation of a lymphodepleting antibody like rituximab.
    - It is unclear whether the delay (the later start) is needed – the randomized study[26] did not exclude patients on maintenance bortezomib, rituximab, or other immunomodulatory therapy, but included only 4% of such patients. The reason we recommend the delay is that the immunogenicity of any vaccine is reduced by immunosuppressive/lymphodepleting therapy, and long-term administration of valacyclovir is non-toxic and virtually 100% effective for zoster prevention as long as the patient remains compliant.
        - Lenalidomide maintenance is not considered immunosuppressive[27].

- Valacyclovir should be started with conditioning.
- Valacyclovir should be discontinued.
    - In alloHCT, 1 day before the first dose of the live vaccine. This is to avoid the killing of the live vaccine with valacyclovir, which could reduce its immunogenicity.
    - In autoHCT, 1 month after the second dose of Shingrix. This approximately mimics the scenario from the randomized study[26].
- Give valacyclovir to all adult patients. For pediatric patients, refer to Table 1.
- Use valacyclovir 500 mg po once daily (preferred) or acyclovir 400 mg po twice daily (5mg/kg IV twice daily). For children <40 kg with oral intake, use acyclovir suspension 300 mg/m^2 po twice daily.
- If patient is on ganciclovir/valganciclovir/foscarnet/cidofovir, hold acyclovir/valacyclovir.

Table 1. Pediatric patients treated with acyclovir/valacyclovir

HSV Recipient Serostatus	VZV Recipient Serostatus	Start and End of Prophylaxis
Positive or Negative	Positive	From day 0 until VZV vaccination (24 months or later)
Positive	Negative	From day 0 until 1 month posttransplant. Consider extending prophylaxis to 3 months posttransplant if donor is HSV-seronegative. Consider immunizing VZV-seronegative contacts with VZV vaccine.
Negative	Negative	No prophylaxis. Consider immunizing VZV-seronegative contacts with VZV vaccine.

Exposure prevention for VZV:

- Important for VZV seronegative patients who are not on valacyclovir/acyclovir. Of limited importance for VZV seropositive patients who are not on valacyclovir/acyclovir (they already have the virus, nevertheless, vesicular rash due to a different strain transferred from a contact person has been described). Of probably no importance for patients who are on valacyclovir/acyclovir.
- Consider vaccination of prospective contacts (caregivers, children, related BMT donors) without history of chickenpox or VZV vaccination (seronegative).
- Instruct the patient to avoid skin contact with vaccinees who have developed a rash. Approximately 20% vaccinees develop a rash at 5-42 days post-vaccination.

Post-exposure prophylaxis of VZV:

- Important only for patients who are not on valacyclovir/acyclovir. Definition of exposure: residing in the same household, playmate (face-to-face), other face-to-face contact with an infectious person.
- If a seronegative patient has been exposed to a person with varicella or zoster, give varicella zoster immune globulin (or intravenous immunoglobulin) and/or treat with treatment dose of acyclovir/ valacyclovir for 3 weeks.
- If a seropositive patient has been exposed to a person with varicella or zoster, observe closely.

Therapy of HSV and VZV Disease

HSV Disease:

- Valacyclovir 1000 mg twice daily or Acyclovir 400 mg po three times daily (5 mg/kg IV every 8 hours).
- Treat for 7 days or until resolution of lesions, whichever occurs later.

VZV Disease:

- Acyclovir 10-12 mg/kg every 8 hours for 1-3 days, then (if oral intake possible) switch to acyclovir 800 mg po 5x/d or valacyclovir 1000 mg po three times daily.
- Treat until 2 days after the last new lesion has crusted (generally 10-14 days).
- Hydrate patient to minimize acyclovir/valacyclovir nephrotoxicity.

Resistance to Acyclovir/Valacyclovir:

- HSV resistance is relatively common in immunocompromised persons (~5%). Resistance should be suspected if lesions progress or do not improve within 7-10 days of oral val/acyclovir therapy. Documentation of resistance (mutation of thymidine kinase or DNA polymerase) is of unproven benefit but recommended. Treatment of clinically resistant HSV disease is with high dose IV acyclovir (10 mg/kg every 8 hours). If no improvement of lesions in 7 days, switch to foscarnet. After resolution of lesions, val/acyclovir prophylaxis should be re-started, as recurrent lesions are frequently val/acyclovir-sensitive, and VZV prophylaxis needs to be continued.

- VZV resistance is extremely rare (<0.1%). Other causes of non-resolving zoster like bacterial superinfection should be suspected.

Human Herpes Virus 6 (HHV6)

- >90% adults infected.
- ~40% adult HCT recipients have HHV6 detectable in blood, typically in the first 2 months.
- <10% adult HCT recipients develop HHV6 disease (encephalitis, ?rash, ?pneumonitis, ?bone marrow suppression/graft failure).
    - In Alberta, only 2/854 adult alloHCT recipients transplanted in 2012-2022 developed HHV6 menig/encephalitis (Storek, unpublished).
- **Prevention:** Insufficient data exist whether prophylaxis or preemptive therapy with ganciclovir or foscarnet is indicated – unlikely in Alberta, where the incidence of HHV6 encephalitis has been very low. Thus, in Alberta, we use no prophylaxis or preemptive therapy.
- **Therapy of HHV6 disease:** Ganciclovir or foscarnet, same dose as for CMV disease.

References

1. Kalra A, Williamson T, Daly A, et al. Impact of Donor and Recipient Cytomegalovirus Serostatus on Outcomes of Antithymocyte Globulin-Conditioned Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 2016;22:1654-63.
2. Ousia S, Kalra A, Williamson TS, et al. Hematopoietic cell transplant outcomes after myeloablative conditioning with fludarabine, busulfan, low-dose total body irradiation, and rabbit antithymocyte globulin. Clin Transplant 2020:e14018.
3. Ljungman P. The role of cytomegalovirus serostatus on outcome of hematopoietic stem cell transplantation. Curr Opin Hematol 2014;21:466-9.
4. Ljungman P, Brand R, Hoek J, et al. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. Clin Infect Dis 2014;59:473-81.
5. Ugarte-Torres A, Hoegh-Petersen M, Liu Y, et al. Donor serostatus has an impact on cytomegalovirus-specific immunity, cytomegaloviral disease incidence, and survival in seropositive hematopoietic cell transplant recipients. Biol Blood Marrow Transplant 2011;17:574-85.
6. Schmidt-Hieber M, Tridello G, Ljungman P, et al. The prognostic impact of the cytomegalovirus serostatus in patients with chronic hematological malignancies after allogeneic hematopoietic stem cell transplantation: a report from the Infectious Diseases Working Party of EBMT. Ann Hematol 2019;98:1755-63.
7. Cesaro S, Crocchiolo R, Tridello G, et al. Comparable survival using a CMV-matched or a mismatched donor for CMV+ patients undergoing T-replete haplo-HSCT with PT-Cy for acute leukemia: a study of behalf of the infectious diseases and acute leukemia working parties of the EBMT. Bone Marrow Transplant 2018;53:422-30.
8. Morton S, Danby R, Rocha V, Peniket A, Murphy MF. Transfusion of CMV-unselected blood components may lead to inappropriate donor selection for patients subsequently undergoing allogeneic stem cell transplant. Transfusion medicine 2015;25:411-3.
9. Yahav D, Gafter-Gvili A, Muchtar E, et al. Antiviral prophylaxis in haematological patients: systematic review and meta-analysis. Eur J Cancer 2009;45:3131-48.
10. Chen K, Cheng MP, Hammond SP, Einsele H, Marty FM. Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. Blood Adv 2018;2:2159-75.
11. Douglas G, Yong MK, Tio SY, et al. Effective CMV prophylaxis with high-dose valaciclovir in allogeneic hematopoietic stem-cell recipients at a high risk of CMV infection. Transpl Infect Dis 2023;25:e13994.
12. Kabut T, Weinbergerova B, Folber F, Lengerova M, Mayer J. High-dose aciclovir in CMV infection prophylaxis after allogeneic HSCT: a single-center long-term experience. Bone Marrow Transplant 2023;58:1229-36.
13. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. Blood 1996;88:4063-71.
14. Chemaly RF, Ullmann AJ, Stoelben S, et al. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. N Engl J Med 2014;370:1781-9.
15. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med 2017;377:2433-44.
16. Vyas A, Raval AD, Kamat S, LaPlante K, Tang Y, Chemaly RF. Real-World Outcomes Associated With Letermovir Use for Cytomegalovirus Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: A Systematic Review and Meta-analysis of Observational Studies. Open Forum Infect Dis 2023;10:ofac687.
17. Russo D, Schmitt M, Pilorge S, et al. Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol 2023.
18. Takenaka K, Fuji S, Matsukawa T, et al. Outcomes of allogeneic hematopoietic cell transplantation under letermovir prophylaxis for cytomegalovirus infection. Ann Hematol 2024;103:285-96.
19. Sourisseau M, Faure E, Behal H, et al. The promising efficacy of a risk-based letermovir use strategy in CMV-positive allogeneic hematopoietic cell recipients. Blood Adv 2023;7:856-65.
20. Orofino G, Xue E, Doglio M, et al. Dynamics of polyclonal immuno-reconstitution after allogeneic transplant with post-transplant cyclophosphamide and letermovir. Bone Marrow Transplant 2023;58:1104-11.
21. Ljungman P, Tridello G, Pinana JL, et al. Improved outcomes over time and higher mortality in CMV seropositive allogeneic stem cell transplantation patients with COVID-19; An infectious disease working party study from the European Society for Blood and Marrow Transplantation registry. Front Immunol 2023;14:1125824.
22. Chen K, Arbona-Haddad E, Cheng MP, et al. Cytomegalovirus events in high-risk allogeneic hematopoietic-cell transplantation patients who received letermovir prophylaxis. Transpl Infect Dis 2021:e13619.

23. Mori Y, Jinnouchi F, Takenaka K, et al. Efficacy of prophylactic letermovir for cytomegalovirus reactivation in hematopoietic cell transplantation: a multicenter real-world data. Bone Marrow Transplant 2021;56:853-62.
24. Yong MK, Slavin MA, Chemaly RF, Papanicolaou GA. CMV prevention strategies in allogeneic hematopoietic cell transplantation; the role of prophylaxis and pre-emptive monitoring in the era of letermovir. Transpl Infect Dis 2023;25 Suppl 1:e14171.
25. Jamani K, MacDonald J, Lavoie M, et al. Zoster prophylaxis after allogeneic hematopoietic cell transplantation using acyclovir/valacyclovir followed by vaccination. Blood Advances 2016;1:152-9.
26. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. JAMA 2019;322:123-33.
27. Palazzo M, Shah GL, Copelan O, et al. Revaccination after Autologous Hematopoietic Stem Cell Transplantation Is Safe and Effective in Patients with Multiple Myeloma Receiving Lenalidomide Maintenance. Biol Blood Marrow Transplant 2018;24:871-6.

Appendix: Cumulative Incidence of Post-Herpetic Neuralgia

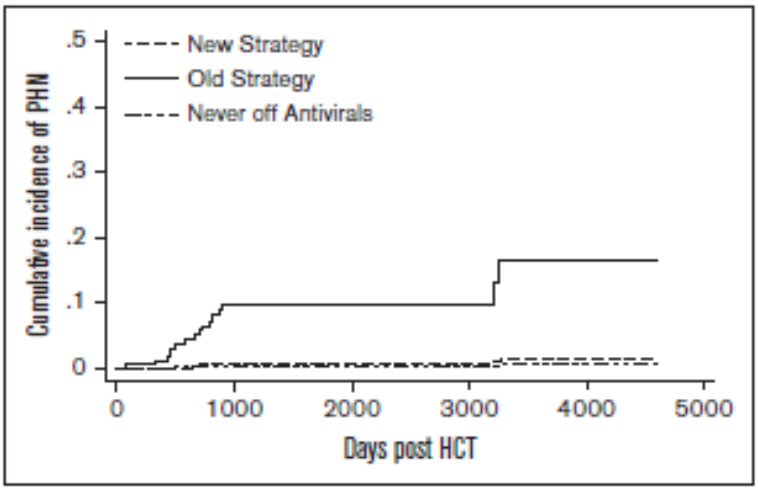


Figure 1 of Appendix. Cumulative incidence of post-herpetic neuralgia (PHN) in patients treated with valacyclovir till 2 years followed by vaccination (New Strategy), patients treated with valacyclovir till approximately 1 year without subsequent vaccination (Old Strategy), and patients who continued valacyclovir till the end of follow up (Never off Antivirals). The difference between the New Strategy and the Old Strategy patients was significant (p=0.02). From Jamani et al.[25]

Epstein-Barr virus (EBV) / Posttransplant Lymphoproliferative Disorder

Presented by: Jan Storek

Summary

EBV Monitoring

- Use an assay reporting DNAemia in IU/ml blood (the only assay ProvLab offers)
- For allograft recipients, monitor weekly until 3 months and then monthly until 12 months posttransplant.
- For autograft recipients, do not monitor.
- If DNAemia >30,000 IU/mL, watch for symptoms/signs of posttransplant lymphoproliferative disorder (PTLD).
- If DNAemia >300,000 IU/mL, treat PTLD preemptively.

Preemptive Therapy of PTLD

- Rituximab weekly (1st dose 375 mg/m^2 i.v.; 2nd-4th dose 1400 mg s.c.) until undetectable EBV DNAemia, to a maximum of 4 doses, *and*
- Taper cyclosporine or other immunosuppression to zero over 1-2 weeks (if no GVHD).

Therapy of PTLD

- Establish PTLD diagnosis by biopsy, or as EBV DNAemia >30,000 IU/mL plus ≥1 of the following:
  - Lymphadenopathy
  - Splenomegaly
  - Mass by imaging
  - B lymphocytosis or kappa/lambda predominance
  - Fever >38.5°C after engraftment, with negative blood cultures, persisting after 48 hours of broad spectrum antibacterials, otherwise unexplained. If fever is the only symptom/sign of PTLD, treat only if EBV DNAemia is >300,000 IU/mL.
- First line therapy: Rituximab and tapering of immunosuppression as for "Preemptive Therapy of PTLD" above. If no response within 2-4 weeks, proceed to second line therapy.
- Second line therapy:
  - If no GVHD and donor is EBV-seropositive:
    - DLI (10^5 T cells/kg), or donor-derived anti-EBV T cells manufactured in our Cellular Therapy Lab (currently unavailable).
    - Consider third-party anti-EBV T cells (less effective but safer than DLI).
  - If no GVHD and donor is EBV-seronegative:
    - Third party anti-EBV T cells – currently available under a trial in Cincinnati (patient has to travel) or from Atara (Tabelecleucel, patient does not have to travel).
    - Consider Blinatumomab or CD19 CAR T cells.
  - If GVHD requiring systemic immunosuppression: No good option. Consider chemo.

- Chemotherapy (eg, CHOP and/or polatuzumab vedotin) may be given while waiting for cellular therapy as a temporizing measure, if PTLD is aggressive. Chemotherapy as definitive therapy is not recommended due to low efficacy and high toxicity.

Background

Epstein - Barr virus[1-3]

- EBV is a gamma-herpes virus infecting primarily pharyngeal epithelial cells and B cells.
- Over 90% of adults are infected (seropositive)[4]:
  - EBV is detectable in blood by PCR at one time in 0-16% healthy donors.
  - EBV is detectable in blood by PCR at one of multiple times in 14-83% monitored HCT recipients.
    - In Alberta, with ATG-based GVHD prophylaxis, 86% seropositive HCT recipients reactivate EBV (have EBV detectable in blood by PCR).[5]
      - First reactivation on median day 35
      - Maximum EBV DNAemia: median 33,000 IU/mL
        - 452,000 IU/mL in pts developing PTLD,
        - 23,000 IU/mL in pts not developing PTLD
      - Maximum EBV DNAemia reached on median day 55
- Infected B cells are either quiescent (latent infection) or transformed to proliferate.
- Transformed B cells are eliminated by T cells in immunocompetent hosts.
- PTLD can develop in immunocompromised hosts.
  - Reported incidence after HCT 0.2% - 71%, in Alberta ~10% (using ATG).[5,6]
  - PTLD may be more frequent than clinically appreciated – of 31 retrospectively monitored patients with EBV DNAemia before death due to various causes, PTLD was detected on autopsy in 19/24 patients[6].

Risk Factors for Developing EBV PTLD after HCT[7]

Major risk factors	• In vivo T cell depletion, particularly using ATG • Ex vivo T cell depletion, particularly without concurrent B cell depletion • Cord blood or marrow graft (compared to unmanipulated blood stem cells) • Donor seropositive with recipient seronegative (D+/R-) serostatus • Second or subsequent HCT
Minor risk factors	• Aplastic anemia (compared to malignancies) • Older recipient • Splenectomy before HCT • Fludarabine in conditioning • Total body irradiation (TBI) in conditioning
Possible risk factor	• RIC or NMAC (compared to myeloablative conditioning)
Major risk-mitigating factors	• Posttransplant cyclophosphamide (without ATG) for GVHD prophylaxis • Rituximab within 2 months before HCT
Minor risk-mitigating factors	• Matched sibling donor • Rituximab 2-6 months before HCT
Possible risk-mitigating factors	• B cell directed CAR T cells or BITEs before HCT • B cell directed antibodies other than rituximab before HCT • Sirolimus for GVHD prophylaxis

* The assignment of the attributes of "major", "minor", or "possible" is based on our opinion, which is based in part on references[5,8-11]. It takes into account whether a risk factor has been found consistently in multiple studies. In addition, a higher weight is attributed to a risk factor for the mortality due to PTLD than a risk factor for the incidence of PTLD. Even lower weight is attributed to a risk factor for EBV reactivation (EBV DNAemia detectable at all or above a threshold).

Clinical Manifestations

- Lymphadenopathy
- Splenomegaly
- Mass by imaging
- B lymphocytosis or kappa/lambda predominance
    - Fever >38.5°C after engraftment, with negative blood cultures, persisting after 48 hours of broad spectrum antibacterial(s), otherwise unexplained

Diagnosis

- Biopsy is the gold standard. Biopsy should include *in situ* hybridization for EBER (EBV-encoded RNA).
- In Alberta, to avoid delay in therapy, we accept for diagnosis at least one of the above clinical manifestations with EBV DNAemia >30,000 IU/mL. However, if fever is the only symptom/sign of PTLD, it should be treated only if EBV DNAemia is >300,000 IU/mL.
    - Rationale for the cutoff of >30,000 IU/mL for diagnosis: This cutoff was originally formulated in 2012, one year after ProvLab's switching from the DNAemia assay measuring EBV DNA per ug blood DNA to the assay measuring EBV genome copies per mL blood. It was based on a retrospective review of 13 patients with biopsy-proven PTLD occurring in Alberta between 2004 and 2009, who had DNAemia determined within 4 days of onset of symptoms/signs of the PTLD. It included conversion of the old units (genome copies/ug DNA) to the newer units (genome copies/mL, which later turned out to be equivalent to

IU/mL), taking WBC into account. The DNAemia in the 13 cases was 42,383-19,169,040 copies/mL (median 1,633,215). The formulation of the cutoff also took into account data from the first year of EBV monitoring using the assay expressing DNAemai as copies/mL (patients undergoing HCT between Feb 2011 and Jan 2012; only biopsy-proven PTLDs were treated). In that year, 9 PTLDs were diagnosed and all of them were preceded by EBV DNAemia >30,000 copies/mL. This cutoff was further validated in 2015 based on a retrospective review of patients undergoing HCT between May 2012 and Dec 2014 (when EBV DNAemia was monitored weekly and PTLD was treated promptly). In this period, 25 PTLDs were diagnosed and all of them were preceded by EBV DNAemia >30,000 copies/mL. The adequacy of diagnosing PTLD clinically/radiologically in patients with EBV DNAemia >30,000 IU/mL was further proven in 17 patients who also had biopsies.[5]

- Rationale for the cutoff of >300,000 IU/mL when fever is the sole manifestation of PTLD: This cutoff was originally (in 2012) established arbitrarily, by consensus of Calgary transplant physicians, to minimize the likelihood of giving rituximab to patients with fever of etiology other than PTLD. This cutoff was validated in 2015 based on a retrospective review of patients undergoing HCT between Feb 2011 and Dec 2014. In this period, 4 patients died due to PTLD and the diagnosis of all the 4 PTLDs was preceded by EBV DNAemia >300,000 IU/mL.
- Rationale for the conversion of EBV genome copies/mL to IU/mL of 1:1. In mid March 2016, ProvLab started to run 2 EBV DNAemia assays, (1) the in-house assay reporting the EBV DNAemia as copies/mL whole blood, and (2) the RealStar EBV PCR assay (Altona Diagnostics) reporting the EBV DNAemia as IU/mL whole blood. The goal was to transition to running only the RealStar as of June 2016. Between mid March 2016 and mid June 2016, 91 EBV DNAemias above quantitation limit (by both assays) were determined. Results of both assays were near-identical (Kalra et al: submitted).

Interventions for Reducing the Incidence or Mortality of PTLD

Options for reducing the incidence or mortality of PTLD include:

- EBV specific T cells[11-13]
  - 70-100% efficacy
  - No toxicity; however, costly and may be rejected (if from 3rd party)
  - Can be given as
    - Prophylaxis (given to all patients early posttransplant)
    - Preemptive therapy (given to patients with high EBV DNAemia in the setting of EBV monitoring)
    - Prompt therapy (given at clinical diagnosis of PTLD in the setting of EBV monitoring)
    - Therapy (given at diagnosis of PTLD in the absence of EBV monitoring)
- Rituximab
  - 60-100% efficacy

    - Can be given as prophylaxis, preemptive therapy, prompt therapy, or therapy (without EBV monitoring) – Table 1
    - Toxicities/disadvantages of rituximab:
        - Infusion reactions
        - Hypo-IgM/IgG
        - Neutropenia,[12] which may be clinically significant[13-15]
        - Vaccination onset needs to be moved to at least 6 months after the last rituximab dose
- Reduction of immunosuppressive drug(s) preemptively
    - Efficacy and toxicity (GVHD?) in the setting of preemptive or prompt therapy not well studied
    - In the setting of Therapy, reduction of immunosuppression (RI) studied only in addition to rituximab
    - Addition of RI to rituximab ↓'ed mortality due to PTLD & ↑'ed overall survival[16]
- Purging grafts of B cells (theoretical)
- Alemtuzumab instead of ATG
    - PTLD still occurs, though less than with ATG[17-20]
    - Alemtuzumab may be associated with more CMV disease and other non-EBV viral infections.[21] Moreover, impact of alemtuzumab on relapse has not been well studied whereas ATG with myeloablative conditioning has not been associated with increased relapse in 5 randomized studies.[22]
- CD19-directed CAR T cells or Blinatumomab
    - So far only case reports of success.[23-26]
    - Theoretically, blinatumomab needs a minimum number of T cells for efficacy.

Table 1. Comparison of four strategies of management of PTLD with rituximab[7]

Management Strategy	Number of evaluable patients	Number of controls	Management strategy in controls	Efficacy Endpoint	% patients who achieved the efficacy endpoint	Comment	Reference
Therapy without EBV Monitoring	12 w PTLD	None	n/a	Sustained CR	67%		Faye 2001[27]
	146 w PTLD	None	n/a	Cure or improvement	63%		Styczynski 2009[28]
	144 w PTLD	None	n/a	Not dying 2° PTLD	61%		Styczynski 2013[16]
	27 w PTLD	None	n/a	CR	74%		Zhu 2019[29]
	19 w PTLD	None	n/a	Sust. regression	73%		Kalra 2018[6]
	70 w PTLD	None	n/a	CR	69%		Luo 2020[30]
Prompt therapy	5 w PTLD	None	n/a	Regression	100%		Wagner 2004[31]
	6 w PTLD	None	n/a	CR	67%		Kinch 2007[32]
	6 w PTLD	None	n/a	Not dying 2° PTLD	17%		Sanz 2014[33]
	87 w PTLD	None	n/a	ORR	51%*		Garcia-C. 2019[34]
	266 total, 24 w PTLD	199 total, 19 w PTLD	Therapy w/o EBV Monitor.	Sust. regression	75 vs 73% (N.S.)	No impact on OS	Kalra 2018[6]
				PTLD incidence	11 vs 6% (p=.06)		
				Mortality 2° PTLD	1 vs 1% (N.S.)		
Preemptive therapy	93 w high EBV	None	n/a	EBV undetectable	83%	2 patients died of PTLD	Garcia-Cadenas 2015[35]
	55 w high EBV	None	n/a	EBV not high	91%	3 patients died of PTLD	Coppoletta 2011[36]
	9 w high EBV	None	n/a	Not dying 2° PTLD	44%		Pinana 2016[37]
	17 w high EBV	None	n/a	Not dying 2° PTLD	100%		Ahmad 2009[38]
	49 total	85 total	Therapy w/o EBV Monitor.	PTLD incidence	6 vs 12% (N.S.)	Impact on OS not reported	VanEsser 2002[39]
				Mortality 2° PTLD	0 vs 6% (N.S.)**		
	35 total	30 total	Therapy w/o EBV Monitor.	PTLD incidence	6 vs 17% (N.S.)	Impact on OS not reported	Blaes 2010[40]
				Mortality 2° PTLD	3 vs 7% (N.S.)		
	320 total	872 total	Therapy w/o EBV Monitor. or Prompt Therapy	PTLD incidence	SHR=1.02 (N.S.)	Impact on OS not reported	Kinzel 2022[5]
				Mortality 2° PTLD	SHR=0.16 (N.S.)		
Prophylaxis	55 total	68 total	Preemptive therapy	EBV high	14 vs 49% (p<.001)		Dominietto 2012[12]

				PTLD incidence	0 vs 3% (N.S.)	No impact on OS or mortality 2° PTLD	
	51 total	147 total	Prompt therapy***	EBV reactivation	2 vs 13% (p<.001)	No impact on NRM. Impact on OS not reported	Van Besien 2019[41]
				PTLD incidence	0 vs 8% (p=.041)		
				Mortality 2° PTLD	0 vs 3% (N.S.)		
	43 total	43 total	Prompt therapy***	EBV reactivation	0 vs 53% (p<.001)	Impact on NRM or OS not reported	Patel 2023[42]
				PTLD incidence	0 vs 14% (p=.02)		
				Mortality 2° PTLD	0 vs 9% (N.S.)****		

* Additional 15 patients with PTLD did not receive rituximab due to poor performance status (n=11) or PTLD diagnosis only post-mortem.
** Significant difference when comparing subroups of patients with high EBV DNAemia.
*** Stated in Van Besien 2019, surmised for Patel 2023 (publication from the same group as Van Besien 2019).
**** Significance analyzed by Chi-square or Fisher's exact test based on raw data reported in the paper.

Abbreviations: OS, overall survival; NRM, non-relapse mortality; PTLD, posttransplant lymphoproliferative disorder; Ref, reference; EBV, Epstein-Barr virus; High EBV, high EBV DNAemia; CR, complete remission; ORR, overall response rate (complete or partial remission); Ctrl, control; N.S., not significant; Sust. regression, sustained regression (regression not followed by later progression of PTLD); SHR, subhazard ratio; Mortality 2° PTLD, mortality due to PTLD; Garcia-C., Garcia-Cadenas; w, with; w/o, without; monitor., monitoring; n/a, not applicable.

In Alberta, since September 2015 we use preemptive therapy with rituximab plus taper of immunosuppression. We use the threshold of 300,000 IU/ml. This is a compromise between trying to minimize the number of deaths due to PTLD and to minimize the number of patients exposed to the risks of rituximab/taper of immunosuppression unnecessarily (Table 2 and 3). The addition of the taper of immunosuppression is an extrapolation from the study of Styczynski et al[16] showing overall survival benefit in the setting of therapy (not preemptive therapy). In the setting of preemptive therapy, the taper of immunosuppression on top of rituximab does not appear to cause GVHD.[15]

The use of preemptive therapy in patients whose conditioning includes ATG is in line with EBMT guidelines.[43] If in the future it is shown that all/most patients with PTLD who have failed rituximab plus taper of immunosuppression respond to other treatment like anti-EBV/CD19 T cells or blinatumomab, therapy of established PTLD (without EBV monitoring) may become the management of choice/

Length of Interval between Rituximab Doses, and When to Stop Rituximab

- In the preemptive therapy setting and therapy setting, treatment has been reported once a week (375 mg/m^2 i.v.), until undetectable DNAemia, maximum 4 doses [16,35,36,38,40]. In Alberta, we adopt the weekly dosing given that
    - It is in line with EBMT guidelines[43].
    - There is no evidence of benefit of more frequent dosing.
    - Weekly dosing saves rituximab, as most patients need only 2-3 doses to achieve undetectable DNAemia[38,40].
    - One dose only may be sufficient (in preemptive setting)[39].
- The only exception to the rule of weekly dosing is in a patient whose PTLD manifests with fever and the fever has not abated after 2-3 days following the first rituximab dose (and immunosuppression taper). In this instance twice weekly dosing is reasonable, so that failure of rituximab with immunosuppression taper can be pronounced early and second line therapy organized in 2 weeks after the first rituximab dose.
- Patients who have reached undetectable DNAemia after being treated for PTLD with rituximab have 100% likelihood of sustained clinical regression of PTLD (based on our experience in 15 patients, Kalra et al, ASH 2015 abstract). Thus, rituximab should be stopped when DNAemia has become undetectable.
- Patients who have not reached undetectable DNAemia after being treated for PTLD with 4 doses of rituximab have ~58% likelihood of clinical progression of PTLD (based on our experience in 12 patients, Kalra et al, ASH 2015 abstract). Thus, patients with persistently detectable EBV DNAemia after 4 weekly rituximab doses should be followed closely. Second line therapy should be instituted in case of PTLD progression or new PTLD diagnosis.

Table 2. PTLD incidence and mortality according to maximum DNAemia (pre-rituximab, if given).**

EBV DNAemia (max)*	Undetectable	<10,000/mL	10,000 – 100,000/mL	100,000 – 1,000,000/mL	>1,000,000/mL
Number of patients with PTLD of total patients in the max DNAemia range (%)	0/56 (0 %)	0/43 (0 %)	0/103 (0 %)	25/82 (30 %)	18/22 (81 %)
Number of patients with *fatal* PTLD of total patients in the max DNAemia range (%)	0/56 (0 %)	0/43 (0 %)	0/103 (0 %)	3/82 (4 %)	2/22 (9 %)

** EBV genome copies/mL, which is near-equivalent to IU/mL.*

*** Data based on 306 Albertan patients who were monitored for EBV DNAemia but not treated preemptively.*

Table 3. Possible EBV DNAemia thresholds for preemptive therapy.**

Cut off EBV DNAemia (max)	Number of PTLDs avoided by preemptive therapy (%) (assuming 100% efficacy of the preemptive therapy)	% Patients treated with rituximab of total 306 patients	% Patients treated with rituximab necessarily (would develop PTLD) of total 306 patients	% Patients treated with rituximab unnecessarily (would not develop PTLD) of total 306 patients	Number of patients dying of PTLD (% of total 306 patients)
100,000	43/43 (100 %)	34 %	14.0 %	20 %	0/306 (0.0 %)
200,000	39/43 (91 %)	25.5 %	12.7 %	12.7 %	1/306 (0.3 %)
300,000	33/43 (77 %)	16.7 %	11 %	6.2 %	1/306 (0.3 %)
400,000	31/43 (72 %)	14.7 %	10.1 %	4.5 %	1/306 (0.3 %)
500,000	23/43 (53 %)	11.4 %	7.5 %	3.9 %	1/306 (0.3 %)
600,000	22/43 (51 %)	10.7 %	7.1 %	3.6 %	2/306 (0.65 %)
700,000	22/43 (51 %)	10.1 %	7.1 %	2.9 %	2/306 (0.65 %)
800,000	20/43 (46.5 %)	9.1 %	6.5 %	2.6 %	3/306 (1.0 %)
900,000	19/43 (44 %)	7.5 %	6.2 %	1.3 %	3/306 (1.0 %)
1,000,000	18/43 (42 %)	7.1 %	5.8 %	1.3 %	3/306 (1.0%)

** EBV genome copies/mL, which is near-equivalent to IU/mL.*

*** Data based on 306 Albertan patients who were monitored for EBV DNAemia but not treated preemptively.*

Second Line Therapy[44-46]

- To be used if no response to rituximab with immunosuppression taper in 2-4 weeks.
- If no GVHD and donor is EBV-seropositive:
    - DLI (10^5 T cells/kg), or donor-derived anti-EBV T cells manufactured in our Cellular Therapy Lab (currently unavailable).
        - The main advantage of anti-EBV T cells over DLI is no toxicity. However, this option, even when available, should be discussed on a case-by-case basis as it is resource-intense and efficacy data are limited (12/16 responders using various donor sources).[47-49]
        - Anti-EBV T cells are manufactured from mononuclear cell apheresis product (10^9 WBCs) in 1-2 days, using IFNg capture system. Our CTL lab uses Prodigy closed system, in which mononuclear cells are incubated overnight with EBV peptides in the presence of a cytokine capture reagent (a bispecific antibody for CD45 and IFNg) and then incubated with anti-IFNg conjugated to a magnetic bead. The magnetic (IFNg secreting, i.e., anti-EBV) T cells are then separated by a magnet.
    - Consider off-shelf third-party anti-EBV T cells (less effective but safer than DLI).[50,51]
        - Currently available under a trial in Cincinnati (patient has to travel) or from Atara (Tabelecleucel, patient does not have to travel).
        - Sustained remission of PTLD occurs in 70-100% cases after infusion of EBV T cells from the original stem cell donor, but in only 50-60% cases after infusion of EBV T cells from a 3rd party, due in part to rejection of the 3rd party cells.
- If no GVHD and donor is EBV-seronegative:
    - Third party off-shelf anti-EBV T cells
    - Consider Blinatumomab or CD19 CAR T cells.
- If GVHD requiring systemic immunosuppression: No good option. Consider chemo.
- Chemotherapy (e.g., CHOP and/or polatuzumab vedotin (anti-CD79b conjugated to monomethylauristatin E, which damages microtubules)) may be given while waiting for cellular therapy as a temporizing measure, if PTLD is aggressive. Chemotherapy as definitive therapy is not recommended due to low efficacy and high toxicity (median survival 2 months, range 1-6).[52]
- Future options may include:
    - EBV thymidine kinase inducers, making EBV-infected cells susceptible to ganciclovir.[53]
    - Checkpoint inhibitors like nivolumab.[54]

References

1. Sanz J, Andreu R. Epstein-Barr virus-associated posttransplant lymphoproliferative disorder after allogeneic stem cell transplantation. Curr Opin Oncol 2014;26:677-83.
2. Rasche L, Kapp M, Einsele H, Mielke S. EBV-induced post transplant lymphoproliferative disorders: a persisting challenge in allogeneic hematopoetic SCT. Bone Marrow Transplant 2014;49:163-7.
3. Gulley ML, Tang W. Using Epstein-Barr viral load assays to diagnose, monitor, and prevent posttransplant lymphoproliferative disorder. Clinical microbiology reviews 2010;23:350-66.
4. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med 2010;362:1993-2000.
5. Kinzel M, Dowhan M, Kalra A, et al. Risk Factors for the Incidence of and the Mortality due to Post-Transplant Lymphoproliferative Disorder after Hematopoietic Cell Transplantation. Transplant Cell Ther 2022;28:53 e1- e10.
6. Kalra A, Roessner C, Jupp J, et al. Risk factors for post-transplant lymphoproliferative disorder after Thymoglobulin-conditioned hematopoietic cell transplantation. Clin Transplant 2018;32.
7. Storek J, Lindsay J. Rituximab for posttransplant lymphoproliferative disorder - therapeutic, preemptive, or prophylactic? Bone Marrow Transplant 2024;59:6-11.
8. Lindsay J, Othman J, Heldman MR, Slavin MA. Epstein-Barr virus posttransplant lymphoproliferative disorder: update on management and outcomes. Current opinion in infectious diseases 2021;34:635-45.
9. Al Hamed R, Bazarbachi AH, Mohty M. Epstein-Barr virus-related post-transplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities. Bone Marrow Transplant 2020;55:25-39.
10. Enok Bonong PR, Zahreddine M, Buteau C, et al. Factors Associated with Post-Transplant Active Epstein-Barr Virus Infection and Lymphoproliferative Disease in Hematopoietic Stem Cell Transplant Recipients: A Systematic Review and Meta-Analysis. Vaccines (Basel) 2021;9.
11. Marjanska A, Styczynski J. Who is the patient at hisk fo EBV reactivation and diseases: expert opinion focused on post-transplant lymphoproliferative disorders following hematopoietic stem cell transplantation. Expert Opin Biol Ther 2023;23:539-52.
12. Dominietto A, Tedone E, Soracco M, et al. In vivo B-cell depletion with rituximab for alternative donor hemopoietic SCT. Bone Marrow Transplant 2012;47:101-6.
13. Kato H, Yamamoto K, Matsuo K, et al. Clinical impact and predisposing factors of delayed-onset neutropenia after autologous hematopoietic stem-cell transplantation for B-cell non-Hodgkin lymphoma: association with an incremental risk of infectious events. Ann Oncol 2010;21:1699-705.
14. McIver Z, Stephens N, Grim A, Barrett AJ. Rituximab administration within 6 months of T cell-depleted allogeneic SCT is associated with prolonged life-threatening cytopenias. Biol Blood Marrow Transplant 2010;16:1549-56.
15. Kinzel M, Kalra A, Khanolkar RA, et al. Rituximab Toxicity after Preemptive or Therapeutic Administration for Post-Transplant Lymphoproliferative Disorder. Transplant Cell Ther 2023;29:43 e1- e8.
16. Styczynski J, Gil L, Tridello G, et al. Response to rituximab-based therapy and risk factor analysis in Epstein Barr Virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Clin Infect Dis 2013;57:794-802.
17. Cohen J, Gandhi M, Naik P, et al. Increased incidence of EBV-related disease following paediatric stem cell transplantation with reduced-intensity conditioning. Br J Haematol 2005;129:229-39.
18. Kennedy-Nasser AA, Bollard CM, Myers GD, et al. Comparable outcome of alternative donor and matched sibling donor hematopoietic stem cell transplant for children with acute lymphoblastic leukemia in first or second remission using alemtuzumab in a myeloablative conditioning regimen. Biol Blood Marrow Transplant 2008;14:1245-52.
19. Delgado J, Pillai S, Benjamin R, et al. The effect of in vivo T cell depletion with alemtuzumab on reduced-intensity allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia. Biol Blood Marrow Transplant 2008;14:1288-97.
20. Fox CP, Burns D, Parker AN, et al. EBV-associated post-transplant lymphoproliferative disorder following in vivo T-cell-depleted allogeneic transplantation: clinical features, viral load correlates and prognostic factors in the rituximab era. Bone Marrow Transplant 2014;49:280-6.
21. Myers GD, Krance RA, Weiss H, et al. Adenovirus infection rates in pediatric recipients of alternate donor allogeneic bone marrow transplants receiving either antithymocyte globulin (ATG) or alemtuzumab (Campath). Bone Marrow Transplant 2005;36:1001-8.
22. Storek J, Mohty M, Boelens JJ. Rabbit anti-T cell globulin in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015;21:959-70.

23. Yan N, Wang N, Zhang P, et al. Case Report: Successful Chimeric Antigen Receptor T Cell Therapy in Haploidentical-Allogeneic Stem Cell Transplant Patients With Post-Transplant Lymphoproliferative Disorder. Frontiers in oncology 2021;11:709370.
24. Luttwak E, Hagin D, Perry C, et al. Anti-CD19 CAR-T therapy for EBV-negative posttransplantation lymphoproliferative disease-a single center case series. Bone Marrow Transplant 2020.
25. Chen S, An L, Han J, et al. Successful Blinatumomab treatment in an allogeneic hematopoietic stem cell transplant recipient with EBV-related post-transplant lymphoproliferative disorder: A case report and literature review. Transpl Immunol 2023;80:101895.
26. Janardan S, Horwitz E, Watkins B, et al. Blinatumomab induces complete response in refractory PTLD after hematopoietic cell transplantation. Blood Adv 2022;6:3058-61.
27. Faye A, Quartier P, Reguerre Y, et al. Chimaeric anti-CD20 monoclonal antibody (rituximab) in post-transplant B-lymphoproliferative disorder following stem cell transplantation in children. Br J Haematol 2001;115:112-8.
28. Styczynski J, Einsele H, Gil L, Ljungman P. Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. Transpl Infect Dis 2009;11:383-92.
29. Zhu CY, Zhao SS, Wang XK, et al. Outcome of Rituximab-Based Treatment for Post-Transplant Lymphoproliferative Disorder After Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Center Experience. Annals of transplantation : quarterly of the Polish Transplantation Society 2019;24:175-84.
30. Luo XY, Mo XD, Xu LP, et al. A retrospective analysis on anti-CD20 antibody-treated Epstein-Barr virus-related posttransplantation lymphoproliferative disorder following ATG-based haploidentical T-replete hematopoietic stem cell transplantation. Ann Hematol 2020;99:2649-57.
31. Wagner HJ, Cheng YC, Huls MH, et al. Prompt versus preemptive intervention for EBV lymphoproliferative disease. Blood 2004;103:3979-81.
32. Kinch A, Oberg G, Arvidson J, Falk KI, Linde A, Pauksens K. Post-transplant lymphoproliferative disease and other Epstein-Barr virus diseases in allogeneic haematopoietic stem cell transplantation after introduction of monitoring of viral load by polymerase chain reaction. Scand J Infect Dis 2007;39:235-44.
33. Sanz J, Arango M, Senent L, et al. EBV-associated post-transplant lymphoproliferative disorder after umbilical cord blood transplantation in adults with hematological diseases. Bone Marrow Transplant 2014;49:397-402.
34. Garcia-Cadenas I, Yanez L, Jarque I, et al. Frequency, characteristics, and outcome of PTLD after allo-SCT: A multicenter study from the Spanish group of blood and marrow transplantation (GETH). Eur J Haematol 2019;102:465-71.
35. Garcia-Cadenas I, Castillo N, Martino R, et al. Impact of Epstein Barr virus-related complications after high-risk allo-SCT in the era of pre-emptive rituximab. Bone Marrow Transplant 2015;50:579-84.
36. Coppoletta S, Tedone E, Galano B, et al. Rituximab treatment for Epstein-Barr virus DNAemia after alternative-donor hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2011;17:901-7.
37. Pinana JL, Sanz J, Esquirol A, et al. Umbilical cord blood transplantation in adults with advanced hodgkin's disease: high incidence of post-transplant lymphoproliferative disease. Eur J Haematol 2016;96:128-35.
38. Ahmad I, Cau NV, Kwan J, et al. Preemptive management of Epstein-Barr virus reactivation after hematopoietic stem-cell transplantation. Transplantation 2009;87:1240-5.
39. van Esser JW, Niesters HG, van der Holt B, et al. Prevention of Epstein-Barr virus-lymphoproliferative disease by molecular monitoring and preemptive rituximab in high-risk patients after allogeneic stem cell transplantation. Blood 2002;99:4364-9.
40. Blaes AH, Cao Q, Wagner JE, Young JA, Weisdorf DJ, Brunstein CG. Monitoring and preemptive rituximab therapy for Epstein-Barr virus reactivation after antithymocyte globulin containing nonmyeloablative conditioning for umbilical cord blood transplantation. Biol Blood Marrow Transplant 2010;16:287-91.
41. Van Besien K, Bachier-Rodriguez L, Satlin M, et al. Prophylactic rituximab prevents EBV PTLD in haplo-cord transplant recipients at high risk. Leuk Lymphoma 2019;60:1693-6.
42. Patel C, Pasciolla M, Abramova R, et al. Pre-Hematopoietic Stem Cell Transplantation Rituximab for Epstein-Barr Virus and Post-Lymphoproliferative Disorder Prophylaxis in Alemtuzumab Recipients. Transplant Cell Ther 2023;29:132 e1- e5.
43. Styczynski J, Reusser P, Einsele H, et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant 2009;43:757-70.
44. DiNardo CD, Tsai DE. Treatment advances in posttransplant lymphoproliferative disease. Curr Opin Hematol 2010;17:368-74.
45. Heslop HE. How I treat EBV lymphoproliferation. Blood 2009;114:4002-8.

46. Atallah-Yunes SA, Salman O, Robertson MJ. Post-transplant lymphoproliferative disorder: Update on treatment and novel therapies. Br J Haematol 2023;201:383-95.
47. Moosmann A, Bigalke I, Tischer J, et al. Effective and long-term control of EBV PTLD after transfer of peptide-selected T cells. Blood 2010;115:2960-70.
48. Icheva V, Kayser S, Wolff D, et al. Adoptive transfer of epstein-barr virus (EBV) nuclear antigen 1-specific t cells as treatment for EBV reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. J Clin Oncol 2013;31:39-48.
49. Kallay K, Kassa C, Reti M, et al. Early Experience With CliniMACS Prodigy CCS (IFN-gamma) System in Selection of Virus-specific T Cells From Third-party Donors for Pediatric Patients With Severe Viral Infections After Hematopoietic Stem Cell Transplantation. J Immunother 2018;41:158-63.
50. Doubrovina E, Oflaz-Sozmen B, Prockop SE, et al. Adoptive immunotherapy with unselected or EBV-specific T cells for biopsy-proven EBV+ lymphomas after allogeneic hematopoietic cell transplantation. Blood 2012;119:2644-56.
51. Prockop S, Doubrovina E, Suser S, et al. Off-the-shelf EBV-specific T cell immunotherapy for rituximab-refractory EBV-associated lymphoma following transplantation. J Clin Invest 2020;130:733-47.
52. Socie G, Barba P, Barlev A, et al. Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy. Bone Marrow Transplant 2024;59:52-8.
53. Perrine SP, Hermine O, Small T, et al. A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. Blood 2007;109:2571-8.
54. Kassa C, Remenyi P, Sinko J, Kallay K, Kertesz G, Krivan G. Successful nivolumab therapy in an allogeneic stem cell transplant child with post-transplant lymphoproliferative disorder. Pediatr Transplant 2018;22:e13302.

Pneumocystis and Bacterial Prophylaxis

Presented by: Jan Storek

Summary

- Bacterial prophylaxis peritransplant
  - GCSF – only autologous HCT recipients and cord blood transplant recipients
    - Start on day 7. Discontinue when ANC>1.0/nl
    - In adults, use 300 micrograms qd sc for <70 kg patients, 480 micrograms qd sc for >70 kg patients
    - In children, use 5 micrograms/kg daily sc
  - No growth factors routinely for allogeneic HCT recipients (except for cord blood)
  - No growth factors routinely for CAR T cell recipients (except if late neutropenia)
  - No antibacterials peri-transplant routinely (both autologous and allogeneic HCT recipients, except some autoimmune diseases (see pertinent chapter)
  - No IVIG routinely. IVIG can be considered for very low IgG (<4g/L), or low IgG (4-6 g/L) associated with severe or recurrent non-neutropenic infections.
- *Pneumocystis jirovecii* and *Streptococcus pneumoniae* prophylaxis
  - Both autologous and allogeneic HCT recipients, and CAR T cell recipients.
  - Start at engraftment. If CD4 ≥ 200/microliter at 12 months, discontinue PJP and *Pneumococcal* prophylaxis. If CD4 < 200/microliter at 12 months, continue until 24 months. Continue/resume prophylaxis when treating GVHD with immunosuppressive drugs, until ≥ 3 months after discontinuation of immunosuppressive therapy (systemic and topical), when cGVHD is inactive.
  - Pretransplant prophylaxis should be considered in patients with substantial immune deficiency, including lymphoma/myeloma patients after mobilization chemotherapy, acute leukemia patients after induction/consolidation chemotherapy, or CLL patients treated with alemtuzumab.
  - Prefer cotrimoxazole (sulfamethoxazole + trimethoprim)
    - In adults, 400/80 mg po qd
    - In children, 375/75 mg/m^2 po qd
  - For cotrimoxazole-intolerant patients (only if intolerance has been well documented), use Dapsone 50 mg po qd every day (1 mg/kg po qd in children), plus Penicillin V 600 mg po qd (150-300 mg po qd in children). Penicillin can be omitted in autologous HCT recipients.
  - In splenectomized patients, give Penicillin (dose as above) indefinitely, except when patient is on cotrimoxazole.

Background

The literature on bacterial/*Pneumocystis* prophylaxis after HCT contains few randomized trials. Most of the randomized trials on bacterial prophylaxis are of limited value due to the emergence of bacterial resistance to the drug studied in the randomized trial after the follow-up period of the trial. Most of the trials on *Pneumocystis* prophylaxis were performed in HIV patients and recommendations were extrapolated to HCT patients. The literature has been well summarized in international guidelines[1,2]. These recommendations, including Calgary-specific deviations, are summarized below.

Recommendations for Peritransplant & Early Post-HCT (< 3 month) Period

- Dental consult pretransplant
- Hand washing/sanitizing
- Single-bed rooms and other hospital infection control
- Household contacts and health care workers should be up-to-date with vaccines
- No gut decontamination (resistance, compliance, cost)
- No antibiotic-impregnated central catheters (controversial efficacy, high cost)
- No systemic antibacterials peritransplant
    - Advantage:
        - Low rate of bacterial infection or fever (but no survival benefit)
    - Disadvantages:
        - Resistance
        - *C. difficile*
- Growth factors
    - AutoHCT: GCSF from day 7. Despite no effect on OS, there is reduction of infections and shortening of hospital stay.
    - AlloHCT: No growth factors routinely, because
        - GVHD may be induced/worsened by GM-CSF or G-CSF[3]
        - T cell reconstitution may be impaired by G-CSF (if ATG used)[4], which may negatively impact NRM and OS[5]
    - CAR T cells: No growth factors routinely due to insufficient information on risk:benefit
        - OK to use GCSF in case of late neutropenia.
- No routine IVIG (only a marginal or undetectable reduction in rates of bacterial infections).
    - OK to give IVIG with very low IgG (<4g/L), or low IgG (4-6 g/L) associated with severe or recurrent non-neutropenic infections.
    - This also applies to the late post-HCT (d> 100) period.
- For *Pneumocystis* prophylaxis, see next section.

Recommendations for Late Post-HCT (d >100) Period

- *Pneumocystis jirovecii* pneumonia (PJP) incidence in pre-prophylaxis era was 4% in the first 3 months and 6% later after allogeneic HCT[6]. When PJP prophylaxis was used until approximately 6 months in allo HCT recipients not getting ATG (typically getting only CNI+MTX for GVHD prophylaxis), PJP incidence was ≤1%. However, with ATG, in Albertan patients using PJP prophylaxis until approximately 6 months, we have noted PJP incidence over 3%[7]. Specifically, in 278 patients without grade 2-4 aGVHD or moderate-severe cGVHD who discontinued PJP prophylaxis at 6 months or soon thereafter, no PJP occurred in the first 6 months, 8 PJPs occurred at 7-12 months, 2 PJPs occurred at 13-24 months, and no PJP at >24 months. As approximately 30% of patients with PJPs need to be treated in the ICU and approximately 15% were fatal, in 2018 we decided to extend PJP prophylaxis until 12 months, and to 24 months in patients with CD4 T cell counts < 200/microliter at 12 mo. CD4 T cell count < 200/microliter is a well-recognized risk factor for PJP (reviewed by Messiaen PE et al.,[8] consistent with Evernden C et al.[7]). Thus:
    - PJP prophylaxis in Alberta is routinely given to patients from engraftment until 12 mo posttransplant. For patients with CD4 T cell count < 200/microliter at 12 months, prophylaxis is continued until 24 months. Patients treated with immunosuppressive drugs for chronic GVHD should continue PJP until ≥3 months after discontinuation of immunosuppressive therapy (systemic and topical), when cGVHD is inactive.
        - Sulfamethoxazole + trimethoprim (cotrimoxazole) is preferred to dapsone, atovaquone and inhaled pentamidine due to highest efficacy (see Tables) and broader antimicrobial spectrum (including *S.pneumoniae*, *Toxoplasma*, *Nocardia*).
        - Patients with documented allergy to cotrimoxazole may be desensitized (see Appendix). Patients who experience non-allergic toxicity to cotrimoxazole (e.g., cytopenia, ↑ALT, ↑creatinine), should be rechallenged with cotrimoxazole prior to being committed to long-term treatment with a second-line agent.
        - Multiple regimens of cotrimoxazole have been found near 100% efficacious for PJP prophylaxis (e.g., 400/80 mg qd, 800/160 mg qd, 800/160 mg 3x a week) (see Tables). In Alberta, 400/80 mg qd is used due to simplicity.
        - For second-line prophylaxis, dapsone 50 mg qd is preferred[7]. Atovaquone as well as inhaled pentamidine have a high breakthrough PJP rate[7,9].
- *Streptococcus pneumoniae* disease incidence is significantly higher in allogeneic HCT recipients compared to general population (Figure 1). Peak incidence is at 3-24 months posttransplant. Risk factors include:
        - cGVHD (Fig. 1)
        - Splenectomy
        - Hypo-IgG, particularly IgG_2
    - Antibiotics covering *S. pneumoniae* are routinely given to all Albertan HCT recipients from engraftment until the end of PJP prophylaxis, as both cGVHD and low CD4 counts

are risk factors for *S. pneumoniae* disease. In splenectomized patients, *S. pneumoniae* prophylaxis is continued indefinitely.

- In autologous HCT recipients, both PJP and *S. pneumoniae* disease incidences are lower than after allogeneic HCT but higher than in the general population. For simplicity, we use the same PJP/*S. pneumoniae* prophylaxis as for allogeneic HCT recipients. However, for autologous HCT recipients who are cotrimoxazole-intolerant, it is acceptable to give only dapsone and omit penicillin. The rationale is that the incidence of *Pneumococcal* infections after autoHCT is approximately 2-fold lower than after alloHCT (5 vs 12/1000 HCTs,[10] or 5 vs 9/1000 HCTs[11]), which makes *Pneumococcal* prophylaxis less important after auto than alloHCT.
- In CAR T cell recipients, we use the same PJP and *S. pneumoniae* prophylaxis as for allogeneic HCT recipients. The reason is that per limited data available so far, CAR T cell recipients are prone to similar infections and as frequent infections as HCT recipients, albeit possibly not as severe[12], and reconstitution of CD4 T cell counts to >200/microliter appears to take 1 to 2 years, i.e., similar for ATG-conditioned alloHCT recipients[13,14]. This approach is further supported by current guidelines of EBMT, ASCO, ASTCT, and CARTOX.
    - In a study of 300 CAR T cell recipients (mostly anti-CD19) not prophylaxed against PJP, 8 (2.7%) developed PJP, median day 98 (range, 52-251) (median f/u of total cohort unclear but probably <1 year)[15]. This suggests that prophylaxis may be warranted, but risk:benefit should ideally be established (contribution of cotrimoxazole to post-CART cytopenias?).
- Vaccinate patients against *S. pneumoniae* and with other vaccines per standard schedule (see chapter on Vaccination).

References

1. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Preface. Bone Marrow Transplant 2009;44:453-5.
2. Groll AH, Pana D, Lanternier F, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. Lancet Oncol 2021;22:e254-e69.
3. Singh V, Jang H, Kim S, et al. G-CSF use post peripheral blood stem cell transplant is associated with faster neutrophil engraftment, shorter hospital stay and increased incidence of chronic GVHD. Leuk Lymphoma 2021;62:446-53.
4. de Koning C, Gabelich JA, Langenhorst J, et al. Filgrastim enhances T-cell clearance by antithymocyte globulin exposure after unrelated cord blood transplantation. Blood Adv 2018;2:565-74.
5. Orfali N, Zhang MJ, Allbee-Johnson M, et al. Planned Granulocyte Colony-Stimulating Factor Adversely Impacts Survival after Allogeneic Hematopoietic Cell Transplantation Performed with Thymoglobulin for Myeloid Malignancy. Transplant Cell Ther 2021;27:993 e1- e8.
6. Sullivan KM, Meyers JD, Flournoy N, Storb R, Thomas ED. Early and late interstitial pneumonia following human bone marrow transplantation. Int J Cell Cloning 1986;4 Suppl 1:107-21.
7. Evernden C, Dowhan M, Dabas R, et al. High incidence of Pneumocystis jirovecii pneumonia in allogeneic hematopoietic cell transplant recipients in the modern era. Cytotherapy 2020;22:27-34.
8. Messiaen PE, Cuyx S, Dejagere T, van der Hilst JC. The role of CD4 cell count as discriminatory measure to guide chemoprophylaxis against Pneumocystis jirovecii pneumonia in human immunodeficiency virus-negative immunocompromised patients: A systematic review. Transpl Infect Dis 2017;19.
9. Redjoul R, Robin C, Foulet F, et al. Pneumocystis jirovecii pneumonia prophylaxis in allogeneic hematopoietic cell transplant recipients: can we always follow the guidelines? Bone Marrow Transplant 2019;54:1082-8.
10. Engelhard D, Cordonnier C, Shaw PJ, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. Br J Haematol 2002;117:444-50.
11. Youssef S, Rodriguez G, Rolston KV, Champlin RE, Raad, II, Safdar A. Streptococcus pneumoniae infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989-2005. Medicine 2007;86:69-77.
12. Pernas B, Iacoboni G, Los-Arcos I, et al. Patients with aggressive B-cell lymphoma receiving CAR T-cell therapy have a low rate of severe infections despite lack of universal antibacterial and antifungal prophylaxis. Eur J Haematol 2024;113:227-34.
13. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. Haematologica 2021;106:978-86.
14. Baird JH, Epstein DJ, Tamaresis JS, et al. Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. Blood Adv 2021;5:143-55.
15. Zu C, Li W, Zhang M, et al. Outcome of Pneumocystis Jirovecii pneumonia (PcP) in post-CAR-T patients with hematological malignancies. BMC Infect Dis 2024;24:1147.
16. Kulkarni S, Powles R, Treleaven J, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. Blood 2000;95:3683-6.
17. Kumar D, Humar A, Plevneshi A, et al. Invasive pneumococcal disease in adult hematopoietic stem cell transplant recipients: a decade of prospective population-based surveillance. Bone Marrow Transplant 2008;41:743-7.
18. Sullivan KM, Storek J, Kopecky KJ, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic GVHD following marrow transplantation: Clinical outcome and effect on subsequent immune recovery. Biol Blood Marrow Transplant 1996;2:44-53.
19. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. The Dutch AIDS Treatment Group. N Engl J Med 1992;327:1836-41.
20. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. N Engl J Med 1995;332:693-9.
21. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med 1987;316:1627-32.
22. Sangiolo D, Storer B, Nash R, et al. Toxicity and efficacy of daily dapsone as Pneumocystis jiroveci prophylaxis after hematopoietic stem cell transplantation: a case-control study. Biol Blood Marrow Transplant 2005;11:521-9.

23. Souza JP, Boeckh M, Gooley TA, Flowers ME, Crawford SW. High rates of Pneumocystis carinii pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. Clin Infect Dis 1999;29:1467-71.
24. Purdy BH, Philips DM, Summers RW. Desensitization for sulfasalazine skin rash. Ann Intern Med 1984;100:512-4.
25. Pyle RC, Butterfield JH, Volcheck GW, et al. Successful outpatient graded administration of trimethoprim-sulfamethoxazole in patients without HIV and with a history of sulfonamide adverse drug reaction. J Allergy Clin Immunol Pract 2014;2:52-8.

Appendix, including Figures and Tables

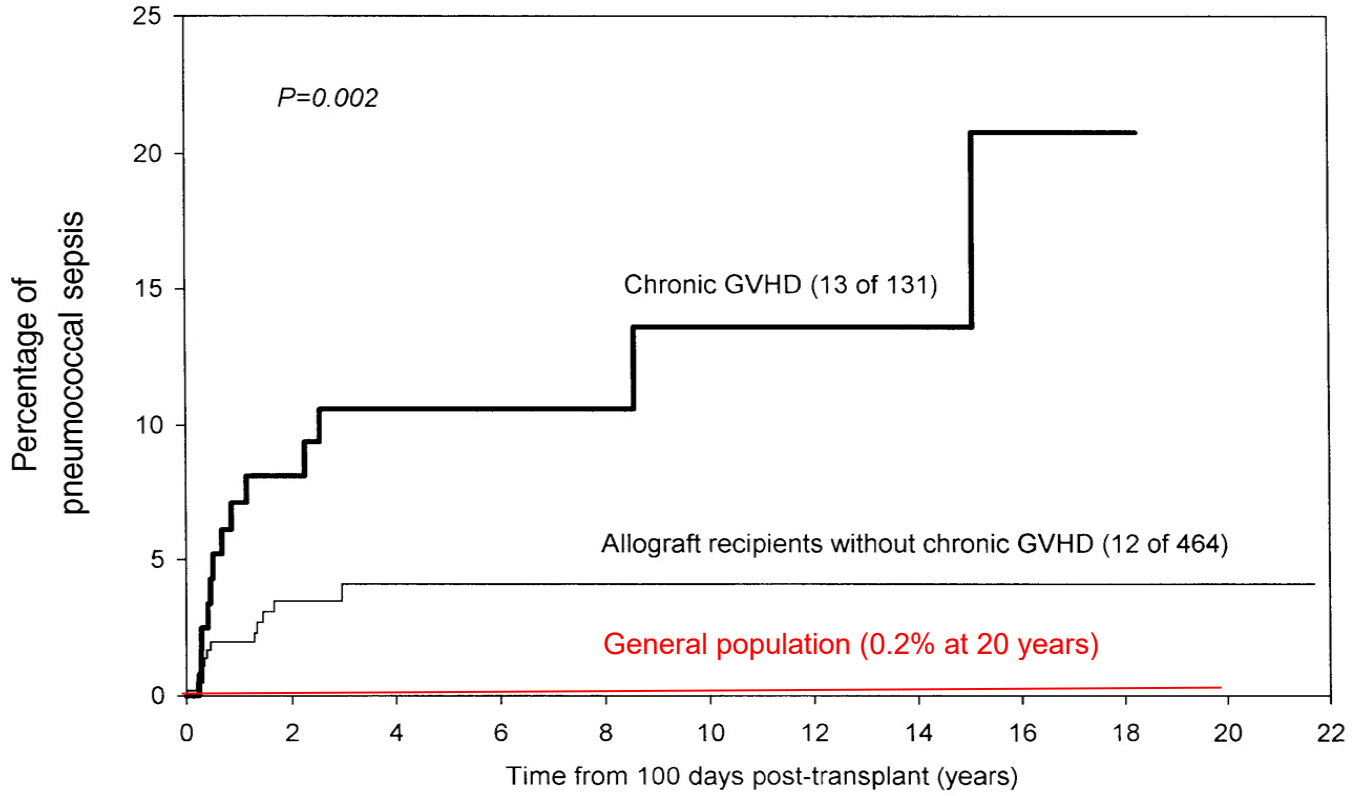


Fig. 1. Incidence of Pneumococcal Sepsis after alloHCT. From Kulkarni, S. et al. Blood 2000;95:3683-3686.[16] Red line represents data on general population from Kumar D. et al. BMT 41:743-747, 2008.[17]

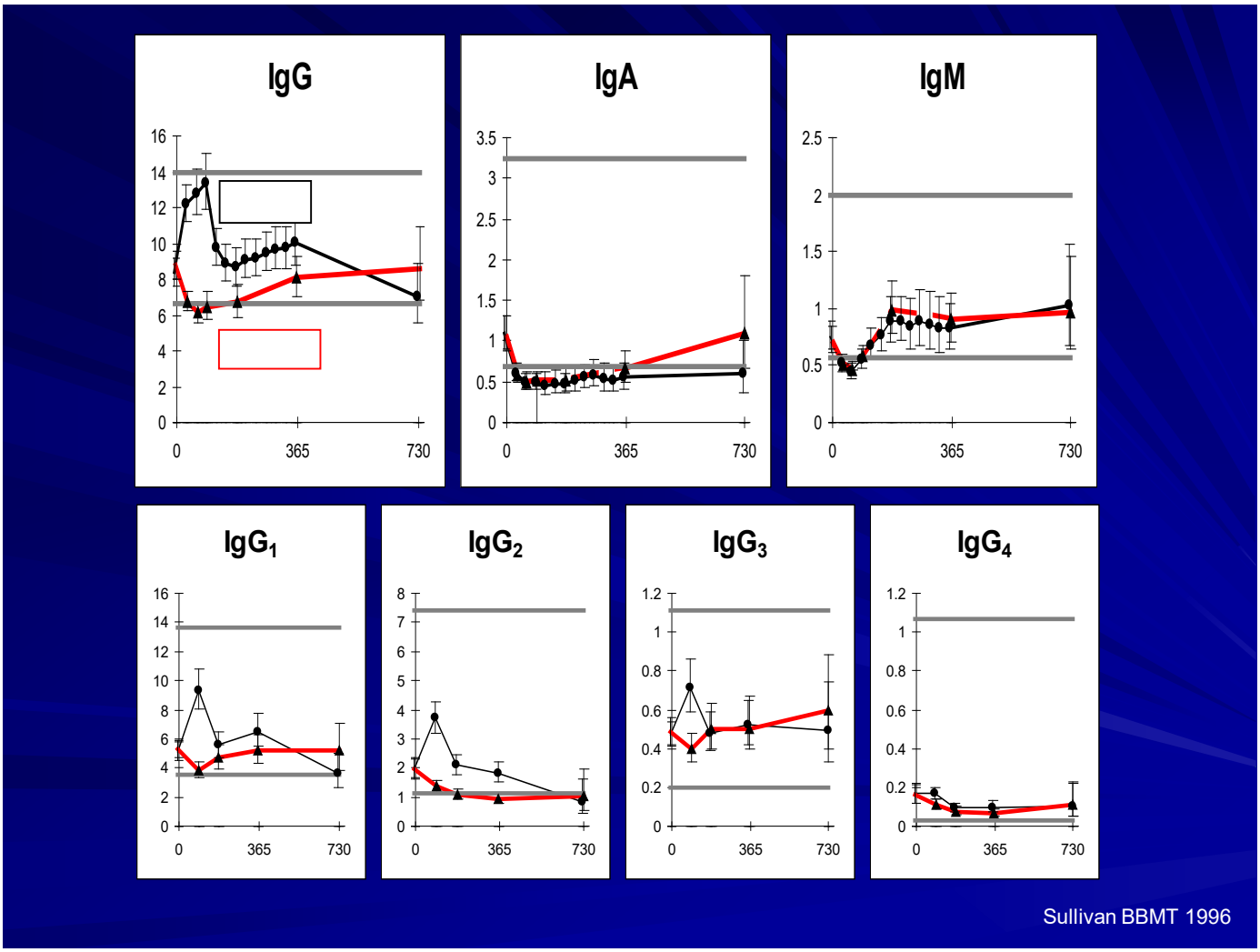


Fig. 2. Serum Ig concentration in patients not receiving IVIgG (red line) and patients receiving IVIgG in the first 12 months posttransplant, showing that whereas IgG levels were higher in the IVIgG group till 1 year, they were paradoxically lower at 2 years, suggesting that the exogenous IgG hampered reconstitution of the production of endogenous IgG. From Sullivan KM et al. BBMT 2:44-53, 1996.[18]

Comparison of prophylactic dosing schedules of Sulfamethoxazole+Trimethoprim and alternative anti-PJP drugs

Schneider MM et al. A controlled trial of aerosolized pentamidine or thrimethoprim-sulfamethoxazole as primary prophylaxis afainst Pneumocystis pneumonia in patient with HIV infection.[19]

	Efficacy (% developing Pneumocystis pneumonia)	Toxicity (% discontinuing drug)
Pentamidine inhaled monthly	11%	3%
Sulfa+Trim 800+160 mg daily	0%	25%
Sulfa+Trim 400+80 mg daily	0%	24%

Bozzette SA et al. A randomized trial of three antiPneumocystis agents in patients with advanced human immunodeficiency virus infection.[20]

	Efficacy (% developing Pneumocystis pneumonia per year)	Toxicity (% discontinuing drug)
Dapsone 50 mg bid	2.6%	75%
Pentamidine inhaled monthly	5.7%	12%
Sulfa+Trim 800+160 mg bid	1.2%	79%

Hughes WT et al. Successful intermittent chemoprophylaxis for Pneumocystis pneumonitis (in pts treated with chemotherapy for acute lymphoblastic leukemia).[21]

	Efficacy (% developing Pneumocystis pneumonia)	Toxicity (% with adverse effect)
Sulfa+Trim 800+160 mg daily	0%	17%
Sulfa+Trim 800+160 mg 3x/week (3 consec.days)	0%	20%

Sangiolo D et al. Toxicity and Efficacy of daily dapsone as Pneumocystis jirovecii prophylaxis after HCT: A case-control study.[22]

	Efficacy (% developing Pneumocystis pneumonia)	Toxicity (% discontinuing drug)
Dapsone 50 mg bid	1.3%	Not given
Sulfa+Trim 800+160 mg bid	0%	Not given

Souza JP et al. High rates of Pneumocystis carinii pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis.[23]

	Efficacy (% developing Pneumocystis pneumonia)	Toxicity (% discontinuing drug)
Dapsone 50 mg bid 3x a week	7.2%	Not given
Sulfa+Trim 800+160 mg bid twice a week	0.4%	Not given

Desensitization Protocol for HCT Patients with Sulfa Allergies

(Modified from Purdy et al.[24] and Pyle et al.[25])

Desensitization should be performed in the clinic (or in hospital), with the patient remaining in the clinic for 30 min after taking a dose. This is more important for a history of anaphylaxis than a history of only rash.

A stock solution (Standard Pediatric Oral Suspension, trimethoprim (TMP) 40 mg plus sulfamethoxazole (SMX) 200 mg per 5 ml) is used, followed by single-strength tablets (80 mg TMP plus 400 mg SMX).

Sulfa Desensitization Schedule: (same for adults and children)
On Days 1 through 5: the **stock suspension is diluted:** One (1) ml of stock + 9 ml saline in a 10 ml syringe = 4 mg/ml SMX

Day 1: Take 0.25 ml = 1 mg SMX
Day 2: Take 0.50 ml = 2 mg SMX
Day 3: Take 1 ml = 4 mg SMX
Day 4: Take 2 ml = 8 mg SMX
Day 5: Take 4 ml = 16 mg SMX

On Days 6 through 9, the **stock solution is used full strength**:

Day 6: Take 0.5ml of stock = 20 mg SMX
Day 7: Take 1 ml of stock = 40 mg SMX
Day 8: Take 2 ml of stock = 80 mg SMX
Day 9: Take 4 ml of stock = 160 mg SMX
Day 10: Take 1 single-strength tablet (400 mg SMX).

If no reaction occurs, patient can continue dosing at 1 single-strength tablet once daily. Allergic reaction can occur up to 30 days into this dosing, however, the reaction is usually mild so the doses do not have to be given in the clinic.
If a mild allergic reaction occurs or if the desensitization process is interrupted for reasons other than allergic reaction, then give a test dose of half the last dose. If the patient tolerates this test dose, then restart dosing at the last dose.
If a severe allergic reaction occurs, administer epinephrine, 0.3-0.5 mL of 1:1000 dilution, subcutaneously every 10-20 min.
If needed, follow by a corticosteroid (eg, 50 mg methylprednisolone IV q 6 h).
If needed, follow by an antihistamine (eg, diphenhydramine 25-50 mg IV or IM or PO q 6 h) and normal saline IV.

Fungal Prophylaxis

Presented by: Ahsan Chaudhry

Summary

- Primary prophylaxis with fluconazole 400 mg daily should be given to all allogeneic hematopoietic cell transplant recipients from days 1 to 28. Fluconazole prophylaxis is not routinely accompanied by galactomannan monitoring except in high risk patients.
- Primary prophylaxis with Posaconazole 300 mg daily is given to patients with Grade 3-4 acute graft-versus-host disease (GVHD) for 90 days.
- CAR-T cell therapy recipients should receive fluconazole prophylaxis during the neutropenic period (ANC <0.5). Posaconazole is recommended for patients with recent allotransplant, prior invasive mold infection, prolonged neutropenia >14 days, or prolonged corticosteroid use >3 days.
- No primary prophylaxis or galactomannan screening should be applied to those who develop grade 1-2 acute GVHD, chronic GVHD (irrespective of severity), or to autologous transplant recipients.
- Secondary prophylaxis may be used. It requires consideration of the etiologic agent identified from the previous episode of invasive fungal disease, and of the previous response to antifungal therapy.
- Empiric antifungal treatment is given to patients with persistent neutropenic fever not responsive to at least 4 days of appropriate antibacterial coverage. Micafungin or liposomal amphotericin B is used. The empiric antifungal treatment will be discontinued after 2 days of absolute neutrophil count (ANC)>0.5/nl for afebrile patients and after 4 days of ANC>0.5/nl for those who are persistently febrile.

Background

Despite the recent development of novel and extended spectrum antifungal antibiotics, invasive fungal infections remain a significant cause of morbidity and mortality in stem cell transplant recipients. Mortality with these infections remains extremely high.
These antifungal standard practice recommendations derive primarily from:

- European Conference on Infections in Leukemia (ECIL 7 guidelines 2018)[1];
- 2016 Aspergillosis[2] and candidemia[3] treatment guidelines of the Infectious Diseases Society of America;
- Analysis of the important supporting literature; and
- Local considerations (fungal epidemiology, drug availability, ongoing construction projects)

Primary Prophylaxis

Primary antifungal prophylaxis is indicated for populations at high risk of developing invasive fungal disease, those being leukemic patients receiving chemotherapy, and allogeneic hematopoietic stem

cell transplant (HSCT) recipients. Conceptually, prophylactic recommendations for the allogeneic HSCT population have been divided into the early neutropenic and the GVHD phases[1].

The risk of invasive candidiasis is greatest in the early post-transplant period (phase I) due to the presence of neutropenia, severe mucositis, and central venous catheter use. In the post-engraftment period (phase II and III), few HSCT recipients require prophylaxis against *Candida* species, unless gastrointestinal GVHD or a central venous catheter (CVC) (the main risk factors) are present. Dissemination of endogenous *Candida* species colonizing the gastrointestinal (GI) tract is the usual cause of invasive candidiasis, although more rarely, it may be spread on the hands of healthcare workers. Autologous hematopoietic cell transplant (HCT) recipients have minimal risk for invasive candidiasis once neutropenia and mucositis resolve.

The risk of mold infection, while higher during the GVHD phase, is also relevant during the initial neutropenic phase. During phase I, prolonged neutropenia, active leukemia and prevalence >8% are the main risk factor for mold infection, being higher in bone marrow and umbilical cord blood transplants, and lower in nonmyeloablative and peripheral blood transplants. In phase II and III, cell-mediated immunodeficiency caused by GVHD and its treatment is the main risk factor, especially in those receiving unrelated donor, mismatched or haploidentical transplants.

For these reasons, even though fluconazole is highly recommended in the initial neutropenic phase in low risk populations, it should be used when combined with a mold-directed diagnostic approach (i.e. galactomannan or CT-based) or a mold-directed therapeutic approach (i.e. empiric antifungal therapy) in high risk populations. Of note, a number of prospective and retrospective studies (as cited below) have evaluated various mold-active antifungals versus fluconazole as primary prophylaxis in the neutropenic phase and have failed to demonstrate differences in overall survival.

Primary antifungal prophylaxis in the neutropenic phase at our center is with fluconazole for 28 days due to a low incidence of invasive mold infection (<4% in past 3yrs). It should start from the end of the conditioning regimen. In high risk patients (UCB, active leukemia, prolonged neutropenia, prolonged steroid exposure), serum galactomannan monitoring twice a week during neutropenia will be added or voriconazole prophylaxis can be considered. If galactomannan screening is positive (defined by optical density ≥0.5 on two consecutive occasions) it will be followed by CT imaging +/- bronchoscopy, followed by anti-aspergillus therapy if proven or probable aspergillosis. Maertens et al. have demonstrated that such a fluconazole plus galactomannan monitoring approach can be highly successful.[46]

Allogeneic HSCT Recipients, Initial Neutropenic Phase

Table 1. ECIL recommendations on primary antifungal prophylaxis in adult allogenic HSCT recipients: re-engraftment period

Antifungal Agent	Pre-engraftment risk of mould infections	
	low	high
Fluconazole 400 mg q24h	A-I	
Posaconazole oral solution 200 mg q8h *or* tablet 300mg q24h following a loading dose of 300 mg q12h on day 1	B-II	B-II
Itraconazole oral solution 2.5 mg/kg q12h	B-I	B-I
Voriconazole 200 mg q12h	B-I	B-I
Micafungin 50 mg q24h	B-I	C-1
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10mg twice weekly) plus fluconazole 400 mg q24h	C-III	B-II
Fluconazole 400 mg q24h		A-III against

* Fluconazole should only be used when combined with a mould diagnostic approach in centers that do not have HEPA-filtered rooms or have a high baseline incidence of mould infection 5-8%.

Allogeneic HSCT Recipients, GVHD Phase

While fluconazole, itraconazole and voriconazole have been studied through the initial neutropenic phase and into the GVHD phase, posaconazole and fluconazole are the only anti-fungals that have been studied specifically in the setting of significant GVHD (grade 2-4 acute or extensive chronic). This was in a head to head prospective, randomized, placebo-controlled trial which revealed reduced proven/probable invasive aspergillosis and fewer deaths from invasive fungal infection in the posaconazole group. Overall survival and treatment–related adverse effects were similar.[36]

In the setting of grades 3-4 acute GVHD (aGVHD), a prophylactic posaconazole strategy can be justified on a number of levels:

- Patients with aGVHD continue to have risk factors for invasive candidiasis, i.e. central venous catheter, potential GI aGVHD involvement, recently healed/healing conditioning-related mucositis.
- The recent large (1800 patients) Italian prospective observational study demonstrated that grade 2-4 aGVHD remains an independent significant risk factor for invasive fungal infection (IFI) (hazard ratio of 6), predominantly invasive aspergillosis.
- In the two most recent trials of mold-active anti-fungal (posaconazole and voriconazole) vs fluconazole (+galactomannan monitoring) essentially performed equally well. In the voriconazole trial, there was no difference in fungal-free survival or overall survival and a majority of invasive aspergillus infections in the fluconazole arm were picked up by galactomannan screening. While

the posaconazole trial demonstrated a reduction in death from fungal infection in the posaconazole arm.

- This will be a relatively small number (19) high risk patient population.

In the setting of chronic GVHD (cGVHD) requiring immunosuppression there are little data to guide prophylaxis:

- In the posaconazole trial, the rate of IFI in those with cGVHD was low in both arms and there was no significant benefit of posaconazole (5% in the posaconazole arm vs. 6% in the fluconazole arm). Details of the cGVHD were not provided.
- The prospective Italian study revealed a striking difference in the incidence of IFI in those with de novo cGVHD (3.2%) versus those with cGVHD preceded by acute GVHD (19.4%)
- There are no studies evaluating a galactomannan screening approach in patients with cGVHD and this approach is impractical to apply as these patients do not routinely have weekly lab work/follow-up.
- Patients with cGVHD are likely not at high risk of invasive candida infections and therefore there is likely limited benefit to fluconazole prophylaxis.

Autologous HSCT recipients

There is no evidence for primary prophylaxis improving outcomes after autologous transplantation. Therefore, we do not use it routinely. Based upon expert opinion only, prophylaxis may be considered for autologous HCT recipients who have, or are expected to have, the following conditions:

- Prolonged neutropenia and mucosal damage from intense conditioning regimens or graft manipulation
- Receipt of fludarabine or 2-CDA (2-chlorodeoxyadeno-sine) within 6 months of HCT

CAR T-cell therapy recipients

Invasive fungal infections are rare after CAR-T cell therapy and typically occur in patients with other risk factors such as prolonged neutropenia or additional immunosuppression[62]. There is little evidence to choose between an anti-yeast or anti-mold prophylactic strategy in this population[63]. Consensus guidelines from EBMT, ASTCT, CARTOX, and other groups recommend fluconazole prophylaxis during the severe neutropenic period (ANC <0.5). Anti-mold prophylaxis is recommended in the following patients:

Recent allogeneic stem cell transplant
Prior invasive mold infection
Prolonged neutropenia >14 days
Prolonged corticosteroid use >72 hours

Secondary Prophylaxis

Patients who received treatment for suspected or proven invasive fungal infection earlier in their disease course are at high risk of recurrent infection during subsequent treatment. The goal of secondary prophylaxis is to prevent relapse of prior invasive fungal disease, or the occurrence of another invasive fungal disease during a new high risk period (prolonged neutropenia, or a period of severe immunosuppression). No randomized clinical trials exist to guide choice of secondary prophylaxis, and no standard approach exists. Small retrospective studies have been published using liposomal amphotericin B, voriconazole, and caspofungin.[37-39] Benefit from secondary antifungal prophylaxis has been suggested by two large retrospective studies of allogeneic HSCT receiptients[40,41], and a prospective study of voriconazole in this population[42]. No randomized clinical trials have been conducted.

The choice of antifungal agent should be based on: 1) the etiologic agent identified from the previous episode of invasive fungal disease; and 2) the previous response to antifungal agents (ECIL 7)[1].

Where ongoing antifungal therapy is considered prudent, clinicians must be mindful of drug interactions, especially between azoles, calcineurin inhibitors and QT intervals.

Empiric Antifungal Therapy during Febrile Neutropenia

Early studies demonstrated that treatment of neutropenic patients with persistent or recurrent fever (variously defined as fever after 4 – 7 days of broad-spectrum antibacterial therapy) with amphotericin B reduced the incidence of documented invasive fungal infection and improved survival.[44] This has led to a strategy of empiric antifungal therapy for patients with persistent fever in neutropenia, and over time the agent of choice has moved away from amphotericin B deoxycholate to less toxic alternatives.

Several principles guide the choice of initial empiric antifungal therapy:

- Liposomal amphotericin B (L ampho B) is as effective as amphotericin B deoxycholate (AMBd), with fewer breakthrough infections at completion of therapy. There are also fewer infusion-related adverse events (IRAEs) and less nephrotoxicity.[45] AMBd receives a D1 grading in the presence of risk factors for renal toxicity and should be avoided.[1]
- Caspofungin is as effective as L ampho B in empiric treatment of suspected invasive fungal infections[48-50]
- Voriconazole actually failed the 10% non-inferiority cut-off when compared with L ampho B for empiric therapy and did not receive FDA approval for this indication. It is included in the table below because it is superior to AMBd for the treatment of IA,[52] effective therapy for candidiasis, and efficacious for prevention of break through invasive fungal disease. [53]
- Fluconazole has no activity against *Aspergillus* species or other molds, and is not approved by the FDA for this indication.

- Only amphotericin B preparations, posaconazole and isavuconazole would be expected to have activity against *Mucorales* species.

The caveat is that empiric antifungal therapy has never been directly compared with placebo or other antifungal strategies. Less desirable aspects of this strategy include over-treatment of patients without invasive fungal disease, with the associated side effects and costs. The strategy is also limited by the fact that fever is a non-specific marker of fungal infection and will miss invasive fungal disease not associated with fever (estimated to be approximately 7% from the preemptive strategy literature[46]).

Table 2. Dose and grading of antifungal agents

Antifungal Agent	Daily Dose	ECIL 7 Grading[1]
L ampho B[47,48]	3-5 mg/kg	AI
Caspofungin[48-50]	50 mg	AI
Itraconazole[51]	200 mg i.v.	BI
Voriconazole[52,53]	2 X 6 mg/kg i.v./po	AI
Posaconazole[60]	300x2/300mg	
Isavuconazole[61]	372q8hx3/372mg	
Micafungin[54,55]	100mg	BII
AMBd[47]	0.5 - 1 mg/kg	BI/DI
Fluconazole[56]	400 mg i.v.	CI

For patients with prolonged antibiotic resistant fever in neutropenia (3-5 days of fever despite appropriate antibacterial coverage and no clinical or radiographic focus of infection) empiric antifungal therapy with L ampho B or Caspofungin/Micafungin will be added. Axial imaging studies (equivalent to HRCT of chest, and ultrasound/CT abdomen and pelvis) will be carried out for patients who remain febrile after 72-96 hours of empiric antifungal therapy. If these studies fail to demonstrate a clinical focus, treatment with G-CSF will also be instituted.

Empiric antifungal coverage should be discontinued in afebrile patients once ANC > 0.5 for two days. In patients with persistent fever and no clinical or radiographic focus of infection, empiric treatment with antifungal antibiotics should be discontinued once ANC > 0.5 for four days. Alternative causes including CVC infection, drug fever and GVHD should also be considered.

References

1. Maertens J Antimicrob Chemother 2018; 73: 3221–3230.
2. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327-60.
3. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503-35.
4. Maertens JA, Frere P, Lass-Florl C, Heinz W, Cornely OA. Primary antifungal prophylaxis in leukaemia patients. Eur J Cancer. 2007;Suppl 5: 43-8.
5. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348-59.
6. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med. 1992;326(13):845-51.
7. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. J Infect Dis. 1995;171(6):1545-52.
8. Rotstein C, Bow EJ, Laverdiere M, Ioannou S, Carr D, Moghaddam N. Randomized placebocontrolled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. Clin Infect Dis. 1999;28:331-40.
9. Schaffner A, Schaffner M. Effect of prophylactic fluconazole on the frequency of fungal infections, amphotericin B use, and health care cost in patients undergoing intensive chemotherapy for hematological neoplasias. J Infect Dis. 1995;172:1035-41.
10. Winston DJ, Chandrasekar PH, Lazarus HM, Goodman JL, Silber JL, Horowitz H, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized, placebo-controlled, double-blind, multicenter trial. Ann Intern Med. 1993;118:495-503.
11. Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with haematological malignancies. Blood. 2003;101:3365-72.
12. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy patients. A meta-analysis of randomized-controlled clinical trials. Cancer. 2002;94:3230-46.
13. Rijnders BJ, Cornelissen JJ, Slobbe L, Becker MJ, Doorduijn JK, Hop W, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. Clin Infect Dis. 2008;46:1401-8.
14. Huijgens PC, Simoons-Smit AM, Van Loenen AC, Prooy E, van Tinteren H, Ossenkoppele GJ, et al. Fluconazole versus itraconazole for the prevention of fungal infections in haemato-oncology. J Clin Pathol. 1999;52:376-80.
15. Nucci M, Biasoli I, Akiti T, Silveira F, Solza C, Barrieros G, et al. A double-blind, randomized, placebo-controlled trial of itraconazole capsules as antifungal prophylaxis for neutropenic patients. Clin Infect Dis. 2000;30:300-5.
16. Vreugdenhil G, Van Dijke BJ, Donnelly JP, Novakova IRO, Raemaekers JMM, Hoogkamp-Korstanje MAA, et al. Efficacy of itraconazole in the prevention of fungal infections among neutropenic patients with hematological malignancies and intensive chemotherapy. A double blind, placebo controlled study. Leuk Lymph. 1993;11:353-8.
17. Menichetti F, Del Favero A, Martino P, Bucaneve G, Micozzi A, Girmenia C, et al. Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomized, placebo-controlled, double-blind, multicenter trial. Clin Infect Dis.1999;28:250-5.
18. Morgenstern GR, Prentice AG, Prentice HG, Ropner JE, Schey SA, Warnock DW. A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. Br J Haematol. 1999;105:901-11.
19. Harousseau J-L, Dekker AW, Stamatoullas-Bastard A, fassas A, Linkesch W, Gouveia J, et al. Itraconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo multicenter trial comparing itraconazole and amphotericin B. Antimicrob Agents Chemother. 2000;44:1887-93.
20. Boogaerts M, Maertens J, van Hoof A, de Bock R, Fillet G, Peetersman M, et al. Itraconazole versus amphotericin B plus nystatin in the prophylaxis of fungal infections in neutropenic cancer patients. J Antimicrob Chemother. 2001;48:97-103.
21. Glasmacher A, Cornely O, Ullmann AJ, Wedding U, Bodenstein H, Wandt H, et al. An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. J Antimicrob Chemother. 2006;57:317-25.

22. Glasmacher A, Prentice A, Gorschluter M, Engelhart S, Hahn C, Djulbegovic B, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol. 2003;21:4615-26.
23. Winston DJ, Maziarz RT, Chandrasekar PH, Lazarus HM, Goldman M, Blumer JL, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomised trial. Ann Intern Med. 2003;138:705-13.
24. Marr KA, Crippa F, Leisenring W, Hoyle M, Boeckh M, Balajee SA, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood. 2004;103:1527-33.
25. Vardakas KZ, Michalopoulos A, Falagas ME. Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. Br J Haematol. 2005;131:22-8.
26. Rousey SR, Russler S, Gottlieb M, Ash RC. Low-dose amphotericin B prophylaxis against invasive aspergillus infections in allogeneic marrow transplantation. Am J Med. 1991;91:484-92.
27. Perfect JR, Klotman ME, Gilbert CC, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. J Infect Dis. 1992;165:891-7.
28. Tollemar J, Ringden O, Andersson S, Sundberg B, Ljungman P, Tyden G. Randomized double-blind study of liposomal amphotericin B (Ambisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. Bone Marrow Transplant. 1993;12:577-82.
29. Kelsey SM, Goldman JM, McCann S, Newland AC, Scarffe JH, Oppenheim BA, et al. Liposomal amphotericin B (Ambisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study. Bone Marrow Transplant. 1999;23:163-8.
30. Timmers GJ, Zweegman S, Simoons-Smit AM, van Loenen AC, Touw D, Huijgens PC. Amphotericin B colloidal dispersion (Amphocil) vs. fluconazole for the prevention of fungal infections in neutropenic patients: data of a prematurely stopped clinical trial. Bone Marrow Transplant. 2000;25:879–84.
31. Schwartz S, Behre G, Heinemann V, Wandt H, Schilling E, Arning M, et al. Aerosolized amphotericin B inhalations as prophylaxis of invasive Aspergillus infections during prolonged neutropenia: results of a prospective, randomized trial. Blood. 1999;93:3654-61.
32. Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasisrelated death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood. 2000;96:2055-61.
33. Marks DI, Kibbler C, Pagliugi A, Ribaud P, Solano C, Heussel CP, et al. Voriconazole vs Itraconazole for primary prophylaxis of invasive fungal infection in allogeneic hematopoietic cell transplant (HCT) recipients. In: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA, 2009.
34. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Gersten ID, et al. Randomized, double-blind trial of fluconazole vs voriconazole for the prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010;116(24):5111-8.
35. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis. 2004;39:1407-16.
36. Ullmann AJ , Lipton JH , Vesole DH , Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007;356:335-47.
37. Uhlenbrock S, Zimmermann M, Fegeler W, Jürgens H, Ritter J. Liposomal amphotericin B for prophylaxis of invasive fungal infections in high-risk paediatric patients with chemotherapy-related neutropenia: interim analysis of a prospective study. Mycoses. 2001 Dec;44(11-12):455-63.
38. Cordonnier C, Maury S, Pautas C, Bastié JN, Chehata S, Castaigne S, et al. Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. Bone Marrow Transplant. 2004 May;33(9):943-8.
39. de Fabritiis P, Spagnoli A, Di Bartolomeo P, Locasciulli A, Cudillo L, Milone G, et al. Efficacy of caspofungin as secondary prophylaxis in patients undergoing allogeneic stem cell transplantation with prior pulmonary and/or systemic fungal infection. Bone Marrow Transplant. 2007 Aug;40(3):245-9.
40. Fukuda T, Boeckh M, Guthrie K, Mattson DK, Owens S, Wald A, et al. Invasive aspergillosis before allogeneic hematopoetic stem cell transplantation: 10 year experience at a single transplant center. Biol Bone Marrow Transplant. 2004;10:494-503.
41. Martino R, Parody R, Fukuda T, Maertens J, Theunissen K, Ho A, et al. Impact of the intensity of the pretransplant conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell

transplantation: a retrospective survey of the infectious diseases working party of the European Group for Blood and Marrow Transplantation. Blood. 2006;108:2928-36.
42. Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, et al. Voriconazole for secondary prophylaxis of invasive fungal infection in allogeneic stem cell transplant recipients: results of the VOSIFI study. Hematologica. 2010;95(10):1762-8.
43. Bjerke JW, Meyers JD, Bowden RA. Hepatosplenic candidiasis-a contraindication to marrow transplantation? Blood. 1994;84:2811-4.
44. Bow EJ, Loewen R, Vaughan D. Reduced requirement for antibiotic therapy targeting gram-negative organisms in febrile, neutropenic patients with cancer who are receiving antibacterial chemoprophylaxis with oral quinolones. Clin Infect Dis. 1995;20(4):907-12.
45. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med. 1999;340(10):764-71.
46. Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeken E, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis. 2005;41:1242-50.
47. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. N Engl J Med. 1999;340:764-71.
48. Walsh TJ, Teppler H, Donowitz GR, Maertens J, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med. 2004;351:1391-1402.
49. Maertens J, Madero-Lopez L, Reilly AF, Lehrnbecher T, Groll AH, Jafri HS, et al. Caspofungin vs liposomal AmB for empirical therapy in pediatric neutropenic patients with persistent fever: a randomized, double-blind, multicenter trial. Pediatr Infect Dis J. 2010;29(5):415-20.
50. Lafaurie M, Lapalu J, Raffoux E, Breton B, Lacroix C, Socie G, et al. High rate of breakthrough invasive aspergillosis among patients receiving caspofungin for persistent fever and neutropenia. Clin Microbiol Infect. 2010;16(8):1191-6.
51. Ohta K, Kosaka SN, Nakao Y, Kumura T, Hagihara K, Sakamoto E, et al. Efficacy and safety of intravenous itraconazole as empirical antifungal therapy for persistent fever in neutropenic patients with hematological malignancies in Japan. Int J Hematol. 2009;89:649-55.
52. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann J-W, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347:408–15.
53. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, et al. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med. 2002;346(4):225-34.
54. Tamura K, Urabe A, Yoshida M, Kanamaru A, Kodera Y, Okamoto S, et al. Efficacy and safety of micafungin, an echinocandin antifungal agent, on invasive fungal infections in patients with hematological disorders. Leuk Lymphoma. 2009;50:92–100.
55. Kubiak X. Caspofungin vs micafungin for empirical therapy in adult neutropenic patients with persistent fever: a retrospective analysis. In: 48th ICAAC; 2008. Washington, DC, 2008.
56. Malik IA, Moid I, Aziz Z, Khan S, Suleman M. A randomized comparison of fluconazole with amphotericin B as empiric anti-fungal agents in cancer patients with prolonged fever and neutropenia. Am J Med. 1998;105(6):478-83.
57. Roychowdhury M, Pambuccian SE, Aslan DL, Jessurun J, Rose AG, Manivel JC, et al. Pulmonary complications after bone marrow transplantation: an autopsy study from a large transplantation center. Arch Pathol Lab Med. 2005;129(3):366-71.
58. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis. 2002;34(1):7-14.
59. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813-21.
60. Johan A Maertens, Galia Rahav, Dong-Gun Lee, Alfredo Ponce-de-León, Isabel Cristina Ramírez Sánchez, Nikolay Klimko, Anne Sonet, Shariq Haider, Juan Diego Vélez, Issam Raad, Liang-Piu Koh, Meinolf Karthaus, Jianying Zhou, Ronen Ben-Ami, Mary R Motyl, Seongah Han, Anjana Grandhi, Hetty Waskin, on behalf of the study investigators.

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet 2021; 397: 499–509

61. Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoff mann, Bernhardt Zeiher, Andrew J Ullmann. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other fi lamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016; 387: 760–69
62. Jessica S. Little, Muneerah M Aleissa, Katherine Beluch, Isabel Helena Gonzalez-Bocco, Francisco M Marty, Jennifer Manne-Goehler, Sophia Koo, Sarah P Hammond, Caron A. Jacobson; Low Incidence of Invasive Fungal Disease Following CD19 Chimeric Antigen Receptor T-Cell (CAR-T) Therapy for Non-Hodgkin Lymphoma. *Blood Adv* 2022.
63. Will Garner, P Samanta, G Haidar. Invasive fungal infections after anti-CD19 CAR T therapy. Journal of Fungi 2021;7(2).

Graft Failure, Poor Graft Function, Chimerism

Presented by: Jan Storek and Adam Bryant

Summary

- **Primary Graft Failure**, after excluding relapse, medications, or viral infections, is treated by a 2nd HCT, except if palliation is appropriate.
    - Palliation is appropriate in patients with poor prognosis malignancy at 1st HCT or poor performance status/elderly.
    - Choose a haploidentical or another suitable donor available ASAP.
        - Can be the same or different donor than for the first HCT.
    - Graft: Filgrastim-mobilized PBSCs
    - Conditioning: Fludarabine 150 mg/m^2 + Cyclophosphamide 29 mg/kg + TBI 2Gy
    - GVHD prophylaxis: Posttransplant cyclophosphamide (PTCy) + tacrolimus + MMF
- **Poor Graft Function or Secondary Graft Failure**, after excluding relapse, medications, and viral infections, can be treated with a TPO agonist, or a filgrastim-mobilized and CD34 cell-enriched PBSC boost.
    - If absent or declining donor chimerism (suggesting graft rejection), PBSC boost should not be given. Instead, consider 2nd HCT as for primary GF.
- **Chimerism** of blood T cells (CD3+) and blood malignancy lineage cells (CD13/33+ cells in case of myeloid leukemia or CD19+ cells in case of B cell malignancy) is routinely determined in allotransplant recipients at 3 months. This is to:
        - assess risk for relapse
        - generate baseline values for potential later chimerism testing (when relapse or graft rejection is suspected).
    - No intervention for low donor chimerism alone should be done, as no intervention with level A, B, or C evidence exists, that could decrease the risk of relapse or graft failure.

Nomenclature

We use the following definitions, endorsed by EBMT, ASTCT, CIBMTR, and APBMT[1,2]:

- Neutrophil recovery: The first of 3 successive days with ANC ≥0.5/nl after post-HCT nadir.
- Platelet recovery: The first of 3 consecutive days with PLT ≥20/nl in the absence of platelet transfusion for 7 consecutive days.
- Graft Failure (GF), which may be due to graft rejection or other causes:
  - Primary GF: Lack of achievement of ANC ≥0.5/nl with associated pancytopenia by day 30 (PBSC or BM) or by day 42 (cord blood).
  - Secondary GF: Decline in hematopoietic function necessitating blood products or growth factor support, after neutrophil and platelet recovery.
- Poor graft function (PGF): Frequent dependence on transfusions and/or growth factors in the absence of other explanations, such as relapse, medications, or infections.
- Donor chimerism
  - Full: >95% for both myeloid and lymphoid lineages
  - Mixed (partial): 5-95% for both myeloid and lymphoid lineages
  - Absent: <5% for both myeloid and lymphoid lineages

Graft Failure

- Risk factors[3-8]
  - Non-malignant disease
  - Cell dose (CD34 or TNC)
  - Graft type (PBSC < BM < cord blood)
  - Low-intensity conditioning
  - GVHD prophylaxis (PTCy > CNI+antimetabolite or ATG-based)
  - HLA disparity
  - ABO major mismatch
  - Donor-Specific Antibodies
    - Risk may be reduced by desensitization (eg, plasmapheresis, IVIG, rituximab)
  - Splenomegaly
- Management of primary GF[3]
  - Rule out relapse, medications, or viral infections
  - If responsive to growth factors, treat as PGF (below), unless absent or clearly declining donor chimerism
  - Determine eligibility for 2nd HCT. Risk factors for poor outcome include:
    - Poor prognosis underlying disease[7,9], and
    - Older age / poor performance status/organ dysfunction[9,10]

- Per Japanese registry study[10], no combination of risk factors resulted in zero OS. Most impactful risk factors were:
    - Age ≥55
    - ECOG 4 (no self-care, confined to bed or chair)

- 2nd HCT, using PBSCs:
    - Survival 10-30% irrespective of conditioning, GVHD prophylaxis, and whether original vs new donor. This is per large single-center or registry analyses, usually from pre-haplo/PTCy era[3,5,6,9].
    - Higher survival has been reported in small, usually single-center or registry studies of salvage haploidentical HCT, allowing short interval from 1st to 2nd HCT
        - Due to chance or publication bias?
        - Duke Univ group (senior author Rizzieri) reported in 2012 on 11 adult patients receiving fludarabine+cyclophosphamide+2GyTBI+alemtuzumab, all on day -1[11]. With a median F/U of 1 year, 8/11 (73%) survived.
            - However, in their subsequent report on a total of 28 patients with a median follow up of 3 years, survival at 4 years was only ~20%[12].
            - Median time from 1st to 2nd HCT was ~42 days.
        - PTCy-based GVHD prophylaxis appears associated with good OS, but based on small studies with short F/U
            - Prata *et al* reported in 2019 on 23 mostly adult patients from French registry receiving fludarabine-based conditioning (usually Flu+Cy+TBI, doses not given) and PTCy-based GVHD prophylaxis. Median F/U was not given. OS at 1 y was 56%.
                - Median time from 1st to 2nd HCT was 63 days.
            - Albert *et al* reported in 2021 on 12 **pediatric** patients receiving fludarabine+treosulfan+cyclophosphamide+rituximab+alemtuzumab and PTCy-based additional GVHD prophylaxis[13]. With a median F/U of 2 years, 11/12 patients survived.
                - 3 patients had GF diagnosed before d28.
                - Median time from 1st to 2nd HCT 46 days.
            - Giammarco *et al* reported in 2021 on 19 adult patients receiving fludarabine+cyclophosphamide+2GyTBI with PTCy-based GVHD prophylaxis[14]. With a median F/U of <1 year, 1-year survival was 66%.
                - 14/19 pts surviving but, 3 with GF, so survival at 1 y will be at best 11/19 (58%)
                - Median time from 1st to 2nd HCT 42 days.
            - Harada *et al* reported in 2022 on 33 adult patients from Japanese registry receiving fludarabine+cyclophosphamide (or melphalan, busulfan, or TBI instead of cyclophosphamide) and PTCy-based

GVHD prophylaxis.[15] With a median F/U of 1 year, 1-year survival was 47% (61% in a subgroup of patients with a regular (not reduced) dose of PTCy of 50 mg/kgx2).
        - Median time from 1st to 2nd HCT 49 days.
    - In summary, 2nd HCT within 40 to 50 days from 1st HCT, thus usually from a haploidentical donor, and using PTCy-based GVHD prophylaxis appears appealing, but F/U so far too short.
  - Calgary results with Fludarabine+5GyTBI: 10/11 died within 1 year post-2nd HCT, so only 1/11 survived
    - 1/10 who got ATG-based GVHD prophylaxis (in 2001-2023)
    - 0/1 who got PTCy-based GVHD prophylaxis (in 2024)
  - New conditionings & GVHD prophylaxis for Calgary (starting July 2024):
    - Fludarabine 50 mg/m^2 days -4, -3, -2
    - Cyclophosphamide 14.5 mg/kg days -4, -3
    - TBI 2 Gy day -1
    - Standard PTCy + tacro + MMF
    - This is based on Giammarco *et al*, but abbreviated, and tacro used instead of CSA. The original Giammarco *et al* (2021) conditioning is:
      - Fludarabine 30 mg/m^2 days -6, -5, -4, -3, -2
      - Cyclophosphamide 14.5 mg/kg days -6, -5
      - TBI 2 Gy day -1
      - Standard PTCy + tacro + MMF
- Management of **secondary** GF has not been adequately studied.
  - If absent or clearly declining mixed donor chimerism, consider 2nd HCT as for primary GF.
  - If full chimerism or stable/increasing mixed chimerism, consider PBSC boost as for PGF.

Poor Graft Function

- Risk factors[3,16]
  - Same as for GF, plus
  - GVHD
  - SOS/VOD
- Management[3,16]
  - Growth factors
    - Thrombopoietin (TPO) agonist
      - In 5 recent case series, each with 11-48 (total 97) adult alloHCT patients with PGF, eltrombopag at doses of 50-150 mg at variable timing post alloHCT (1-14 months) resulted in overall and complete responses of 58-

83% and 50-67%, respectively, without severe toxicity.[17-21] Median time to response varied from 3-10 weeks for platelets and 3-28 weeks for all lineages. Patients who achieved CR maintained responses for the duration of study follow-up (10-43 months) and some were able to stop TPO agonist without reoccurrence of PGF.
    - Given a signal for potential efficacy and a good safety profile and despite the studies lacked controls, we recommend a trial of TPO agonist in all patients with PGF.
  - See also Cytopenia and Transfusion chapter
- Filgrastim-mobilized and CD34 cell-enriched PBSC boost.
  - Efficacy and toxicity in recent studies is summarized in Table 1.
  - CR was reported in 62% to 92% patients.
    - Onset of rising blood counts in ~2 weeks
    - Maximum response in 1-3 months
  - Toxicity is acceptable – aGVHD in 0-23% patients, usually grade 1-2, and cGVHD in 0-50% patients, usually mild to moderate.
  - Given the probable efficacy and acceptable toxicity and despite the studies lacked controls, we recommend a PBSC boost in patients who failed a TPO agonist.
    - Recommended dose is $5x10^6$ CD34 cells/kg, infused fresh[22].
  - Chimerism: All studies in Table 1 used patients with full donor chimerism. In one study (Cuadrado *et al*),[23] patients with mixed chimerism were also included. Their outcome did not differ from those with full chimerism.
    - We recommend giving PBSC boost to patients with full chimerism or stable/increasing mixed chimerism.
    - We do not recommend giving PBSC boost to patients with absent of declining donor chimerism. This is due to the theoretical concern that the PBSC would be rejected.
  - Before PBSC boost, the following should be ruled out: relapse and medication- or viral infection-induced cytopenia.

Table 1. Summary of publications describing outcome of CD34-selected stem cell boosts in adults with poor graft function.

Publication	N	Time[a]	Content	Response[b]	GVHD[c]	Survival
Stasia 2014[24]	41	NR	CD34 3.45 x 10^6/kg CD3 2.5-10 x10^3/kg	76% CR 7% PR	22% aGVHD 7% cGVHD	63% 3-y
Haen 2015[25]	20	NR	CD34 4.6 x 10^6/kg CD3 2 x10^3/kg	92% CR	5% aGVHD NR cGVHD	53% 2y
Klyuchnikov 2014[26]	32	150	CD34 3.4 x 10^6/kg CD3 9 x10^3/kg	81% CR 0% PR	19% aGVHD 19% cGVHD	45% 2y
Askaa 2014[27]	18	113	CD34 4.9 x 10^6/kg CD3 11 x10^3/kg	72% CR	22% aGVHD 50% cGVHD	48% 2y
Ghobadi 2017[22]	26	NR	CD34 5.0 x 10^6/kg CD3 NR	62 % CR 19% PR	23% aGHVD 31% cGHVD	65% 1y
Mohty 2019[28]	10	120	CD34 4.8 x 10^6/kg CD3 1.3 x 10^3/kg	70% CR 30% PR	0 % aGVHD 0% cGVHD	80% 1y 70% 3y
Cuadrado 2020[23]	62	450	CD34 5.0 x 10^6/kg CD3 4.3 x 10^3/kg	62 % CR 13% PR	11% aGVHD 8% cGVHD	70% 1y 54% 5 y

[a] Median time (days) from stem cell transplant to infusion of CD34 selected cells; NR = Not reported
[b] Individual study response definitions varied. Response definitions presented here CR = hematologic improvement in all 3 lineages without transfusion dependence PR = hematologic improvement in 1-2 lineages
[c] aGHVD grade II-IV; cGVHD total (limited + extensive; mild + moderate + severe)

Chimerism Techniques

Chimerism (% cells of donor versus recipient origin) can be determined using one of the techniques described in Table 2.

In Calgary, we use fluorescent dye-labeled short tandem repeat (STR) polymorphism, multiplexed (a total of 16 polymorphic genomic segments are assayed), and analyzed by capillary electrophoresis. The reasons are the very high quantitation accuracy, which facilitates comparison of current result to previous result(s), high informativeness (which means that chimerism can be reliably determined in >99% donor-recipient pairs), acceptable sensitivity (no data exist suggesting that sensitivity below 1-5% is clinically valuable), and applicability to all donor-recipient pairs (irrespective of sex matching).

The principle of the assay is explained using the following example: in a short tandem repeat segment of genome, the donor has 3 tetranucleotide repeats (GCTG GCTG GCTG) on both paternal and maternal chromosomes whereas the recipient has 4 tetranucleotide repeats (GCTG GCTG GCTG GCTG) on both paternal and maternal chromosomes (simple scenario, as in reality most persons are heterozygous). In a post-transplant patient specimen, the segment of genome is amplified by PCR, using primers for conserved sequences flanking the segment. The PCR product is subjected to electrophoresis, which separates the 3 tetranucleotide repeat amplicons from the 4 tetranucleotide repeat amplicons (the former amplicons move faster). As the amplicons are fluorescent dye-labeled, the ratio of donor to recipient chimerism is determined as the ratio of

fluorescence of the donor (3 repeat) amplicons to the fluorescence of the recipient (4 repeat) amplicons.

Table 2. Techniques to determine chimerism (courtesy of F. Khan).

Technique	Analytical Sensitivity (%)	Quantitation Accuracy	Informativeness (likelihood of finding alleles different between donor & recipient)
Fluorescent dye-labeled STR, multiplex, capillary electrophoresis	1-5	Very High	High
^{32}P-labeled STR/VNTR, multiplex, gel electrophoresis	1-5	Moderate	High
XY Cytogenetics	10-20	Low	Sex-mismatched only
XY FISH	0.1-0.2	Very High	Sex-mismatched only, potential origin of sex-mismatched cells from transfusion, mother or offspring
RFLP	5-20	Moderate	Moderate
Real time PCR using *'indels'* (insertion/deletion polymophism)	0.001-0.1	Moderate	Moderate-High

Chimerism Clinical Utility

- Chimerism of blood cells **can** be used for:
  - Diagnosis of graft rejection (with or without autologous reconstitution)
    - Rejection is defined as <5% donor cells among both myeloid cells and T cells, in the absence of relapse.
  - Risk assessment for relapse:
    - In Alberta, we routinely determine chimerism of sorted blood malignancy lineage cells and T cells at 3 months post-transplant (baseline). Subsequent chimerism determination can be done when/if rejection or relapse is suspected. Low % donor cells at 3 mo is only a risk factor for relapse, it is not diagnostic of relapse. Per our analysis of patients undergoing first allo-HCT in Alberta between 2010 and 2020[29], most of whom received Flu+Bu+ATG+4GyTBI conditioning, PBSCs, and additional GVHD prophylaxis with MTX+CSA,
      - Patients with full T cell chimerism at 3 mo had a lower risk of relapse (22% vs 36%)
        - PPV was only 34% and NPV 81%

- Patients with full chimerism among leukemia lineage cells (eg, CD13/33+ cells in case of AML or CD19+ cells in case of B-ALL) at 3 mo had a lower risk of relapse (20% vs 45%)
    - PPV was only 45% and NPV 79%
- Chimerism of blood cells alone **cannot** be used as an indication for an intervention.
    - No agreement among experts on which intervention, if any, should be used[1].

Table 3. Interpretation of blood chimerism results.

	% Donor Among Blood	
	CD3 Cells	Leukemic Lineage Cells
Normal	>95%	>95%
Benign mixed chimerism	5 – 95%, stable or increasing	5 – 95%, stable or increasing
Graft Rejection**	<5%*	<5%
Impending relapse or bonified relapse	Typically >95% or stable/increasing	Decreasing***

* In Alberta (using MAC, PBSCs, and ATG-based GVHD prophylaxis), <5% donor T cells with >95% donor myeloid cells does not appear to be a risk factor for rejection (Storek, unpublished, 2023).
** With or without autologous hematopoietic reconstitution.
*** Per preliminary analysis on a small number of Albertan patients transplanted in 2010-2020 (performed by Storek in May 2021), >5% drop of donor chimerism may predict relapse with PPV=79% and NPV=81%.

References

1. *Kharfan-Dabaja MA, Kumar A, Ayala E, et al. Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell Transplantation: A Report on Behalf of the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther 2021;27:642-9.*
2. *Sureda A, Carpenter PA, Bacigalupo A, et al. Harmonizing definitions for hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism in allogeneic hematopoietic cell transplantation: a report on behalf of the EBMT, ASTCT, CIBMTR, and APBMT. Bone Marrow Transplant 2024;59:832-7.*
3. *Ozdemir ZN, Civriz Bozdag S. Graft failure after allogeneic hematopoietic stem cell transplantation. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2018;57:163-7.*
4. *Chen J, Pang A, Zhao Y, et al. Primary graft failure following allogeneic hematopoietic stem cell transplantation: risk factors, treatment and outcomes. Hematology 2022;27:293-9.*
5. *Mata JR, Zahurak M, Rosen N, DeZern AE, Jones RJ, Ambinder AJ. Graft Failure Incidence, Risk Factors, and Outcomes in Patients Undergoing Non-Myeloablative Allogeneic Hematopoietic Cell Transplantation Using Post-Transplant Cyclophosphamide. Transplant Cell Ther 2024;30:588-96.*
6. *Kotb A, Alzahrani H, Alahmari A, et al. Incidence and risk factors for secondary graft failure in uniformly treated patients with severe aplastic anemia receiving fludarabine and cyclophosphamide for conditioning and matched sibling bone marrow graft as stem cell source. Cytotherapy 2023;25:1331-7.*
7. *Park JH, Lee JH, Lee JH, et al. Incidence, Management, and Prognosis of Graft Failure and Autologous Reconstitution after Allogeneic Hematopoietic Stem Cell Transplantation. J Korean Med Sci 2021;36:e151.*
8. *Zulch E, Inoue Y, Cioccio J, et al. Impact of post-transplant cyclophosphamide and splenomegaly on primary graft failure and multi-lineage cytopenia after allogeneic hematopoietic cell transplantation. Leuk Res 2024;143:107530.*
9. *Nagler A, Labopin M, Swoboda R, et al. Long-term outcome of second allogeneic hematopoietic stem cell transplantation (HSCT2) for primary graft failure in patients with acute leukemia in remission: A study on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 2023;58:1008-16.*

10. *Harada K, Kimura SI, Fuji S, et al. Prognostic factors in salvage transplantation for graft failure following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2021;56:2183-93.*
11. *Kanda J, Horwitz ME, Long GD, et al. Outcomes of a 1-day nonmyeloablative salvage regimen for patients with primary graft failure after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2012;47:700-5.*
12. *Katsanis E, Hennig T, Robinson JE, et al. Revisiting a single day salvage conditioning following graft failure. Bone Marrow Transplant 2022;57:1845-7.*
13. *Albert MH, Sirin M, Hoenig M, et al. Salvage HLA-haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide for graft failure in non-malignant disorders. Bone Marrow Transplant 2021;56:2248-58.*
14. *Giammarco S, Raiola AM, Di Grazia C, et al. Second haploidentical stem cell transplantation for primary graft failure. Bone Marrow Transplant 2021;56:1291-6.*
15. *Harada K, Najima Y, Kato M, et al. Outcomes of salvage haploidentical transplantation using posttransplant cyclophosphamide for graft failure following allogeneic hematopoietic stem cell transplantation. Int J Hematol 2022;116:744-53.*
16. *Huang XJ. Overcoming graft failure after haploidentical transplantation: Is this a possibility? Best Pract Res Clin Haematol 2021;34:101255.*
17. *Aydin S, Dellacasa C, Manetta S, et al. Rescue treatment with eltrombopag in refractory cytopenias after allogeneic stem cell transplantation. Ther Adv Hematol 2020;11:2040620720961910.*
18. *Giammarco S, Sica S, Chiusolo P, et al. Eltrombopag for the treatment of poor graft function following allogeneic stem cell transplant: a retrospective multicenter study. Int J Hematol 2021;114:228-34.*
19. *Halahleh K, Gale RP, Da'na W, et al. Therapy of posttransplant poor graft function with eltrombopag. Bone Marrow Transplant 2021;56:4-6.*
20. *Marotta S, Marano L, Ricci P, et al. Eltrombopag for post-transplant cytopenias due to poor graft function. Bone Marrow Transplant 2019;54:1346-53.*
21. *Tang C, Chen F, Kong D, et al. Successful treatment of secondary poor graft function post allogeneic hematopoietic stem cell transplantation with eltrombopag. J Hematol Oncol 2018;11:103.*
22. *Ghobadi A, Fiala MA, Ramsingh G, et al. Fresh or Cryopreserved CD34(+)-Selected Mobilized Peripheral Blood Stem and Progenitor Cells for the Treatment of Poor Graft Function after Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 2017;23:1072-7.*
23. *Cuadrado MM, Szydlo RM, Watts M, et al. Predictors of recovery following allogeneic CD34+-selected cell infusion without conditioning to correct poor graft function. Haematologica 2020;105:2639-46.*
24. *Stasia A, Ghiso A, Galaverna F, et al. CD34 selected cells for the treatment of poor graft function after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2014;20:1440-3.*
25. *Haen SP, Schumm M, Faul C, Kanz L, Bethge WA, Vogel W. Poor graft function can be durably and safely improved by CD34+-selected stem cell boosts after allogeneic unrelated matched or mismatched hematopoietic cell transplantation. J Cancer Res Clin Oncol 2015;141:2241-51.*
26. *Klyuchnikov E, El-Cheikh J, Sputtek A, et al. CD34(+)-selected stem cell boost without further conditioning for poor graft function after allogeneic stem cell transplantation in patients with hematological malignancies. Biol Blood Marrow Transplant 2014;20:382-6.*
27. *Askaa B, Fischer-Nielsen A, Vindelov L, Haastrup EK, Sengelov H. Treatment of poor graft function after allogeneic hematopoietic cell transplantation with a booster of CD34-selected cells infused without conditioning. Bone Marrow Transplant 2014;49:720-1.*
28. *Mohty R, Brissot E, Battipaglia G, et al. CD34(+)-selected stem cell "Boost" for poor graft function after allogeneic hematopoietic stem cell transplantation. Curr Res Transl Med 2019;67:112-4.*
29. *Khanolkar RA, Tripathi G, Dharmani-Khan P, et al. Incomplete chimerism following myeloablative and anti-thymocyte globulin-conditioned hematopoietic cell transplantation is a risk factor for relapse and chronic graft-versus-host disease. Cytotherapy 2022;24:1225-31.*

Donor Lymphocyte Infusion (DLI) or Second Allogeneic HCT for Relapse

Presented by: Adam Bryant

Summary

- Patients who relapse after stem cell transplant have poor prognosis.
- Patients with acute leukemia relapsed after transplant may be considered for donor lymphocyte infusion (typically with chemotherapy), second allotransplant, palliative chemotherapy, targeted immunotherapy, clinical trials, or palliative care.
- Fit patients with relapsed B-acute lymphoblastic leukemia should be considered for CAR T-cell therapy[1, 2].
- Criteria for eligibility for 2nd allo-HCT:
  - >1 year after first transplant for acute leukemia or MDS, and
  - Favorable additional risk factors:
    - Young (preferably age < 40)
    - Fit (KPS ≥ 80 or ECOG 0-1)
    - Disease in remission at time of second transplant
- Selected patients with AML or MDS may be candidates for DLI. These include patents with the following characteristics
  - with hematologic relapse (>5% marrow blasts, peripheral blood blasts, extramedullary disease)
    - < 1 year post alloHCT
    - > 1 year post alloHCT and non-candidate for second alloHCT
  - with minimal residual disease that is
    - defined by disease-identifying cytogenetic, morphologic, molecular, or immunophenotypic means (not incomplete donor chimerism)
    - documented on
      - 3-month post-transplant marrow **AND** demonstrated to be worsening at subsequent time point(s) 4-6 weeks later
      - documented at clinical suspicion of relapse beyond 3 months (and if deemed necessary by clinician discretion) demonstrated to be worsening at subsequent time point(s)
  - without options for clinical trials or targeted chemo/immunotherapy
  - without history of gr3-4 aGVHD or mod-sev cGVHD, and without any active GVHD
  - who are motivated and fit
- When administered without chemotherapy, donor lymphocytes should be administered every 1-2 months based on disease response and the presence or absence of GVHD.

- Donor lymphocytes for DLI should be collected in a single apheresis session and divided into three aliquots of the following cell doses:
    - 1 x 10^6 CD3+ cells/kg (infused fresh, others cryopreserved in 10% DMSO)
    - 1 x 10^7 CD3+ cells/kg
    - 1 x 10^8 CD3+ cells/kg
- Options for patients with relapsed MPN (with < 5% blasts), CML or CLL include novel therapies (later-generation TKIs, B-cell receptor antagonists, BCL-2 inhibitors) if the patient has not previously been exposed to them. Other options include DLI or palliative/supportive care. Second allogeneic transplants will be rare in this population.

Background

Despite the use of intensive, myeloablative conditioning, relapse remains the most common cause of treatment failure following allogeneic and autologous stem cell transplantation. Selected patients with chemosensitive disease may be considered for repeat transplants. Criteria for patient selection are reviewed below.

Acute Leukemia

The natural history of acute leukemia that has relapsed following allogeneic bone marrow transplantation has a grim prognosis, with 2-year survival estimates consistently less than 20%[3].

Aside from conventional chemotherapy, as described above, non-transplant options for acute leukemia patients who relapse after allogeneic transplant include cellular therapy in the form of donor lymphocyte infusion (DLI). While AML is of intermediate sensitivity to DLI (reported response rates vary from 0 – 60%), most patients treated in this way do not experience prolonged survival due to graft-versus-host disease, infection and relapse. Despite the sensitivity of ALL to graft-versus-leukemia effects, responses to DLI in this disease are almost never seen and tend to be short-lived.

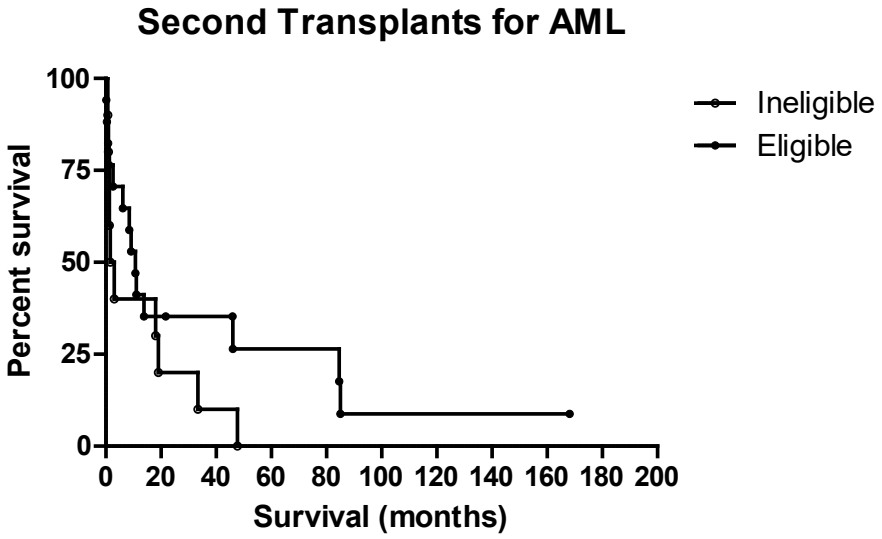
Second allogeneic transplants have been offered to highly selected patients with acute leukemia that has relapsed after a prior transplant. Overall survival following a second allogeneic transplant is limited by high TRM (30-36%) and frequent relapses (44-70%). Most reports describe 2-year overall survival between 18-44%[4-16]. While second transplants may be of benefit to some patients who relapse, it is clear that they are only offered to a minority: in a review of second transplants carried out for the CIBMTR by Eapen *et al.,* only 6% of acute leukemia patients reported to the registry who relapsed received a second transplant[11]. In registry studies and case series, uni- and multivariable analysis of risk factors associated with relapse and survival outcomes have identified common favourable risk factors including

- younger age (variable cutoffs) [6, 7, 13]
- fitness (ECOG 0-1, KPS ≥ 80) [4, 8, 11, 14]
- disease remission at second alloHCT [5, 9-14]

- time to relapse from first alloHCT (most >12 mo) [4-8, 12-15]

Several reports have described the negative effect of rapid relapse after allogeneic transplant, many with a cutpoint of 12 months[4-8, 12-15]. Results from our program, shown in the figure below, suggest that patients retransplanted within one year of an allogeneic transplant experience poor outcomes. It is reasonable to take this as a cutoff.

Figure 1.



Outcome of second allogeneic transplants performed in Calgary for patients with AML who have relapsed following a prior allogeneic transplant. Eligible patients (top line) are those who remained in remission for > 1 year following their initial transplant.

In one 2023 report by Lu *et al.* of 199 acute leukemia cases, risk factors identified in multivariable analysis appeared to be additive. In their report patients at second alloHCT with favourable risk factors including a) MRD -ve CR and b) an HCT-CI score of 0 and c) a second donor with mismatched haplotype, had a 2-year overall survival estimate of 63% compared to 43% in patients having two of the favourable risk factors and 20% in patients with none ($p = 0.0001$)[10].

Given the inconsistency in risk associations reported across series, no one risk factor should necessarily be sufficient to preclude consideration of alloHCT. Based on the combined analysis of available registry studies and case series, and our own local experience, we advocate that patients be selected for second alloHCT if their disease remains in remission at for at least 12 months after transplant, and if on a case by case basis they are deemed more favourable based on the presence and number of favourable risk factors identified above.

The optimal conditioning intensity for second alloHCT remains an unresolved question. A retrospective EBMT registry study involving 215 AML patients undergoing second alloHCT noted no

significant difference in 2 year OS (31 v 40%, p =0.41), 2 year relapse risk (58 v 20% 51%, p= 0.24), and 2 year NRM (15 v 28%, p=0.89) in patients who received reduced intensity versus myeloablative conditioning, respectively[11]. In 10 case series and registry studies involving 3,777 patients in which both RIC and MAC regimens were used[4, 5, 7-9, 11-14, 16], conditioning was associated with survival outcomes in univariable (and not multivariable) analysis in just one 129-patient series[4]. This suggests that decreased TRM expected with reduced intensity conditioning is offset by its increased associations with relapse, ultimately have a net zero impact on overall survival. Barring concerning patient comorbidities, our center favours a myeloablative TBI-based conditioning regimen for second alloHCT, regardless of donor type.

The benefits of using a same or different stem cell donor for second alloHCT has been debated and explored. A recent large retrospective EMBT registry study involving 598 AML patients receiving second alloHCT looked at outcomes comparing recipients of a same MUD or MRD, different MUD/MRD, or different haplo donor. Ultimately they found no differences in 2 year OS (36 v 28 v 23%; p=0.21) relapse rate (51 v 49 v 44%; p=0.90) and NRM (25 v 37 v 34%; p=0.28) in comparing transplant recipients using the same matched donor, different matched donor, or different haplo donor[17]. Given that using a new or repeated donor does not appear to have clear impact on clinical outcomes, our centre favours selecting donors for second alloHCT instead based on availability and other standard donor factors, as summarized in this manual's Donor Selection chapter.

Use of Azacitidine and Donor Lymphocyte Infusions to Control Relapsed Leukemia

The impact of donor lymphocyte infusions (DLI) on relapsed leukemia was first described by Kolb and coworkers in 1990[18]. They demonstrated that patients with cytogenetic or hematological relapse of CML could achieve a second disease-free state after the infusion of lymphocytes from their original stem cell donor. Graft-versus-host disease was observed in most responders. While DLI appeared to induce durable remissions in CML, responses in acute leukemia are uncommon. Augmenting DLI with chemotherapy increases response rates but also adds toxicity, without substantially prolonging survival. One exception may be combining DLI with azacitidine, a low-toxicity alternative to higher dose chemotherapy. Two reports have been published in sufficient detail to understand the outcome of this strategy:

- The German Cooperative Transplant Study Group (Schroeder *et al.*, 2015) described the results of a multicenter retrospective study of azacitidine plus planned DLI in 154 patients with myeloid disorders (AML (n=124), MDS (n=28) or MPN (n=2))[19]. Patients received azacitidine in a five-day 100 mg/m^2 or seven-day 75 mg/m^2 schedule, after which DLI was administered to 105 patients. Reasons for not administering DLI included progressive disease, coexisting GVHD, non-availability of the donor or achievement of CR with azacitidine alone. The overall response rate was 33% (27% CR, 6% PR) and two-year OS 29%. Factors associated with higher likelihood of survival include early relapse (molecular relapse only or fewer than 13% blasts at time of relapse) and a diagnosis of MDS. GVHD occurred in 31%. Given that some patients received the azacitidine+DLI for molecular relapse only and thus some of them may

have been cured ever without the azacitidine+DLI, it is unclear whether this therapy has a meaningful clinical efficacy. However, given the relatively low toxicity and the possibility of meaningful clinical efficacy, we are willing to offer this option to highly motivated patients.

- A subset of 30 patients in the above publication were described in a previous report[20]. These patients received azacitidine 100 mg/m^2/day for five days every four weeks with escalating DLI after every second cycle. Twenty-two patients received DLI and seven (23%) achieved CR and two (7%) PR. Patients with MDS, AML with MDS-related change, early relapse and high-risk cytogenetics were more likely to show response.

At our center DLI was typically considered for patients with acute leukemia or MDS who have franks relapsed after alloHCT. Owing to local data describing inconsistent outcomes in patients with minimal residual disease documented on their day +100 bone marrow biopsy, our center originally avoided use of DLI for this subpopulation. In a prospective observation report by Shah *et al.* (BBMT 2018)[21] of 269 AML patients with MRD assessments done by 7-color flow cytometry on bone marrow aspirates at days 30, 100, and 180 post alloHCT, day +30 MRD positivity was strongly predictive of relapse incidence (HR 11, 95% CI 4.3-27; p <0.001) and of shorter OS (HR 4.3, 95% CI 2.0-9.6; p<0.001). These strong prognostic trends were also reported with patients MRD +ve at days 100 and 180. In original Schroder *et al.* report on 105 DLI recipients and a subsequent reports by Rautenberg *et al* using the same protocol[22], patients with molecular-only relapse has substantially superior survival outcomes compared to those with hematologic relapse (2 year OS 62 v 25%; p=0.003 and 55 v 29%; p<0.0001). Owing to publication bias, retrospective data, varied definitions of molecular relapse (ie. including small proportions of patient with mixed chimerism), and the lack of standardized MRD testing, these observations are challenging to apply directly to practice. They do, however point to a clear trend reported in these studies and elsewhere that those receiving DLI with the smallest amount of disease burden at relapse tend to have better survival outcomes[4, 19, 22-24]. Locally we have given DLI in 2018 and 2019 for molecular relapse in 3 patients with AML, B-ALL, T-ALL. As of September 2023, two are still alive more than 59 (B-ALL) and 60 months (AML) post DLI, with one death (T-ALL) more than two years post DLI (30 months).

To consolidate the above retrospective with local observations that patients with MRD +ve at the 100 day mark have mixed survival outcomes, we will consider DLI for patients meeting the following criteria:

Patients with AML or MDS

- who relapse
  - < 1 year post alloHCT
  - > 1 year post alloHCT and non-candidate for second alloHCT
- with relapse defined as

- hematologic relapse: >5% marrow blasts, peripheral blood blasts, extramedullary disease
- molecular relapse that is
  - defined by disease-identifying cytogenetic, morphologic, molecular, or immunophenotypic means (not incomplete donor chimerism)
  - documented on
    - 3 month post-transplant marrow **AND** demonstrated to be worsening at subsequent time point(s) 4-6 weeks later
    - documented at clinical suspicion of relapse beyond 3 months (and if deemed necessary by clinician discretion) demonstrated to be worsening at subsequent time point(s)

- without options for clinical trials or targeted chemo/immunotherapy
- without a history of gr3-4 aGVH or mod-sev cGVH
- who are motivated and fit

Patients with B- or T-ALL could be considered for DLI if meeting the above criteria and options.

Given the alternatively dismal outcomes for relapsed leukemia after allotransplant, and somewhat favourable survival and toxicity outcomes above, in 2017 our center adopted and has used the Azacitidine and DLI schedule described in the above report, which involves 8 total cycles of Azacitidine, with 4 escalating DLI doses, each DLI occurring after 2 Azacitidine cycles. After more than 5 years using this protocol, and more than 25 years using DLI altogether, Calgary DLI recipients have rarely received more than 2 DLI doses (Table 1). Common reasons for not proceeding beyond one dose included disease progression, GVHD, other toxicity, or death.

Max DLIs Received	No. Pts (%)
1	67 (70)
2	19 (20)
3	7 (7)
4	3 (3)
	96

Table 1: Maximum DLI Doses Received by 96 DLI Recipients in Calgary, 1996-2023

- Harvesting, aliquoting, and freezing to target 4 different DLI doses in Calgary has proven restrictively labour intensive. Owing to both total harvest yield and loss of cell viability in the freeze-thaw process, it is also rare that our center achieves target viable cells for infusion at all doses, particularly at the highest concentrations. Given these challenges and the rarity with which our center proceeds with a 4th DLI dose, we will adapt the regimen above to target 6

cycles of Azacitidine and 3 DLI doses, while keeping the dose intensity of the 4th dose increment described in the original Schroeder < 1 year post alloHCT

- > 1 year post alloHCT and non candidate for second alloHCT report.

We will use the following adapted schedule:

- Week 1: Azacitidine 100 mg/m2/d x 5
- Week 5: Azacitidine 100 mg/m2/d x 5
- Week 6: DLI #1 (1 x 10e6 T cells/kg)
- Week 9: Azacitidine 100 mg/m2/d x 5
- Week 13: Azacitidine 100 mg/m2/d x 5
- Week 14: DLI #2 (1 x 10e7 T cells/kg)
- Week 17: Azacitidine 100 mg/m2/d x 5
- Week 21: Azacitidine 100 mg/m2/d x 5
- Week 22: DLI #3 (1 x 10e8 T cells/kg))

This protocol was adopted by the Alberta Blood and Marrow Transplant Program for treatment of relapsed AML and MDS in 2017. As of March 2021 we have treated 13 patients with mixed results. Median follow-up of surviving patients is 720 days, range 102-1202 days. Median overall survival for the entire cohort is 185 days with 43% of patients alive at one year. Three-year overall survival is 16%. As of September 2023 Calgary has performed DLI in 29 patients using this protocol. Of the 22 patients with at least 24 month follow-up, 2 year OS is 41%. Of the 9 patients surviving more than two years post DLI, 7 remain alive and are approaching or well past 4 years since their infusion.

Indolent Diseases: Chronic Myelogenous Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL)

In the era of numerous effective TKIs and accumulating targeted therapies, Calgary rarely performs alloHCT, let alone DLI for CML and CLL: since 2014, Calgary has performed DLI for two relapsed CML cases and none for CLL. The short review below summarizes experience with DLI in these conditions.

In CML and CLL the risk of recurrence is related to the status of the disease at the time of transplantation. Outcomes of transplantation for CML beyond first chronic phase or for CLL that has transformed to aggressive lymphoma remain inferior to those of less advanced disease. Outcomes of transplantation for CLL with adverse cytogenetics (17p-, 11q-), advanced stage at diagnosis or that is fludarabine-refractory are inferior to those of patients without these features[25].

The management of relapsed CML and CLL after transplant should take into account prior therapies the patient has received and the existence of newer therapies that the patient may not have been exposed to prior to undergoing transplant. In CML, later-generation tyrosine kinase inhibitors (dasatinib, nilotinib, bosutinib and ponatinib) may not have been available to the patient prior to

transplant. Similarly, in CLL, patients may not have received B-cell receptor antagonists (ibrutinib or idelalesib) or a BCL-2 inhibitor (venetoclax). It is reasonable to use these agents in the post-transplant relapse setting if the patient has not previously been exposed.

The existence of an immunological graft-versus-leukemia effect in these diseases is well described. In both diseases relapses are more common using T-cell depleted grafts, relapses are less common once chronic GVHD develops, responses are delayed and tend to deepen over time. Donor lymphocyte infusions (DLI) are a practical way of exploiting this graft-versus-leukemia effect, although they are not without significant toxicities of their own. The majority of patients who respond to DLI develop some degree of acute or chronic GVHD and 8% of patients treated with DLI develop aplasia and may require retransplantation.

The table below summarizes the response of relapsed CML to DLI. While responses are seen in the majority of patients with early relapse, responses in accelerated phase disease are more the exception than the rule. Similar results are observed in CLL, although large series have not been published to date. The existing literature suggests that 44 – 86% of patients with relapsed CLL will respond to DLI, and this response may be enhanced by the addition of rituximab[26, 27]. In the case of CML, the addition of TKI's or interferon may enhance response to DLI, while in CLL chlorambucil or rituximab may be used to delay progression of disease until a graft-versus-leukemia effect occurs[28]. Fludarabine should not be given within 48 hours of DLI as it may abrogate the allogeneic T-cell responses necessary for a graft-versus-leukemia effect to take place.

Table 1. Response of Relapsed CML to DLI

	Molecular or Cytogenetic Relapse	Chronic Phase	Accelerated Phase	Total
Van Rhee	11/11	8/14	1/5	20/30 (66%)
Collins	3/3	25/34	5/18	33/42 (78%)
Drobyski	_	_	6/8	6/8 (75%)
Porter	_	6/8	0/3	6/11 (54%)
Kolb	14/17	39/53	1/14	54/84 (64%)
MacKinnon	8/8	9/10	2/4	19/22 (86%)
Bacigalupo	_	_	_	10/18 (55%)
Alyea	15/19		0/5	15/24 (62%)
Verdonck	_	9/9	4/5	13/14 (93%)
Sehn	NS	NS	NS	19/23 (82%)

Response to DLI in relapsed CML by phase at relapse. Adapted from Dazzi et al.[19]

The literature is surprisingly silent on the topic of repeat transplantation for relapsed CML or CLL. While such transplants have no doubt taken place, they are likely restricted to the small number of patients whose disease fails to respond to DLI and whose performance status, comorbidities and

disease status permits. It remains uncertain what additional benefit is to be derived from retransplantation in the setting of disease that fails to respond to the graft-versus-leukemia effect engendered by DLI.

References

1. *Perl AE, Altman JK, Cortes JE, Smith CC, Litzow M, Baer MR et al. Final results of the chrysalis trial: a first-in-human phase 1/2 dose-escalation, dose-expansion study of gilteritinib (ASP2215) in patients with relapsed/refractory acute myeloid leukemia (R/R AML). In: Am Soc Hematology, 2016.*
2. *Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. New England Journal of Medicine 2019; **381**(18)**:** 1728-1740.*
3. *Rautenberg C, Germing U, Haas R, Kobbe G, Schroeder T. Relapse of Acute Myeloid Leukemia after Allogeneic Stem Cell Transplantation: Prevention, Detection, and Treatment. Int J Mol Sci 2019; **20**(1).*
4. *Aljasem HA, Messner HA, Lipton JH, Kim DDH, Viswabandya A, Thyagu S et al. Outcome following second allogeneic hematopoietic cell transplantation: A single-center experience. Eur J Haematol 2018; **100**(3)**:** 308-314.*
5. *Choi Y, Choi EJ, Lee JH, Lee KH, Jo JC, Park HS et al. Second allogeneic hematopoietic stem cell transplantation in patients with acute leukemia relapsed after allogeneic hematopoietic stem cell transplantation. Clin Transplant 2021; **35**(3)**:** e14199.*
6. *Christopoulos P, Schmoor C, Waterhouse M, Marks R, Wäsch R, Bertz H, Finke J. Reduced-intensity conditioning with fludarabine and thiotepa for second allogeneic transplantation of relapsed patients with AML. Bone Marrow Transplant 2013; **48**(7)**:** 901-907.*
7. *Eapen M, Giralt SA, Horowitz MM, Klein JP, Wagner JE, Zhang MJ et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. Bone Marrow Transplant 2004; **34**(8)**:** 721-727.*
8. *Gyurkocza B, Storb R, Chauncey TR, Maloney DG, Storer BE, Sandmaier BM. Second allogeneic hematopoietic cell transplantation for relapse after first allografts. Leuk Lymphoma 2019; **60**(7)**:** 1758-1766.*
9. *Kharfan-Dabaja MA, Labopin M, Polge E, Nishihori T, Bazarbachi A, Finke J et al. Association of Second Allogeneic Hematopoietic Cell Transplant vs Donor Lymphocyte Infusion With Overall Survival in Patients With Acute Myeloid Leukemia Relapse. JAMA Oncol 2018; **4**(9)**:** 1245-1253.*
10. *Lu Y, Zhang JP, Zhao YL, Xiong M, Sun RJ, Cao XY et al. Prognostic factors of second hematopoietic allogeneic stem cell transplantation among hematological malignancy patients relapsed after first hematopoietic stem cell transplantation: A single center study. Front Immunol 2022; **13:** 1066748.*
11. *Nagler A, Labopin M, Dholaria B, Finke J, Brecht A, Schanz U et al. Second allogeneic stem cell transplantation in patients with acute lymphoblastic leukaemia: a study on behalf of the Acute Leukaemia Working Party of the European Society for Blood and Marrow Transplantation. Br J Haematol 2019; **186**(5)**:** 767-776.*
12. *Orti G, Sanz J, Bermudez A, Caballero D, Martinez C, Sierra J et al. Outcome of Second Allogeneic Hematopoietic Cell Transplantation after Relapse of Myeloid Malignancies following Allogeneic Hematopoietic Cell Transplantation: A Retrospective Cohort on Behalf of the Grupo Español de Trasplante Hematopoyetico. Biol Blood Marrow Transplant 2016; **22**(3)**:** 584-588.*
13. *Ruutu T, de Wreede LC, van Biezen A, Brand R, Mohty M, Dreger P et al. Second allogeneic transplantation for relapse of malignant disease: retrospective analysis of outcome and predictive factors by the EBMT. Bone Marrow Transplant 2015; **50**(12)**:** 1542-1550.*
14. *Schneidawind C, Hagmaier V, Faul C, Kanz L, Bethge W, Schneidawind D. Second allogeneic hematopoietic cell transplantation enables long-term disease-free survival in relapsed acute leukemia. Ann Hematol 2018; **97**(12)**:** 2491-2500.*
15. *Shaw BE, Mufti GJ, Mackinnon S, Cavenagh JD, Pearce RM, Towlson KE et al. Outcome of second allogeneic transplants using reduced-intensity conditioning following relapse of haematological malignancy after an initial allogeneic transplant. Bone Marrow Transplant 2008; **42**(12)**:** 783-789.*
16. *Tachibana T, Tanaka M, Hagihara M, Fujimaki K, Kanamori H, Nakajima H. Outcomes in patients with acute lymphoblastic leukemia who underwent second allogeneic hematopoietic cell transplantation for relapse after first transplantation. Int J Hematol 2022; **116**(4)**:** 594-602.*
17. *Shimoni A, Labopin M, Finke J, Ciceri F, Deconinck E, Kröger N et al. Donor selection for a second allogeneic stem cell transplantation in AML patients relapsing after a first transplant: a study of the Acute Leukemia Working Party of EBMT. Blood Cancer J 2019; **9**(12)**:** 88.*
18. *van Rhee F, Kolb HJ. Donor leukocyte transfusions for leukemic relapse. Curr Opin Hematol 1995; **2**(6)**:** 423-430.*
19. *Schroeder T, Rachlis E, Bug G, Stelljes M, Klein S, Steckel NK et al. Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions--a retrospective multicenter analysis from the German Cooperative Transplant Study Group. Biol Blood Marrow Transplant 2015; **21**(4)**:** 653-660.*

20. *Schroeder T, Czibere A, Platzbecker U, Bug G, Uharek L, Luft T et al. Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation. Leukemia 2013;* ***27****(6)****:*** *1229-1235.*
21. *Shah MV, Jorgensen JL, Saliba RM, Wang SA, Alousi AM, Andersson BS et al. Early Post-Transplant Minimal Residual Disease Assessment Improves Risk Stratification in Acute Myeloid Leukemia. Biol Blood Marrow Transplant 2018;* ***24****(7)****:*** *1514-1520.*
22. *Rautenberg C, Bergmann A, Germing U, Fischermanns C, Pechtel S, Kaivers J et al. Prediction of Response and Survival Following Treatment with Azacitidine for Relapse of Acute Myeloid Leukemia and Myelodysplastic Syndromes after Allogeneic Hematopoietic Stem Cell Transplantation. Cancers (Basel) 2020;* ***12****(8).*
23. *Ghiso A, Raiola AM, Gualandi F, Dominietto A, Varaldo R, Van Lint MT et al. DLI after haploidentical BMT with post-transplant CY. Bone Marrow Transplant 2015;* ***50****(1)****:*** *56-61.*
24. *Rettig AR, Ihorst G, Bertz H, Lübbert M, Marks R, Waterhouse M et al. Donor lymphocyte infusions after first allogeneic hematopoietic stem-cell transplantation in adults with acute myeloid leukemia: a single-center landmark analysis. Ann Hematol 2021;* ***100****(9)****:*** *2339-2350.*
25. *Michallet M. Autologous and Allogeneic Transplantations for Chronic Lymphocytic Leukemia,. In: Faguet G (ed) Chronic Lymphocytic Leukemia: Molecular Genetics, Biology, Diagnosis and Management. Humana Press: Totowa, New Jersey, 2004, pp 255-268.*
26. *Delgado J, Thomson K, Russell N, Ewing J, Stewart W, Cook G et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood 2006;* ***107****(4)****:*** *1724-1730.*
27. *Khouri IF, Lee MS, Saliba RM, Andersson B, Anderlini P, Couriel D et al. Nonablative allogeneic stem cell transplantation for chronic lymphocytic leukemia: impact of rituximab on immunomodulation and survival. Exp Hematol 2004;* ***32****(1)****:*** *28-35. e-pub ahead of print 2004/01/17; doi: 10.1016/j.exphem.2003.09.021*
28. *Alousi AM, Uberti J, Ratanatharathorn V. The role of B cell depleting therapy in graft versus host disease after allogeneic hematopoietic cell transplant. Leuk Lymphoma 2010;* ***51****(3)****:*** *376-389.*

Neutropenic Fever

Presented by: Ahsan Chaudhry

Summary

- Febrile neutropenia is a medical emergency and should be treated rapidly. The initial evaluation should include blood cultures drawn peripherally and through a central line (if present). Further investigations should be carried out based on foci identified on clinical examination.
- Empiric antibiotics should be administered within one hour of presentation.
- Empiric therapy for **stable patients, without a clinical focus**:
    - Piperacillin/tazobactam 4.5 g IV stat and every 6 hours, OR ceftazidime/cefepime 2 g IV every 8 hours.
    - Gentamicin 7 mg/kg (AIBW for obese) IV q24-36h if beta lactam resistance is suspected, or for probable gastrointestinal (GI) source.
    - Above doses assume normal renal function.
- Additional empiric therapy for **unstable patients:**
    - Gentamicin 7mg/kg (AIBW for obese) IV q24-36h for probable GI source
    - Vancomycin 1 gram (or 25mg/kg) IV loading dose for CVC or Pulmonary source.
    - IV fluids, oxygen, early ICU support.
- If blood cultures positive, adjust coverage based on organism and sensitivity.
- If blood cultures negative but persisting fever or patient clinically unwell, continue antibacterials until ANC ≥0.5/nl for 2 consecutive days.
- If blood culture negative, afebrile, and *clinically well* after 72 hours, discontinue antibacterials.
- Empirical anti-fungal therapy should be considered in patients who have persistent or recurrent fever after 4-7 days of treatment with broad spectrum antibacterials. (See chapter on Fungal prophylaxis).

Definitions

Fever: single core temperature of ≥ 38.5°C (or oral > 38.3), or a core temperature of ≥ 38.3°C (or oral>38.0) sustained over a 1 hour period.

Neutropenia: an absolute neutrophil count of <0.5/nl, or an ANC that is expected to decrease to <0.5/nl during the next 48 hours.

Investigations

In addition to a focused history, review of systems and physical examination, all patients with fever in neutropenia should be investigated as follows:

1. Routine blood cultures drawn through central line and peripheral vein.

2. Chest X-ray (posterior-anterior (PA) and lateral views) if clinically indicated.
3. Culture specimens from other sites of suspected infection should be obtained if clinically indicated
4. If fevers persist then repeat blood cultures should be drawn every 48 hours from central line only.
5. If cultures are positive then should repeat cultures until negative.

Empiric Therapy

Both ASCO (American Society of Clinical Oncology) and Surviving Sepsis campaigns recommend TTA (time to antibiotic) of < 60minutes.

Stable Patients

1. Piperacillin/tazobactam at 4.5 grams every 6 hours
2. Ceftazidime/Cefepime 2 grams q8h is given to patients who may have allergy to penicillin, recognizing that 5% of patients may still cross react.
3. True **penicillin** anaphylaxis likely requires an Infectious Diseases consult, but consider:
    - Aztreonam 2 grams IV every 6 hours (only gram-negative coverage) + vancomycin 1 gram IV every 12 hours (gram-positive coverage), OR
    - Tobramycin 6mg/kg/day + Levofloxacin 500 mg IV daily, OR
    - *Ciprofloxacin 400 mg IV every 12 hours + clindamycin 600mg IV every 8 hours*

Unstable Patients

Severe sepsis is a syndrome defined by evidence for SIRS (systemic inflammatory response syndrome) (defined by ≥ two of the following criteria):

- body temperature > 38°C or < 36°C,
- heart rate > 90 beats/minute,
- respiratory rate > 20/minute,
- Pa CO_2 < 32 mmHg,
- an alteration in the total leukocyte count to > 12×10^9/L or < 4×10^9/L, or the presence of >10% band neutrophils in the leukocyte differential
- PLUS evidence of infection and end-organ dysfunction (altered mental status, hypotension (systolic blood pressure < 90 mmHg, mean arterial pressure < 70 mmHg, or systolic blood pressure decrease of > 40 mmHg,) elevated serum lactate >4 mmol/L, oliguria (urine output <0.5 mL/kg/hour), and/or hypoxia.

Patients with sepsis or pneumonia with bacteremia have mortality >50% despite prompt antibiotics. Aggressive fluid resuscitation, oxygen and early physiological goal directed therapy, including ICU support, is critical.

1. Meropenem 500 mg q6h, Gentamicin 7 mg /kg/day (AIBW) given every 24-36 hours, or Ciprofloxacin (750mg po bid/400mg IV q12) may be initiated if antimicrobial resistance or GI source is suspected.
2. Vancomycin may be added empirically for SIRS, hospital acquired pneumonia (HAP), gram-positive bacteremia, endocarditis, meningitis, or osteomyelitis. Vancomycin loading dose (25-30mg/kg ABW) should be considered if practical for HAP or SIRS (although TTA may be more important). Maintenance dosing (15mg/kg ABW) is then continued q12h until discontinuation or dose adjustment per trough level.
   - If vancomycin is used only empirically, it should generally be discontinued after 24-48 h.
   - Vancomycin trough levels should be considered if plasma creatinine >40 mmol/L above baseline, BMI >40, age >60, or treatment duration >7d. Trough target level is 15-20 mg/L for HAP/MRSA and 10-15 mg/L for empiric therapy. First trough level should be determined at steady state (pre 4th or 5th dose) and repeated after adjustment in new steady state, every 7-10 d or if concurrent nephrotoxic drugs.
   - Vancomycin may be added ***temporarily*** in the case of blood cultures showing gram-positive organisms, although in this case one set of blood cultures each should be collected peripherally and centrally to confirm persistent bacteremia and exclude a false-positive (i.e. contaminated) blood culture.
   - There is no proven advantage to adding vancomycin empirically in the setting of persistent or recrudescent fever and neutropenia in an otherwise asymptomatic hemodynamically stable patient. If vancomycin was added empirically at the outset of therapy for neutropenic fever, it should be stopped if blood cultures have incubated for 48 hours and demonstrated no pathogenic gram-positive organisms.

Re-Assessment

Patients are reassessed for response to treatment daily. Antibacterial coverage is adjusted to ensure coverage of organisms grown in culture, preferably based on *in vitro* sensitivity testing.

De-Escalation

Two randomized controlled trials compared de-escalation strategies in hematologic malignancy patients undergoing chemotherapy or HCT with FN without microbiologic diagnosis (Table 3). The How Long study compared empiric antibiotic therapy (EAT)-free days among 157 neutropenic patients randomized to de-escalation using ECIL-4 criteria versus standard of care based on hospital-specific protocols. EAT-free days was significantly lower in the experimental group, with an absolute difference of 6.4 days. There was no difference in crude mortality (0 in both groups), and mean days of fever did not differ significantly between groups. Another randomized trial compared short (minimum 72 hours) versus extended carbapenem in 281 patients with fever of unknown origin with median 14 days of neutropenia. Carbapenem treatment duration significantly differed: 3 versus 8 days. Primary composite outcome was treatment failure (carbapenem-sensitive infection, fever recurrence,

septic shock, respiratory insufficiency, or death) from Day 4 to neutropenia recovery, and was nonsignificantly higher in the short duration group (19% vs. 15%), which met criteria for non-inferiority.

There have also been several observational studies that compare clinical outcomes in patients undergoing early de-escalation of empiric broad-spectrum antibiotics versus continuation through ANC recovery, with the six adopting an ECIL-4-based de-escalation strategy.

Table 1. Reassessment criteria for patients

Persistent fever after 3 to 5 days of treatment:	Afebrile after initial antimicrobial treatment with no etiology identified:	Positive blood cultures/focus:
1. Repeat blood cultures and other investigations as indicated above. 2. Imaging on day 5 – enhanced CT of chest+abdomen+pelvis if good renal function. If poor renal function, then nonenhanced CT of chest plus US of abdomen. 3. Empirical antifungal treatment as indicated (see chapter on Fungal prophylaxis). 4. Add vancomycin for 48hrs if criteria are met, e.g. skin and soft tissue infection, catheter related infection, pneumonia or hemodynamic instability.	1. High risk patients should continue antibiotics until ANC greater than 500 cells/mm³ for 2 consecutive days. 2. Antimicrobials are stopped for ATG (antithymocyte globulin) related fevers if afebrile and blood culture is negative after 48 hours. 3. Discontinuation or simplification of anti pseudomonal antibiotics possible after 72 h or more of apyrexia plus clinical recovery while still neutropenic	1. Treat according to sensitivities if available. 2. For blood culture positive for gram positive microorganism, repeat another set of blood culture centrally and peripherally before starting Vancomycin to rule out possibility of contamination. 3. For documented infection with positive culture, the duration of antimicrobial therapy depends on the type, site and source of infection. 4. Consider central line source if > 2hr difference in TTP (time to positivity). 5. Investigate focus appropriately and treat according to common pathogens.

References

1. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb; 52(4):e56–e93.
2. Rybak M, Lomaestro B, Rotshafer JC, Moellering R Jr, Craig W, Billeter M, et al. Therapuetic monitoring of vancomycin in adult patients: a consensus review of the ASHP, IDSA, and SIDP. Am J Health-Syst Pharm. 2009; 66:82-98.
3. Blondel-Hill E, Fryters S. Bugs & Drugs. 1998-2015 Alberta Health Services.
4. Mohammedi I, Descloux E, Argaud L, Le Scanff J, Robert D. Loading dose of vancomycin in critically ill patients: 15mg/kg is a better choice than 500mg. Int J Antimicrob Agents. 2006; 27:259-62.
5. Wang JT, Fang CT, Chen YC, Chang SC. Necessity of a loading dose when using vancomycin in critically ill patients. J Antimicrob Chemother. 2001; 47:246.
6. Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. Antimicrob Agents Chemother. 1984; 25:433-7.
7. Contreiras C, Legal M, Lau TT, Thalakada R, Shalansky S, Ensom MH. Identification of risk factors for nephrotoxicity in patients receiving extended duration, high trough vancomycin therapy. CJHP. 2014; 67:126-32.
8. Yolin-Raley DS, Dagogo-Jack I, Niell HB, Soiffer RJ, Antin JH, Alyea EP 3rd, et al. The utility of routine chest radiography in the initial evaluation of adult patients with febrile neutropenia undergoing HSCT. J Natl Compr Canc Netw. 2015;13:184-9
9. Kimura S, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, et al. Antibiotic prophylaxis in hematopoietic stem cell transplantation. A meta-analysis of RCTs. J Infect. 2014; 69:13-25.
10. Satlin M, Vardhana S, Soave R, Shore TB, Mark TM, Jacobs SE, et al. Impact of prophylactic levofloxacin on rates of bloodstream infection and fever in neutropenic patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2015; 10:1808-14.
11. Aguilar-Guisado M, Espigado I, Martin-Pena A, et al. Optimisation of empirical antimicrobial therapy in patients with haeatological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol 2017 ;(12):e573-83.
12. George X. Huang et al. Preadmission Penicillin Allergy Evaluation Before Hematopoietic Stem Cell Transplantation Optimizes Febrile Neutropenia Treatment and Inpatient Resource Utilization. Transplantation and Cellular Therapy
13. Yoshino N, Kimura SI, Kawamura K, Nakata Y, Matsuoka A, Ishikawa T, Meno T, Nakamura Y, Kawamura M, Kawamura S, Takeshita J, Misaki Y, Yoshimura K, Gomyo A, Okada Y, Tamaki M, Kusuda M, Kameda K, Akahoshi Y, Sato M, Tanihara A, Nakasone H, Kako S, Kanda Y. Clinical impact of a change in antibiotics or the addition of glycopeptide antibiotics for persistent febrile neutropenia after autologous stem cell transplantation. J Infect Chemother. 2024 Jun 24:S1341-321X(24)00173-9. doi: 10.1016/j.jiac.2024.06.018. Epub ahead of print. PMID: 38925426.
14. Sheu M, Molina Garcia S, Shrivastava G, Patel M, Mushtaq A, Crilley T, Anwer F, Majeed A. Yield of repeat blood cultures in acute myeloid leukemia patients with febrile neutropenia and bacteremia following allogeneic hematopoietic stem cell transplant. Transpl Infect Dis. 2024 Aug;26(4):e14345. doi: 10.1111/tid.14345. Epub 2024 Jul 16. PMID: 39012614.
15. Ishikawa, K.; Masaki, T.; Kawai, F.; Ota, E.; Mori, N. Systematic Review of the Short-Term versus Long-Term Duration of Antibiotic Management for Neutropenic Fever in Patients with Cancer. *Cancers* **2023**, *15*, 1611. https://doi.org/10.3390/cancers15051611
16. Short versus extended treatment with a carbapenem in patients with high-risk fever of unknown origin during neutropenia: a non-inferiority, open-label, multicentre, randomised trial,de Jonge, Nick A et al.The Lancet Haematology, Volume 9, Issue 8, e563 - e572

Central Venous Access Device (CVAD) and its Complications

Presented by: Ahsan Chaudhry and Robin Pommier

Summary

- **Line Type Preferences**
  - **Recipients (Autologous transplant, Allogeneic transplant, Chimeric antigen receptor T-Cells (CAR T-cells):**
    - The recommended catheter for recipients is the *Trifusion™ 12F triple lumen carbothane apheresis catheter*
    - If a tunneled line or apheresis is not necessary, a silicone double lumen Groshong peripherally inserted central catheter (PICC) can be considered.
      - CAR T-cells that require gravity infusion (e.g. tisagenlecleucel) cannot be infused through a valved PICC, such as a Groshong.
  - **Donors:**
    - Peripheral venous access is preferred for collection from all donors. Two large-bore antecubital lines will be inserted just prior to apheresis.
    - If large bore antecubital lines cannot be inserted, a *double-lumen temporary Quinton Mahurkar* (8 French diameter, length 15 cm) will be inserted under image guidance and removed prior to the patient leaving the hospital.

- **Prevention of CVAD Infections**
  - The central venous catheter care clinical bundle (including hand hygiene, maximal barrier precautions, and chlorhexidine skin antisepsis) will be used for placement and maintenance of all CVADs.
    - Rigorous attention to hand hygiene and aseptic technique is essential before inserting, removing, or manipulating the CVAD.
    - Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before CVAD insertion and during dressing changes.
    - Use sterile gauze or sterile, transparent, semi permeable dressing on CVAD insertion site. For tunneled CVADs, dressings may be removed as per unit policy and procedure.
  - Promptly remove CVAD lines that are no longer being used.
  - Insertion of CVAD on right side is preferred. Avoid femoral vein.
  - Remove CVAD if not used or used infrequently.

- **Treatment of CVAD Infections**
  - **Empiric Treatment:**
    - Collect bacterial cultures from CVAD entrance/exit site and blood (central and peripheral) prior to initiating treatment.
    - Vancomycin to cover gram positive organisms.

        - In systemically ill patients, add Tazocin, ceftazidime or meropenem to cover gram negatives.
    - **Treatment of Proven or Complicated Infection:**
        - Treat according to IDSA guidelines as described in main text below.

- **Prevention of Line Occlusion**
    - Diligent care and maintenance as outlined in nursing vascular access device infusion therapy Clinical Care Topic (CCT)
    - CVADs are typically flushed/locked with 0.9% sodium chloride.
        - **Exception**: CVADs inserted for the purpose of apheresis are locked with 4% sodium citrate for the lifetime of the catheter.

- **Treatment of Line Occlusion (Thrombotic or Mechanical)**
    - Thrombotic occlusion will be treated with r-tPA.
    - Unless mechanical occlusion is suspected radiographic imaging is not necessary prior to r-tPA instillation.
    - If a mechanical issue is suspected or signs of tip malposition, an x-ray and/or dye study will be carried out.
    - For chemical occlusion consult Advanced Venous Access Service (AVAS) for assessment.

- **Treatment of Line Related Venous Thrombosis**
    - There is insufficient evidence to recommend routine removal of clinically necessary, functioning and non-infected CVAD's in the setting of catheter-related thrombosis. If anticoagulation is not feasible then line removal is indicated.

Background

Multi-lumen catheters are placed prior to transplant to facilitate transfusions, blood draws and medication administration and are preferably tunneled to decrease infection risk.

Line Type Preferences

Autologous Transplant and CAR T-cell Recipients:

- For autologous transplant and CAR T-cell recipients, a rigid line is needed for apheresis. The current recommended catheter used prior to apheresis is the *Trifusion™ 12F triple lumen carbothane apheresis catheter* and is to remain in place until after autologous transplant.
- CVAD lines inserted for the purpose of apheresis are locked with 4% sodium citrate for the life time of the catheter.

- If a patient has had a previously installed implanted vascular access device (IVAD), it need not be removed prior to transplant but another catheter may also be placed.
- If a peripherally inserted central catheter (PICC) will be used for transplant instead of a tunneled CVAD a Bard Groshong silicone PICC line is preferred. Other valved PICCs have been found to hemolyze blood samples.
    - CAR T-cells that require gravity infusion (e.g. tisagenlecleucel) cannot be infused through a valved PICC, such as a groshong.

Allogeneic Transplant:
- In allogeneic transplantation, a large bore, triple lumen catheter is preferred for transfusions and medication administration. The current CVAD recommendation is the same line used for autologous transplant.
- Since the CVAD is not inserted for the purpose of apheresis it is standardly flush/locked with 0.9% sodium citrate.
- If a PICC line needs to be inserted pre transplant a Bard Groshong silicone line is preferred.

Donors:
- Two large bore antecubital lines are to be inserted.
- If large bore antecubital line insertion is not possible or donor is unwilling a double lumen temporary Quinton Mahurkars (8 French diameter), length 15 cm, is inserted the day of collection to facilitate apheresis and then removed post apheresis.
- A patient or donor with a temporary non-tunneled CVAD (e.g. Quinton Mahurkars) must remain in hospital until the line is removed.

Complications Associated with Central Venous Catheters

Bleeding Following Insertion
- The bleeding risk associated with insertion of a tunneled central line is variable and depends on coagulative function as well as operator experience and skill.
- To minimize bleeding risk for line insertion, ensure platelets >50 and INR <1.4 prior to line insertion, or as specified by radiologist.
- Avoid high dose heparin.
- Bleeding can be managed with local pressure to site, hemostatic dressing, reversal of anticoagulation (i.e. heparin from line, PT and PTT must be checked), clotting factors if necessary, tranexamic acid.
- Rarely, surgical intervention may be required to repair site.

Abbreviations: INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

Catheter-Related Infections

Catheter-related infections are important causes of morbidity, mortality and health care costs, with an infection rate of approximately 5 per 1000 catheter days in the critical care population. In a meta-analysis of 2573 catheter-related blood infections, case-mortality rate was 14% with 19% of deaths due to catheter-related infection.[1] Mortality was the highest with *Staph. aureus* at 8.2% and lowest with coagulase negative *Staph.* at 0.7%[1].

Skin organisms predominate in the first few weeks as they migrate into the catheter tract and cause tip infections. In long term catheters, hub infections become a more common source. Line infections can also result from hematogenous seeding from other sites.

- Peripheral IV – 0.5/1000 catheter days
- Cuffed Tunneled CVAD – 1.6/1000
- PICC – 2.1/1000
- Temporary non cuffed CVAD – 2.7/1000

Catheters made of Teflon, silicone elastomer, or polyurethane are less likely to cause infection than catheters of polyvinyl chloride or polyethylene[2,3]. Surface irregularities enhance the microbial adherence of some organisms (i.e. coagulase negative *Staph.*, *Acinetobacter calcoaceticus*, *Pseudomonas aeruginosa*). Some catheters are also more thrombogenic, which can contribute to subsequent infections. Host factors can be important; for example *Staph. aureus* adheres to proteins such as fibronectin that are commonly present on catheters and this can make infection difficult to clear. In addition, coagulase negative *Staph.* adheres well to polymer surfaces and can produce an extra cellular polymer "slime" which allows it to withstand host defenses by killing neutrophils and acting as a barrier to antibiotics and phagocytes. *Candida* can also produce slime in presence of glucose-containing fluids, which may contribute to increased fungal infections in people on total parenteral nutrition. The most common organisms cultured from patients with central line infections are as follows[4]:

- Coagulase negative *Staphylococcus* (50%)
- Gram negative organisms (20%)
    - Increasing third generation cephalosporin resistance in E.coli and Klebsiella, increasing imipenem and ceftazidime resistance among pseudomonas aeruginosa
- *Staphylococcus aureus* (30%)
    - Rare MRSA

History Suggesting Catheter-Related Infection:

Components of the patient history supporting the presence of a catheter-related infection include continuous or persistent bacteremia, sepsis after infusing through a line, blood cultures of organisms known to colonize/infect lines, catheter thrombosis, clinical improvement with catheter removal, and the lack of another clinical source of infection. Physical exam findings are unreliable but can include fever, shock or inflammation/purulence at the exit, entrance or tunnel site.

Diagnostic Tests:

If a catheter-related infection is suspected, the following tests should be ordered:

- Gram stain and culture of exudate if present
- Culture of line tip if removed (best if plated at bedside)[5]
    - Positive result when >15 colony-forming units present on tip
- Central and peripheral blood cultures drawn prior to antibiotics (min 10 mL/bottle, yield increases 3% per additional mL blood up to 20 mL)
    - A difference in the time to positivity of ≥120 minutes between centrally- and peripherally-drawn blood cultures is 91% sensitive, and 94% specific for catheter infection[5]
    - Negative predictive value for central line infection when negative culture drawn from central line prior to antibiotics: 99%[6]
    - Cultures of *Staph. aureus*, coagulase negative *Staph.* and *Candida* are most suggestive of central line-related infection

Prevention of CVAD Infections (Adapted from IDSA Guidelines)[2]

- Rigorous attention to hand hygiene and aseptic technique is essential before inserting, removing, or manipulating the CVAD.
- Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before CVAD insertion and during dressing changes.
- Evaluate the catheter site daily by palpation through the dressing for tenderness and by inspection if transparent dressing; if opaque dressing this does not need to be removed.
- Consider removal of CVAD if intraluminal catheter thrombosis cannot be corrected
- Promptly remove CVAD lines that are no longer being used, non-functional or bulging.
- Diligent care and maintenance as outlined in nursing vascular access device infusion therapy Clinical Care Topic (CCT)

Treatment of CVAD Infections

Definite indications for tunneled catheter removal are as follows[7]:

- Complicated infections (septic thrombosis, endocarditis, osteomyelitis, possible metastatic seeding).
- Tunneled catheter pocket infections or port abscess.
- Persistently positive cultures or persistent fever (>72 hours) while on treatment for a known line infection
- Relapse after antibiotics are discontinued.
- Fungal catheter-related blood infection, candida, mycobacteria, *Pseudomonas aeruginosa*, *Staph. Aureus.*

There should be a low threshold for catheter removal with catheter related blood stream infections including *Burkholderia cepacia*, *Actinobacter baumannii*, *Stenotrophomonas* species, *Bacillus* species, and *Corynebacterium* species. For coagulase negative *Staph.* bacteremia, recurrence by 12 weeks was seen in 20% of patients with line salvage versus 3% with line removal; another study found *Staph. aureus* patients were 6.5 times more likely to relapse or die of infection without line removal (studies were done without antibiotic lock therapy)[7,8]. Reinsertion of central lines should be postponed until after serial negative blood cultures are obtained; although not always practical, this is ideally done after negative blood cultures are obtained 5-10 days after completion of antibiotics.

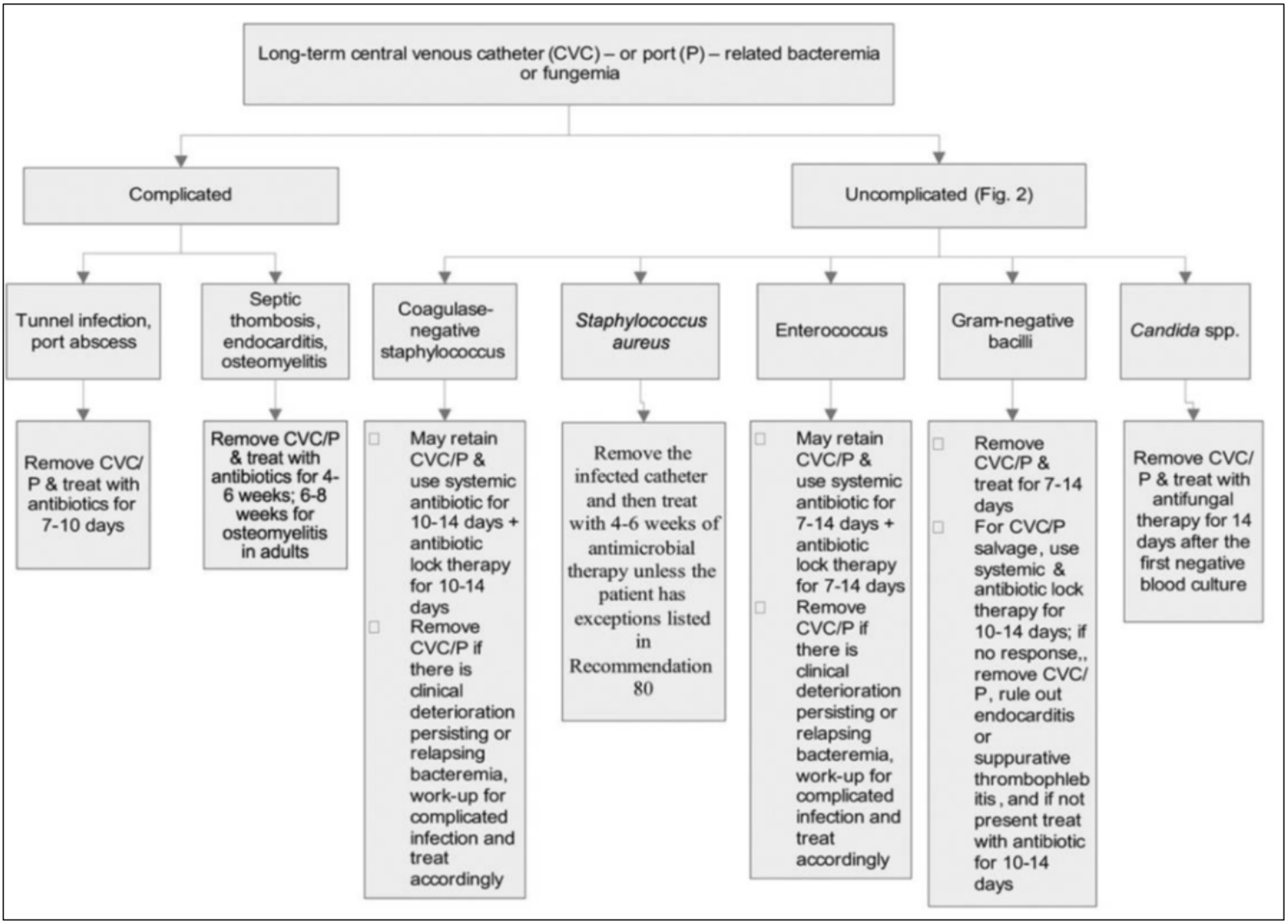
There are limited prospective randomized controlled trials examining the optimal treatment choices and duration of therapy for CVAD infections. Based largely on published guidelines, the following empiric therapy is suggested[7]:

- Vancomycin in hospitals/areas with MRSA; if resistance to vancomycin is seen, daptomycin is the alternative and linezolid is not indicated as empiric therapy for catheter-related bloodstream infection (CRBSI)
    - Covers *Staph. aureus*, coagulase negative *Staph.* and *Enterococci*
- Gram negative bacilli coverage (including *Pseudomonas*) in neutropenic/markedly immunocompromised or severely ill patients
    - Tazocin
    - Alternatives could include meropenem or Third or fourth generation antipseudomonal cephalosporin (i.e., cefepime, ceftazidime)
- Empiric fungal coverage in high risk patients/suspected fungal disease, patients on TPN or with prolonged use of antibiotics, known candida colonization
- Step down antibiotics once organisms/ sensitivities are known
- Avoid use of topical antibiotic ointment or cream at insertion sites

The optimal duration of therapy remains controversial. General guidelines include the following[7]:

- If prompt antibiotic response, treat 10-14 days for pathogens other than coagulase negative *Staph.* (7 days plus antibiotic lock therapy or 10-14 days) if no valvular heart disease or intravascular prosthetic device
- 4-6 weeks antibiotics should be considered if persistent bacteremia or fungemia after catheter removal (>72 hours post catheter removal), endocarditis, septic thrombosis
- 6-8 weeks of therapy for the treatment of osteomyelitis
- For complicated infections, consultation with Infectious Diseases is suggested

Figure 1. Approach to the treatment of a patient with long-term central venous catheter (CVAD) or a port (P)-related bloodstream infection[7].



Antibiotic Lock Therapy

Antibiotic lock therapy, with pharmacologic doses of antibiotics instilled into the lumen of a line daily for hours, could be considered in uncomplicated tunneled CVAD infections (i.e., no tunnel infection or abscess) with *Staph. aureus*, coagulase negative *Staph*., and gram negative bacilli. This method is not effective in fungemia, and responses with coagulase negative *Staph*. have been better than with *Staph. aureus* and *Pseudomonas*. When data from four trials were pooled, antibiotic lock therapy plus IV antibiotics were associated with clearance of an organism in 138/167 (82%) of catheter infections compared to pooled data from 14 trials showing clearance of 342/514 (66.5%) with IV antibiotics alone (response rate (RR) of catheter salvage 1.24)[9].

Two weeks of antibiotic lock therapy can be considered in CVAD infections with coagulase negative *Staph.* and gram negative bacilli and in uncommon situations with *Staph. aureus* where line removal is not feasible.

- Ethanol locks have also been associated with decreased primary catheter related bloodstream infections. WARNING: Alcohol should not be used to soak or declot polyurethane catheters because alcohol is known to degrade polyurethane catheters over time with repeated and prolonged exposure. (e.g. Trifusion™ catheter).

Specific Management Challenges

Staphylococcus aureus:

- *Staph. aureus* bacteremia is associated with a high risk of metastatic infections and provides a management challenge (25% - 32% occult endocarditis in patient with staph aureus bacteremia), hematogenous complications in 25-30%.
- Beta-lactam drugs (cloxacillin or cefazolin) are preferred therapy if the *Staph. aureus* is sensitive.
- If the bacteremia is not cleared by 72 hours after antibiotics, long-term therapy is required (minimum 4 weeks).[5]
- Non-tunneled catheters should be removed.
- Tunneled catheters should be removed and must be removed in the presence of abscess or tunnel site infection.
- Search for metastatic infection is indicated, starting with a TTE (transthoracic echocardiography) if there are no contraindications, and clinical monitoring for osteomyelitis, septic arthritis, and other sites of infection.
- ID consultation will likely be needed.

Enterococcus:

- Ampicillin is treatment of choice +/- gentamicin; vancomycin in cases of ampicillin resistance.
- Daptomycin in cases of VRE (vancomycin-resistant *Enterococcus)* based on susceptibility.
- Line removal is preferred. Lines should be removed in the case of vancomycin resistant species.

Fungal infections:

- If there is documented catheter-related fungal infection, the CVAD should be removed.[7,10]
- Antifungal therapy should continue until 14 days after last positive blood cultures and signs/symptoms resolved.

Septic thrombophlebitis:

- The most common organisms implicated in septic thrombophlebitis are *Staph. aureus*, *Candida* species and gram negative bacilli; the presence of thrombus greatly increases the risk of CVAD-related infections.
- In the presence of septic thrombophlebitis, the catheter should be removed.

- Surgical consultation is indicated in the case of suppurative thrombophlebitis, infection persists on antibiotics or there is pseudo aneurysm formation.
- Routine anticoagulation of patients with septic thrombophlebitis is not recommended. It can be considered for selected patients, such as those who are highly symptomatic of their thrombosis.
- Thrombolysis is not indicated. Infectious disease consultation is suggested.

Catheter-Related Thrombosis or Mechanical Occlusion

Line Occlusion

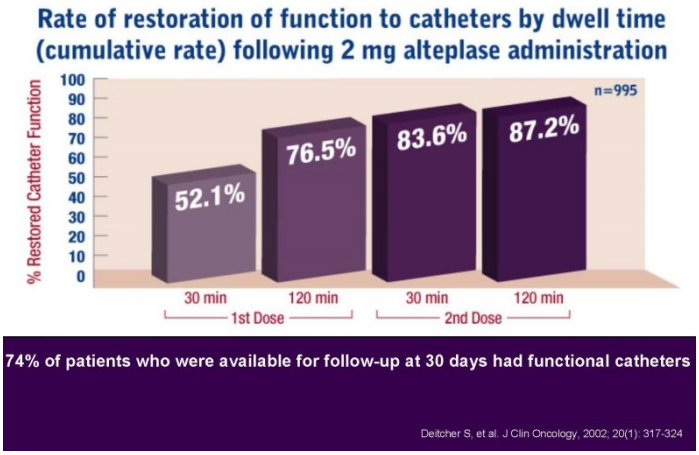
Prevention of Line Occlusion

- Diligent care and maintenance as outlined in nursing vascular access device infusion therapy Clinical Care Topic (CCT)
- CVADs are typically flushed/locked with 0.9% sodium chloride.
    - **Exception**: CVADs inserted for the purpose of apheresis are locked with 4% sodium citrate for the lifetime of the catheter.
- 0.9% sodium chloride flush/locks are standardly used over other locking agents as there is insufficient evidence to recommend one lock solution over the other [16].
- CVADs inserted with the purpose of apheresis are locked with 4% sodium citrate instead of heparin due to the higher risk of HIT[17]

Thrombotic occlusions:

- Occluded CVADs should be treated with r-tPA.
- Unless mechanical occlusion is suspected radiographic imaging is not necessary prior to tPA instillation.
- 2 mg alteplase (Cathflo) is reconstituted with 2.2mL sterile water by a certified RN. As much as possible up to 2mg is instilled into the blocked CVAD lumen and as per nursing procedure.
- Place r-tPA into lumen for 2-24 hours then aspirate. R-tPA can be aspirated after 30 minutes if line access is urgent.
- Can be repeated x1 if unsuccessful; tPA can be left in situ overnight.

Figure 2. Rate of restoration of function to catheters by dwell time (cumulative rate) following 2 mg alteplase administration. Note: subjects with occluded, no dialysis CVADs were enrolled, not specifically neutropenic patients.



Mechanical occlusions:

- If line patency is not restored, consider consulting interventional radiology (line stripping, TPA drip in IR). If this is unsuccessful the line is to be removed as soon as safe to do so.

Catheter-Related Venous Thrombosis

The incidence of symptomatic catheter-related deep vein thrombosis (DVT) in patients with malignancies is approximately 3-4%, although ultrasound surveillance documents clots in about 12% of patients[11]. A small series in bone marrow transplant patients showed an incidence as high as 50% although the majority were asymptomatic[12]. Risk factors include malplacement of the catheter, >1 insertion attempt, a previous CVAD, placement of the catheter on the left-hand side and malignancy.

Symptoms that suggest an upper extremity DVT include erythema and swelling (which may be exercise-dependent or gravity-dependent), and pain or tenderness at the base of the neck, superclavicular fossa, arm or shoulder. Collateral blood flow often develops and vessels may be visible. Embolization is the major cause of morbidity and mortality, and pulmonary embolism (PE) occurs in up to 20% of patients with symptomatic thrombosis. The following tests may confirm the diagnosis:

- Ultrasound or venogram of extremity
- If symptoms of respiratory compromise/pulmonary embolism, workup requires a PE protocol CT scan or V:Q scan; rarely pulmonary angiogram is indicated

Prophylaxis of CVAD-related Thrombosis and Deep Venous Thrombosis

- DVT prophylaxis should be carried out as per established guidelines for the medical patient in the absence of significant bleeding, coagulopathy or thrombocytopenia (platelets < 50)[12]. Options for

thromboprophylaxis include low-dose unfractionated heparin, low molecular weight heparin or mechanical prophylaxis.
- Mobilization should be encouraged
- Use of anticoagulation for routine prophylaxis of catheter-related thrombosis is not recommended[13-15].

Treatment of CVAD-related Thrombosis and Deep Venous Thrombosis
- Anticoagulation should be continued for the duration of line placement if removal is not feasible.
- Anticoagulation duration is controversial and catheter-related thrombosis should be treated as per established guidelines for provoked DVT[12,15,19,20].
    - Catheter-related thrombosis should be treated as a provoked thrombosis and treated with anticoagulation for a total of 3 months.
    - Patients whose lines have been removed and who experience bleeding complications while on anticoagulation may be taken off of anticoagulation before completing 3 months of treatment provided symptoms of catheter-related thrombosis have resolved. They should be reimaged in 10-14 days to exclude propagation of venous thrombus if anticoagulation is discontinued early.
    - Patients with active malignancy should receive anticoagulation.
    - Tinzaparin 175 IU/kg once daily or DOAC may provide easier and more reliable anticoagulation compared with warfarin in patients taking multiple interacting medications, antibiotics and/or with unpredictable dietary intake. Caution should be exercised when using low molecular weight heparins in individuals with impaired renal function.
    - Awareness of drug interactions with DOAC's.

Catheter Care

- Patients shall be educated about their own catheter care in preparation for outpatient therapy.
- Written instructions for catheter care shall be given to patients prior to discharge (e.g. Adult Cellular Therapy: Important Information When Leaving the Hospital)
    - Include CVAD Emergency Kit (gauze, large transparent dressing (Tegaderm), plastic clamp, needleless connector, alcohol swabs, chlorhexidine sticks)

Catheter Removal

- With all central line removals, informed consent shall be obtained, and sterile technique maintained.
- Central line removals should be done in the supine position during exhalation to minimize air embolus risk.
- All patients shall have their central lines removed once they are no longer using it regularly.
- All patients shall have central lines removed if they are eating/drinking well and not requiring transfusions or IV medications.

- A new line should be inserted if it is needed (i.e. second transplant).
- Prior to line removal, platelets should ideally be >50 and INR <1.4. Send catheter for review if mechanical issue/infection potential suspected during line removal.
- If accidental CVAD removal (falls out, pulled out) pressure and dressing shall be immediately applied, ongoing assessment of patient and vital signs for signs and symptoms of air embolism or other complications. Inspect catheter to ensure it is intact.

References

1. Byers K, Adal, K, Anglim, A. Case fatality rate for catheter-related bloodstream infections (CRSBI): a meta-analysis. Proceedings of the 5th annual meeting of the Society for Hospital Epidemiology of America 1995:Abstract 43.
2. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 2011 May;39(4 Suppl 1): S1-34.
3. Sheth NK, Franson TR, Rose HD, Buckmire FL, Cooper JA, Sohnle PG. Colonization of bacteria on polyvinyl chloride and Teflon intravascular catheters in hospitalized patients. J Clin Microbiol 1983 Nov;18(5):1061-3.
4. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004 Oct;39(3):309-17.
5. Hnatiuk OW, Pike J, Stoltzfus D, Lane W. Value of bedside plating of semiquantitative cultures for diagnosis of central venous catheter-related infections in ICU patients. Chest 1993 Mar;103(3):896-9.
6. DesJardin JA, Falagas ME, Ruthazer R, Griffith J, Wawrose D, Schenkein D, et al. Clinical utility of blood cultures drawn from indwelling central venous catheters in hospitalized patients with cancer. Ann Intern Med 1999 Nov; 131(9):641-7.
7. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009 Jul;49(1):1-45.
8. Raad I, Davis S, Khan A, Tarrand J, Elting L, Bodey GP. Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. Infect Control Hosp Epidemiol 1992 Apr;13(4):215-21.
9. Mermel LA, Farr BM, Sherertz RJ, Raad, II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001 May;32(9):1249-72.
10. Rex JH, Bennett JE, Sugar AM, Pappas PG, Serody J, Edwards JE, et al. Intravascular catheter exchange and duration of candidemia. NIAID Mycoses Study Group and the Candidemia Study Group. Clin Infect Dis 1995 Oct;21(4):994-6.
11. Luciani A, Clement O, Halimi P, Goudot D, Portier F, Bassot V, et al. Catheter-related upper extremity deep venous thrombosis in cancer patients: a prospective study based on Doppler US. Radiology 2001 Sep;220(3):655-60.
12. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):338S-400S.
13. Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol 2006 Feb;17(2):289-96.
14. Heaton DC, Han DY, Inder A. Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. Intern Med J 2002 Mar;32(3):84-8.
15. Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ, American College of Chest Physicians. Antithrombotic and thrombolytic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):110S-112S.
16. Infusion Nursing Society. Infusion Therapy Standards of Practice. USA: Infusion Nursing Society; 2024.
17. Mermel, L. A., & Alang, N. (2014). Adverse effects associated with ethanol catheter lock solutions: a systematic review. Journal of Antimicrobial Chemotherapy, 69(10), 2611–2619.
18. Mian H, Warkentin TE, Sheppard JAI, et al. Autoimmune HIT due to apheresis catheter heparin flushes for stem cell harvesting before autotransplantation for myeloma. Blood. 2017;130(14):1679-1682. doi:10.1182/blood-2017-06-788679

19. Ponec D, Irwin D, Haire WD, Hill PA, Li X, McCluskey ER; COOL Investigators. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: a double-blind placebo-controlled trial--the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) efficacy trial. J Vasc Interv Radiol. 2001 Aug;12(8):951-5.
20. Schiffer CA, Mangu PB, Wade JC, Camp-Sorrell D, Cope DG, El-Rayes BF, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013 Apr 1;31(10):1357-70.

Additional Resources

- ABMTP Foothills Medical Centre. (2023). *Adult Cellular Therapy: Important Information When leaving the Hospital [Brochure]*
- Bard Access Systems. (2007). Instructions for Use: Hickman TriFusion Catheter. Copyright 2007
- Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, et al. Prevention of dialysis catheter lumen occlusion with rt-PA versus heparin Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med. 2011 Jan 27;364(4):303-12.
- Infection Prevention and Control. Calgary Health Region, June 26, 2008 memorandum. Infection Prevention and Control Standards for Skin Antisepsis Prior to Percutaneous Invasive Procedures Performed Outside of the Operating Room – memo.
- Szycher, M. Comparative Chemical Resistance of Polyurethanes: A Critical Review [White paper].

Hepatic Complications and Viral Hepatitis

Presented by: Mona Shafey

Summary

- Established cirrhosis is associated with high risk of severe veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), multiorgan failure, and death in recipients of HDCT/BCT. Myeloablative stem cell transplantation will not be offered to this group of patients. Potential options for reduced intensity conditioning may be explored.

Viral Hepatitis

- All recipients and donors will be screened for hepatitis B and C, with further viral load/nucleic acid testing (NAT) required for those with a positive screening test.
- Hepatology referral for assessment and peri-transplant management is required for patients with chronic active hepatitis B or positive hepatitis C serology, and donors who are HBV NAT positive.
- Recipients with past hepatitis B infection (surface antigen negative, core antibody positive) should receive prophylactic antiviral therapy and undergo regular viral load testing as directed by Hepatology
- Use of mycophenolate mofetil (MMF) has been linked to developing fibrosing cholestatic hepatitis and should not be used in HCV-infected patients.
- Long-term risks of developing cirrhosis and HCC appear to be similar to non-HSCT population with HBV.
- HCV infection in HSCT population is associated with increased risk of morbidity (e.g. early cirrhosis, GVHD, VOD/SOS) and mortality (e.g. fatal VOD/SOS, excess bacterial infection, fibrosing hepatitis) compared to non-HSCT population.

Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS)

- Patients with risk factors for VOD/SOS development should have a fibroscan as part of pre-transplant investigations to assess for baseline liver fibrosis/dysfunction.
- Ursodiol 15-20 mg/kg/day will be given for the first 80 days post-transplant for prophylaxis of VOD/SOS in allogeneic HCT recipients, regardless of conditioning used for transplant
- Serial doppler ultrasounds post transplant can be considered in patients with risk factors for VOD/SOS or for those with established mild VOD/SOS to monitor for progression
- VOD/SOS should be suspected clinically in the patient with weight gain, hyperbilirubinemia, hepatomegaly, +/- ascites early post transplant. The diagnosis should be confirmed by ultrasound, liver biopsy or measurement of hepatic vein wedge pressure gradient if possible.
- Standard treatment of VOD/SOS is supportive, with careful attention to fluid balance and renal perfusion and elimination of hepatotoxic medications. Defibrotide 25 mg/kg/day should be considered for patients with severe or very severe VOD/SOS, and considered pre-emptively in patients with moderate VOD/SOS

Background

Prior to universal screening of blood products, viral hepatitis was very common among BMT recipients. In one Italian program, Locasciulli *et al.* reported that 30 of 145 (21%) consecutive BMT recipients were positive for HBsAg.[1] A high risk of hepatitis C from unscreened blood products has also been reported by Strasser *et al.*, with a risk of hepatitis C of 17% prior to transplant and 32% by day 100.[2] Universal screening of blood products in recent years has reduced the risk of hepatitis B transmission to 1 in 1.7 million and the risk of hepatitis C transmission to 1 in 13 million per screened unit. Currently, the majority of viral hepatitis in BMT recipients is likely acquired from other sources.

Hepatitis C

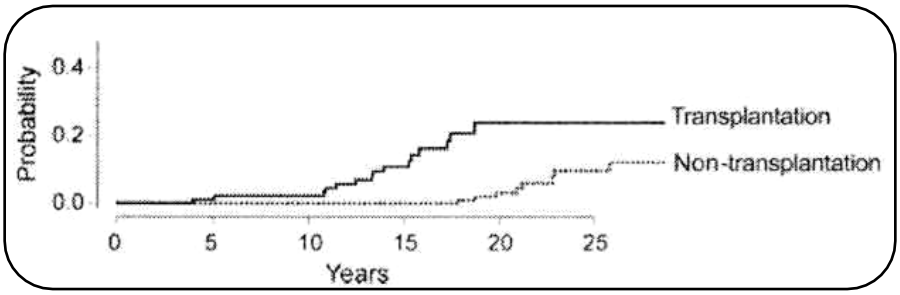
The hepatitis C virus is a single-stranded RNA virus. Transmission is most effective by direct blood-to-blood inoculation. The incubation period is 6 – 12 weeks, followed by a generally mild, self-limiting hepatitis. 85% develop chronic infection, and of these 20% will develop cirrhosis and 5% will die of liver failure or hepatocellular carcinoma (HCC).

The course of hepatitis C after BMT appears to be generally mild. While some reports suggest an increased rate of severe veno-occlusive disease (VOD) in BMT recipients who are positive for the hepatitis C virus (HCV), most suggest that the risk is not substantially higher than in HCV-negative recipients. Strasser *et al.* reported the results of BMT in patients who were HCV-positive at the time of transplant, and they found the risk of severe VOD in HCV-positive patients was 48%, compared with 14% in HCV-negative control patients.[2] The risk of VOD was only increased in this report if patients had elevations of ALT at the time of BMT. Most other reports suggest that the rate of VOD in patients with HCV is approximately 8%, roughly that seen in HCV-negative recipients.[3] Over the long term, patients with hepatitis C do show features of mild, chronic hepatitis after BMT. AST levels are generally higher for 5 to 10 years, although the risk of fulminant hepatic failure (FHF) is not increased. There does not appear to be excessive mortality in long-term (> 3 years) survivors who are HCV+.

Patients with hepatitis C who undergo BMT do appear to be at higher risk of developing cirrhosis than similar patients who do not undergo BMT. As shown in the figure below, in one series measuring time to progression to cirrhosis (from time of infection with HCV), the median time to cirrhosis was 18 years in BMT recipients versus 40 years in non-transplant patients.[4] The cumulative incidence of cirrhosis in transplanted patients was 24% at 20 years.

A recent European prospective trial of 195 patients who had undergone stem cell transplant (134 allogenic, 61 autologous hematopoietic HCT) demonstrated an overall survival probability of 82% and 6.1% death rate due to liver disease. The rate of decompensated liver disease and death was 12% at 20 years post transplant. HCV infection was associated with increased risk of morbidity and mortality while treatment was associated with improved outcomes.[5]

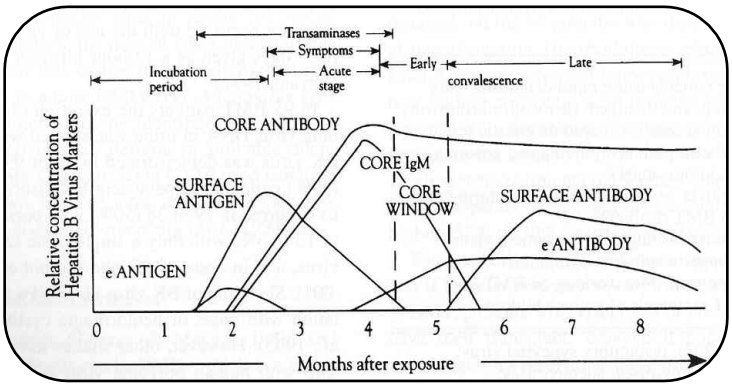
Figure 1. Cumulative Incidence of Cirrhosis Reported by Peffault de Latour *et al*.[4]



Hepatitis B

Worldwide, over 350 million people are hepatitis B virus (HBV) carriers. In general, hepatitis B runs a more aggressive course than hepatitis C. Risk of cirrhosis in patients with hepatitis B is between 12 and 23%, and the risk of decompensation or HCC is between 6 and 15%. As shown in the figure below, Hepatitis B proceeds in a two-stage process: first infection/replication, then immune reaction. It is the immune reaction that is responsible for many of the clinical features of acute infection.

Figure 2. Hepatitis B and BMT



Hepatitis B does not appear to increase the incidence of VOD after transplant. VOD is reported to occur in approximately 8% HBV-exposed recipients. The incidence of serious liver disease is increased in HBV carriers after BMT. Chen *et al.* reported that 81% of hepatitis B carriers developed impaired liver function after a median follow-up of 68 months from alloBMT.[6] In addition, 12% developed FHF (median day+170) post BMT. The risk of chronic hepatitis (19.5% versus 0.3%, p<.001) and cirrhosis (9.8% versus 0%, p<.001) are also higher in these patients.[7] The risk of cirrhosis is comparable with untransplanted patients with HBV. Sustained clearance has been reported in HBsAg+ recipients receiving transplants from donors with natural immunity to HBV.[7,8]

Table 1. Hepatitis B Serology and BMT (adapted from Strasser *et al.*)[9]

Patient Result	Donor Result	Interpretation
Anti-HBs	Anti-HBs	Exposed or vaccinated
Anti-HBc		Exposed. Risk of reactivation present if anti-HBs negative
	Anti-HBc	Exposed. Negligible risk of transmission if HBV DNA negative
HBsAg positive		Active infection: Liver biopsy and start treatment if HBV DNA+
	HBsAg positive	Assess donor for liver disease. Consider different donor or antiviral treatment pre-harvest. Monitor recipient HBV DNA post.

Treatment of Viral Hepatitis

Treatment of chronic viral hepatitis has improved significantly over the past decade. Newer antiviral agents, as well as novel preparations of old agents, have significantly improved the management of these diseases. Management of patients with chronic active hepatitis is best done under the guidance of an experienced Hepatologist.

Lamivudine, a nucleoside analogue antiviral medication originally described as treatment for HIV infection, has shown considerable activity in hepatitis B. Lai *et al.* reported that among non-transplant patients, treatment with lamivudine was associated with normalization of ALT in 72% and a 98% reduction in HBV DNA after 1 year.[10] In the non BMT population, lamivudine is not favoured given its high rate of resistance approaching 70% at 4 years. Higher success rates of viral clearance are seen with the use of tenofovir or entecavir with DNA levels dropping by 6-7 log after 1 year of treatment.[11]

In BMT, lamivudine has been reportedly used in three Japanese autologous peripheral blood stem cell transplant recipients.[12] No effects on engraftment or stem cell collection were noted and HBV DNA remained negative. Lamivudine has also been reported in combination with recipient vaccination in 29 recipients of HBsAg+ marrow (comparison group of 25 historical controls). Rates of HBV hepatitis (48% versus 6.9%, p=.002) and HBV FHF (24% versus 0%, p=.01) were substantially reduced by treatment with lamivudine. The role of passive immunization with hepatitis B immunoglobulin is unclear, but this strategy is not likely to result in sustained benefit.

Newer antiviral agents of use in hepatitis B include tenofovir and entecavir. These agents rapidly suppress viral replication and so result in rapid suppression of the hepatitis B viral load. There is limited data on the use of these newer agents in patients undergoing stem cell transplantation although small case series have demonstrated good outcomes.[13,14]

The interferons are a group of cytokines that exhibit a broad range of antiviral and immunomodulatory activities. Pegylated interferon, in combination with ribavirin, results in sustained clearance of hepatitis C and serum ALT responses in 50-75% of immunocompetent patients depending on the genotype.

Because of concern over the use of immunomodulatory and myelosuppressive agents in the BMT population, there are relatively few reports of interferon therapy for hepatitis C in BMT recipients. One case series, reporting results in 11 patients with thalassemia who underwent BMT, suggests that this treatment is safe and of similar efficacy compared with non-BMT patients (negative HCV viral DNA in 5/11) after 6 to 12 months of treatment.[15] Treatment was delayed 2 to 5 years after BMT to allow for reestablishment of marrow reserve. Treatment of 4 HCV-positive allogeneic BMT recipients with single-agent ribavirin has also been described by Ljungman *et al.*[16] In this series, 1 patient died early while 2 showed clearance of HCV DNA. There were no adverse effects attributable to ribavirin in this small report.

Over the past 5 years, treatment of chronic HCV infection in patients with hematologic malignancies has evolved rapidly as safe and effective direct-acting antivirals (DAAs) have become the standard-of-care treatment. The American Society of Blood and Marrow Transplantation (ASBMT) recommends a complete course of therapy with DAAs prior to transplantation, if clinically feasible[17]. If DAA treatment cannot be completed until after HSCT, DAA therapy can be deferred until after immune reconstitution except in patients who develop fibrosing cholestatic hepatitis C and cases of severe HCV reactivation post transplant. Due to drug-drug interactions (e.g., calcineurin inhibitors), deferring until 6 months after HSCT to start DAA therapy may be considered. Preliminary data show that DAAs are safe and effective, with sustained virologic response (SVR) rate of 85% in HCV-infected HSCT recipients[18]. In this study, patients who received antiviral treatment (AVT) had fewer relapses of HCV-associated non-Hodgkin lymphoma (20% vs. 86%, p=0.015), higher 5-year survival rate (75% vs. 39%, p=0.02, and a trend toward lower rate of progression to cirrhosis (5% vs. 21%, p=0.06). AVT discontinuation post-HCT was 71% in those receiving interferon-containing regimens and 0% in those receiving DAAs (p<0.01). AVT was effective in 12/37 (32%) and 11/13 (85%) of patients receiving interferon based and DAA regimens, respectively (p=0.003). The timing and choice of DAA regimen needs to be individualized, taking into account urgency of transplant, treatment-limiting co-morbidities, HCV genotype and degree of liver disease, and potential for hematologic toxic effects and drug-drug interactions. The website http://www.hcvguidelines.org provides continuously updated guidelines for DAA treatment of patients with HCV infection.

In both the liver transplant and HCT settings, use of mycophenolate mofetil has been linked to development of fibrosing cholestatic hepatitis C, thus this drug should not be used in HCV-infected patients[19].

Veno-Occlusive Disease/ Sinusoidal Obstruction Syndrome (VOD/SOS)

Hepatic veno-occlusive disease (VOD), increasingly referred to as sinusoidal obstruction syndrome (SOS), is a well-recognized complication of all stem cell transplantations, irrespective of the stem cell source, type of conditioning therapy, or underlying disease. Although the incidence has decreased in recent years, it is still between 5 and 15% for myeloablative transplants and up to 5% after RIC alloHCT. The table below describes the patient, disease, and transplant factors associated with SOS.

Table 2. Patient, disease, and transplant factors associated with SOS

Patient Factors	Disease Factors	Transplant Factors
Prior liver disease	Advanced disease	Ablative conditioning
Active hepatitis	Malignant disease	Non T-cell depleted transplant
Age ≥ 20 years	Prior SCT	High dose TBI
Prior fungal infection	Abdominal radiation	Oral or High Busulfan AUC
Hepatitis C infection	Prior hepatotoxic chemotherapy	Unrelated or mismatched donor
Iron overload	Gemtuzumab or inotuzumab ozogamicin	Sirolimus GVHD prophylaxis
HFE C282Y genotype		Norethistrone use
Steatohepatitis		

It is recommended that patients who have risk factors for SOS, particularly those with history of liver disease, iron overload, hepatitis (viral or steato-) or past hepatotoxic therapy, undergo a fibroscan to assess baseline fibrosis/cirrhosis risk, and consider hepatology referral if abnormal.

Prior to assuming SOS however, it is important to consider and rule out: congestive heart failure, fungal or viral liver infections, sepsis- or drug-induced cholestasis, and tumour infiltration of the liver.

The diagnosis of SOS has traditionally used either the Seattle Criteria[20] or the Baltimore Criteria[21] (see Appendix 1). The Baltimore criteria is more specific and less discrepant when corroborated with histopathology and hemodynamic studies, particularly for classic VOD/SOS (onset <21 days). Late onset VOD/SOS does not require hyperbilirubinemia and should be considered when at least two other clinical manifestations are present along with hemodynamic and/or ultrasound evidence of VOD/SOS is confirmed. In an effort to improve early diagnosis and promote early intervention, the European Group for Blood and Marrow Transplantation (EBMT) have revised these diagnostic criteria for adults[24] (Table 3).

Table 3. EBMT criteria for VOD/SOS diagnosis in adults[22]

Classical VOD/SOS	Late-onset VOD/SOS (>21 days after HSCT)
In the first 21 days after HSCT, hyperbilirubinemia (>34 umol/L) AND 2 of the following • Painful hepatomegaly • Weight gain> 5% • Ascites	(a) Classical VOD/SOS beyond day 21 (b) Histologically proven VOD/SOS (c) Two or more of the following PLUS hemodynamic and/or ultrasound evidence of VOD/SOS • Painful hepatomegaly • Weight gain >5% • Ascites

The Cairo/Cooke revised diagnostic criteria[23] for VOD/SOS in children and adults has also been proposed that is not dependent on timing post HSCT and can be diagnosed with (a) Any two of the following – elevated bilirubin (>34 umol/L), unexpected weight gain >5%, excessive platelet transfusions consistent with refractory thrombocytopenia post HSCT, hepatomegaly for age or increased size over pre-HSCT, RUQ pain, ascites confirmed by exam or imaging studies, reversal of portal venous flow by doppler ultrasound, OR (b) hepatic biopsy consistent with VOD/SOS, OR (c) unexplained elevated portal venous wedge pressure. The primary goal of these proposed criteria was to incorporate more signs and increase awareness for earlier detection and more rapid institution of therapy in hopes of improving survival.

Neither the EBMT criteria nor the Cairo/Cooke criteria have been prospectively validated in clinical trials.

Ultrasound features associated with SOS include: increased GB thickness, elevated hepatic artery resistive index (SV-DV/SV), decreased portal flow, and ascites. However, ultrasound results generally have low sensitivity and specificity. Ascites generally shows a high serum-albumin ascites gradient (>11.1 gm/l). Serial doppler ultrasounds post-transplant can be considered in patients with risk factors for VOD/SOS or for those with established mild VOD/SOS to monitor for progression.

The use of transvenous liver biopsy has been shown to confirm diagnosis or reveal an alternate diagnosis in the majority of cases of early posttransplant liver disease. Shulman *et al.* reviewed 60 BMT patients with liver dysfunction who underwent transvenous liver biopsy and measurement of the hepatic venous pressure gradient[24].The wedged hepatic venous pressure gradient ≥ 10 mmHg correlated with a histologic diagnosis of SOS (p =0.001), and this gradient value provided 91% specificity and 86% positive predictive value. Bleeding complications were reported in 11 cases, and there were 3 procedure-related deaths.

In order to promote earlier therapeutic intervention, the EBMT also proposed criteria for severity of grading of VOD/SOS once the diagnosis was made[22] (Table 4). Four stages of severity (mild, moderate, severe, and very severe) are based on five parameters: time since first clinical manifestation of VOD/SOS, bilirubin level and kinetics, transaminase level, weight gain, and renal

function. Importantly, in the presence of two or more risk factors, patients are classified in the upper grade. These criteria were validated in a study of 203 patients with VOD/SOS[25]: 5.9% were mild, 12.8% moderate, 18.2% severe, and 63.1% very severe; the day 100 OS of these groups were 83.3%, 84.3%, 94.6%, and 58.6%, respectively. The day 100 TRM was significantly higher in very severe VOD/SOS at 36.7%, compared to 8.3% in mild, 8.0% in moderate, and 2.7% in severe ($p<0.0001$)[25].

Table 4. EBMT criteria for severity grading of suspected SOS/VOD in adults[24]

	Mild*	Moderate*	Severe	Very Severe (multi-organ dysfunction/failure)
Time since first clinical symptoms of SOS/VOD	>7 days	5-7 days	≤4 days	Any time
Bilirubin (umol/L)	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics			Doubling within 48h	
Transaminases	≤2x normal	>2 and ≤5x normal	>5 and ≤8x normal	>8x normal
Weight Increase	<5%	≥5% and <10%	≥5% and <10%	≥10%
Renal function	<1.2x baseline at transplant	≥1.2 and <1.5x baseline at transplant	≥1.5 and <2x baseline at transplant	≥2 baseline at transplant, or other signs of MOD/MOF

Patients belong to the category that fulfills two or more criteria, classified into the most severe category if criteria achieved in more than one category
*Patients with two or more *risk factors* for SOS/VOD (Table 2) are classified in the upper grade

Treatment of VOD/SOS

Defibrotide (DF) is the only agent with proven efficacy for the treatment of severe/very severe VOD/SOS. Defibrotide is a single-stranded polydeoxyribonucleotide that has anti-inflammatory and antithrombotic properties. Richardson *et al.* reported on the use of defibrotide in 88 patients who developed severe SOS and multisystem organ failure after stem cell transplantation[26]. The patients ranged in age from 8 to 62 years (mean 35 years) and were assessed according to the Baltimore Criteria. Defibrotide was administered IV in doses ranging from 5 to 60 mg/kg per day for a median of 15 days. Complete resolution of SOS was reported in 32 patients (36%), with 35% survival at day +100. There was no worsening of clinical bleeding or attributable grade III or IV toxicity noted in the patients. Grade I/II toxicities included hypotension, fever, abdominal cramping, and hot 75 patients on 40 mg/kg/day of defibrotide. The 141 evaluable patients ranged in age from 0.5 to 63 years (mean 36 years), and 99% of patients were in multisystem organ failure. Complete resolution of SOS was reported in 65 patients (46%), with an overall survival rate of 42% at day +100. There was no difference in response rates between the 2 doses, but the higher dose was associated with more grade III and IV toxicities, as well as a greater risk of bleeding. Early stabilization or lower bilirubin was associated with better outcome[28]. The final results from a defibrotide treatment-IND study for 1000 patients with hepatic VOD/SOS demonstrated Day +100 survival was 58.9% overall; 67.9% in pediatric patients and 47.1% in adult patients, and higher in the subgroup of patients without multi-

organ dysfunction (MOD)[28]. Similarly, a systematic review of 17 defibrotide studies in the treatment of VOD/SOS demonstrated that among those treated with 25 mg/kg/day dosing the Day+100 survival rate was 56%, higher in patients without MOD at 71% vs. 44% with MOD[29].

Given the mortality associated with severe and very severe VOD/SOS, it is mandatory to treat these patients promptly, with initiation of DF as soon as possible. Standard dosing for defibrotide is 25 mg/kg/day with recommended duration of at least 21 days and until resolution of all VOD/SOS symptoms. No dose adjustments are required with renal failure, while in obese patients corrected body weight should be used for dose calculation. In patients where such resolution happens before 21 days, it is possible to stop DF earlier (e.g. to facilitate patient discharge) with close monitoring for the rare possibility of recurrence.

The indication of DF treatment in patients with mild or moderate VOD/SOS is more questionable. In expanded/compassionate access treatment protocols, an earlier treatment initiation after VOD/SOS diagnosis was associated with higher day +100 OS ($p<0.001$)[30]. Up to 32% mortality was seen despite treatment, which while favorable compared to severe/very severe VOD/SOS, it remains significant. The EBMT recommends that patients who fulfill the diagnosis criteria and whose severity grading is moderate should be considered for preemptive DF and closely followed. In patients with mild VOD/SOS, supportive care should be intensified, and severity criteria monitoring should be strictly applied to allow immediate DF initiation in case of deterioration.

Supportive Care Measures

- Careful management of fluid and sodium balance to limit third-space fluid and maintain renal perfusion.
- Limit hepatotoxic medications; wherever possible, antifungal azoles should be substituted for echniochandins
- Transjugular intrahepatic portosystemic shunt (TIPS) may improve fluid balance and symptom control with no benefit on survival.
- While on DF, discontinue any other agents that may increase risk of bleeding.
- Nutritional support is also important, and enteral nutrition should be favored to prevent patient's malnutrition; parental nutrition is associated with fluid overload, infectious complications, and hepatotoxicity and should be avoided.

Preventative Therapy

Results of a randomized controlled trial of ursodiol for SOS prophylaxis were reported by Essell *et al*.[31] The patients were 67 consecutive recipients of allogeneic BMT, and they all received a busulfan plus cyclophosphamide conditioning regimen. Patients were randomly assigned to receive ursodiol, 300 mg twice daily (or 300 mg in the morning and 600 mg in the evening if body weight was > 90 kg), or placebo until day +80. The incidence of SOS was 40% (13 of 32 patients) in placebo recipients and 15% (5 of 34 patients) in ursodiol recipients ($p = .03$). The authors concluded that ursodiol prophylaxis

seemed to decrease the incidence of hepatic complications after allogeneic BMT. A larger randomized controlled trial involving 242 patients reported no significant impact of ursodiol on the incidence of SOS but did report significantly lower incidences of grades III and IV acute GVHD, stage II and IV liver and intestinal GVHD, and stage III and IV skin GVHD[32]. In addition, among the patients given ursodiol, the survival at 1 year was significantly better, (71% versus 55%, p=.02), and the non-relapse mortality rate was lower (19% versus 34%, p=.01), when compared to the control group. In a long-term (10 year) follow-up of this study, the difference in survival and NRM in favor of the ursodiol-treated group was maintained[33]. A systematic review of three RCTs, including the two mentioned above, of ursodiol as compared to placebo demonstrated a reduced risk of SOS on ursodiol; RR 0.34, 95% CI 0.17-0.66 although no significant difference in survival[34]. It is recommended that all patients undergoing allogeneic SCT, regardless of conditioning used, to proceed with ursodiol prophylaxis.

Potentially there may be a role for defibrotide as prophylaxis for SOS; a systematic review of 1230 patients from one RCT, 4 cohort studies and 8 case series studies showed an incidence of about 5% with defibrotide versus controls (14%) with a relative risk of 0.46 (95% CI 0.31-0.73)[35]. British guidelines suggest giving defibrotide at 6.25 mg/kg IV q.i.d. for prophylaxis in adults undergoing allogenic stem cell transplant with a history of pre-existing liver disease, second myeloablative transplant, allogenic transplant for leukemia beyond second relapse, conditioning with busulfan-based regimens, past treatment with gemtuzumab or inotuzumab ozogamicin, diagnosis of primary hemophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis[36]. However, defibrotide did not show a benefit in the prophylaxis of SOS in a randomized phase 3 trial in pediatric and adult patients (n=372) undergoing allo or auto SCT[37]. Given that current studies in this area are limited, as well as the considerable cost and lack of access of defibrotide, further research is needed and routine use of defibrotide is not routinely recommended.

References

1. Locasciulli A, Bacigalupo A, Van Lint MT, Chemello L, Pontisso P, Occhini D, et al. Hepatitis B virus (HBV) infection and liver disease after allogeneic bone marrow transplantation: a report of 30 cases. Bone Marrow Transplant 1990 Jul;6(1):25-9.
2. Strasser SI, Myerson D, Spurgeon CL, Sullivan KM, Storer B, Schoch HG, et al. Hepatitis C virus infection and bone marrow transplantation: a cohort study with 10-year follow-up. Hepatology 1999 Jun;29(6):1893-9.
3. Locasciulli A, Testa M, Valsecchi MG, Bacigalupo A, Solinas S, Tomas JF, et al. The role of hepatitis C and B virus infections as risk factors for severe liver complications following allogeneic BMT: a prospective study by the Infectious Disease Working Party of the European Blood and Marrow Transplantation Group. Transplantation 1999 Nov;68(10):1486-91.
4. Peffault de Latour R, Levy V, Asselah T, Marcellin P, Scieux C, Ades L, et al. Long-term outcome of hepatitis C infection after bone marrow transplantation. Blood 2004 Mar;103(5):1618-24.
5. Ljungman, P., et al., Long-term follow-up of HCV-infected hematopoietic SCT patients and effects of antiviral therapy. Bone Marrow Transplant, 2012. 47(9): p. 1217-21.
6. Chen PM, Chiou TJ, Fan FS, Liu JM, Hsieh RK, Yen CC, et al. Fulminant hepatitis is significantly increased in hepatitis B carriers after allogeneic bone marrow transplantation. Transplantation 1999 Jun ;67(11):1425-33.
7. Hui CK, Lie A, Au WY, Leung YH, Ma SY, Cheung WW, et al. A long-term follow-up study on hepatitis B surface antigen-positive patients undergoing allogeneic hematopoietic stem cell transplantation. Blood 2005 Jul;106(2):464-9.
8. Lau GK, Wu PC, Liang R, Yuen ST, Lim WL. Persistence of hepatic hepatitis B virus after serological clearance of HBsAg with autologous peripheral stem cell transplantation. J Clin Pathol 1997 Aug;50(8):706-8.
9. Strasser SI, McDonald GB. Hepatitis viruses and hematopoietic cell transplantation: A guide to patient and donor management. Blood 1999 Feb;93(4):1127-36.
10. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998 Jul;339(2):61-8.
11. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006 Mar;354(10):1001-10.
12. Endo T, Sakai T, Fujimoto K, Yamamoto S, Takashima H, Haseyama Y, et al. A possible role for lamivudine as prophylaxis against hepatitis B reactivation in carriers of hepatitis B who undergo chemotherapy and autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Bone Marrow Transplant 2001 Feb;27(4):433-6.
13. Aoki, J., et al. Efficacy and tolerability of Entecavir for hepatitis B virus infection after hematopoietic stem cell transplantation. SpringerPlus, 2014. 3, 450 DOI: 10.1186/2193-1801-3-450.
14. Milazzo, L., et al., Late onset of hepatitis B virus reactivation following hematopoietic stem cell transplantation: successful treatment with combined entecavir plus tenofovir therapy. Transpl Infect Dis, 2012. 14(1): p. 95-8.
15. Giardini C, Galimberti M, Lucarelli G, Polchi P, Angelucci E, Baronciani D, et al. Alpha-interferon treatment of chronic hepatitis C after bone marrow transplantation for homozygous beta-thalassemia. Bone Marrow Transplant 1997 Nov;20(9):767-72.
16. Ljungman P, Andersson J, Aschan J, Bjorkstrand B, Hagglund H, Lonnqvist B, et al. Oral ribavirin for prevention of severe liver disease caused by hepatitis C virus during allogeneic bone marrow transplantation. Clin Infect Dis 1996 Jul 23(1):167-9
17. Torres HA et al. Hepatitis C virus infection among hematopoietic cell transplant donors and recipients: American Society for Blood and Marrow Transplantation task force recommendations. Biol Blood Marrow Transplant 2015 21(11):1870-82
18. Kyvernitakis A et al. Hepatitis C virus infection in patients undergoing hematopoietic cell transplantation in the era of direct-acting antiviral agents. Biol Blood Marrow Transplant 2016 22(4)717-22
19. Evans AT et al. Fibrosing cholestatic hepatitis C after hematopoietic cell transplantation: report of 3 fatal cases. Am J Surg Pathol 2015 39(2):212-220
20. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 1993 Feb;118(4):255-67.
21. Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987 Dec;44(6):778-83.
22. Mohty M. et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transpl 2016:51:906-12

23. Cairo MS, Cooke KR, Lazarus HM et al. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoeitic cell transplantation. Br J Haematol 202: 190(6):822-836
24. Shulman HM, Gooley T, Dudley MD, Kofler T, Feldman R, Dwyer D, et al. Utility of transvenous liver biopsies and wedged hepatic venous pressure measurements in sixty marrow transplant recipients. Transplantation 1995 Apr;59(7): 1015-22.
25. Yoon JH et al. Validation of treatment outcomes according to revised severity criteria from European Society for Blood and Marrow Transplantation (EBMT) for sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). Bone Marrow Transpl. 2019 54:1361-8
26. Richardson PG, Murakami C, Jin Z, Warren D, Momtaz P, Hoppensteadt D, et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood 2002 Dec; 100(13):4337-43.
27. Richardson PG, Soiffer RJ, Antin JH, Uno H, Jin Z, Kurtzberg J, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant 2010; 16(7):1005-17.
28. Kernan NA et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Br J Haematol 2018 181:816-827
29. Richardson PG et al. Systematic review of defibrotide studies in the treatment of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). Bone Marrow Transplant 2019 54(12):1951-62
30. Richardson PG et al. Earlier defibrotide iniitation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves day +100 survival following hematopoietic stem cell transplantation. Br J Haematol. 2017 178:112-8
31. Essell JH, Schroeder MT, Harman GS, Halvorson R, Lew V, Callander N, et al. Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998 Jun;128(12 Pt 1):975-81.
32. Ruutu T, Eriksson B, Remes K, Juvonen E, Volin L, Remberger M, et al. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. Blood 2002 Sep;100(6):1977-83.
33. Ruutu et al. Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. Biol Blood Marrow Transplant 2014 20:128-138
34. Tay, J., et al., Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant, 2007. 13(2): p. 206-17.
35. Zhang, L., Y. Wang, and H. Huang, Defibrotide for the prevention of hepatic veno-occlusive disease after hematopoietic stem cell transplantation: a systematic review. Clin Transplant, 2012. 26(4): p. 511-9.
36. Dignan, F.L., et al., BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol, 2013. 163 (4): p. 444-57.
37. Grupp et al. Defibrotide plus best standard of care compared with best standard of care alone for the prevention of sinusoidal obstruction syndrome (HARMONY): a randomized, multicentre, phase 3 trial. Lancet Haematol 2023 10:e333-45

Appendix

Comparison of Seattle and Baltimore Diagnostic Criteria for SOS

Seattle Criteria[22]	Baltimore Criteria[23]
Development of 2 of the following within 20 days of transplant:	Hyperbilirubinemia (> 34 micromolar) within 21 days of transplant *and* 2 of the following:
• Hyperbilirubinemia (> 34 micromolar)	• Ascites
• Tender hepatomegaly	• Hepatomegaly (may be painful)
• Weight gain (> 2%)	• Weight gain (> 5%)

Management of Cytokine Release Syndrome and Neurotoxicity Following Treatment with Immune Effector Cells

Presented by: Andrew Daly
Updated by: Robert Puckrin and Andrew Daly

Summary

- Cytokine Release Syndrome (CRS) and Neurotoxicity (ICANS, Immune Effector Cell-Associated Neurological Syndrome) are common after immune effector cell therapy. They should be considered in the case of fever, hypotension, organ dysfunction and unexplained neurological symptoms within 2-3 weeks of such therapies.
- The ASTCT Consensus Grading system will be used to determine severity of CRS based on changes in vital signs (temperature, blood pressure and need for supplemental O2 or ventilator support). The ASTCT Consensus Grading system will be used to determine the severity of ICANS based on changes in ICE score, level of consciousness, seizure, motor findings, elevated intracranial pressure, or cerebral edema.
- Management of CRS consists of antipyretics, intravenous fluids, supplemental oxygen, tocilizumab, corticosteroids, and treatment of concurrent infection. Corticosteroid prophylaxis may be considered for patients at high risk of CRS. Patients in the Intensive Care Unit will be managed concurrently by the ICU team and the Bone Marrow Transplant service.
- Management of ICANS consists of supportive care and corticosteroids. Tocilizumab may be given if there is concurrent CRS. Careful evaluation for possible metabolic, medication-associated, and infectious causes is essential, including neuroimaging and CSF evaluation when appropriate. Anti-epileptic drug prophylaxis should be given to all patients with ICANS and considered from the time of CAR-T cell infusion for those at increased risk of ICANS.

Background

A range of unique toxicities has been observed in patients treated with CAR T-cell therapy, including cytopenias, infections, and on-target, off-tumor effects such as persistent B-cell aplasia in patients treated with CD19-directed CAR T-cells. Foreign protein expressed as part of the CAR construct may on rare occasions elicit allergic reactions[1]. The most commonly observed serious toxicities of CAR T-cell therapy are Cytokine Release Syndrome (CRS) and Neurotoxicity (NT), which has also been called Immune Effector Cell-Associated Neurological Syndrome (ICANS). Although these toxicities are relatively common, when they are severe they may be life-threatening, especially if not recognized promptly and managed effectively. Table 1 summarizes the rate of CRS and ICANS observed in published trials.

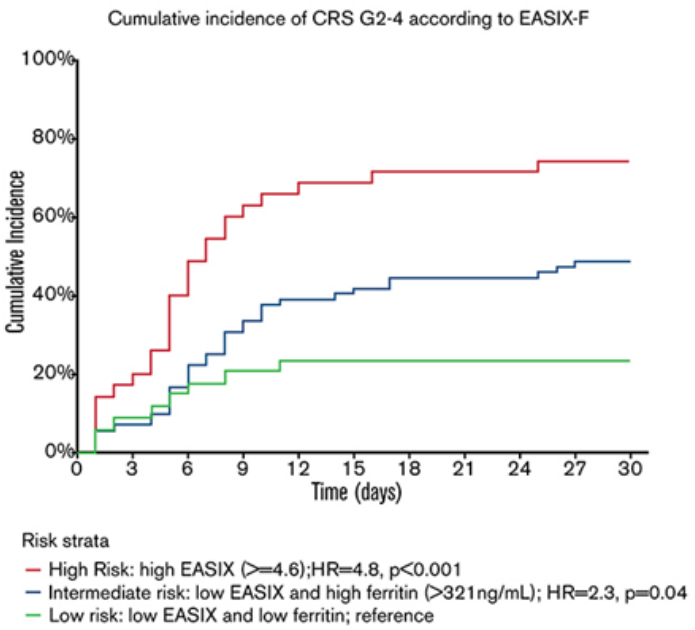
Table 1. Frequency of CRS and ICANS observed in key clinical trials.

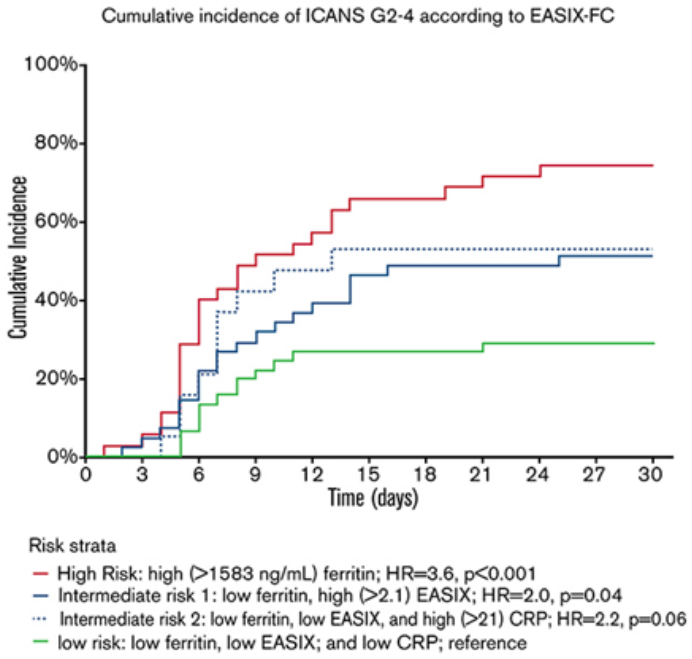
Trial	Product	CRS	Grade ≥3 CRS*	ICANS	Grade ≥3 ICANS
DLBCL					
ZUMA-1[2]	Axi-cel	93%	13%	64%	28%
JULIET[3]	Tisa-cel	58%	23%	20%	11%
TRANSCEND[4]	Liso-cel	42%	2%	30%	10%
ZUMA-7[5]	Axi-cel	92%	6%	60%	21%
BELINDA[6]	Tisa-cel	61%	5%	10%	3%
TRANSFORM[7]	Liso-cel	49%	1%	12%	4%
Mantle cell					
ZUMA-2[8]	Brexu-cel	91%	15%	63%	31%
Follicular lymphoma					
ZUMA-5[9]	Axi-cel	82%	7%	59%	19%
ELARA[10]	Tisa-cel	49%	0%	37%	4%
B-ALL					
ELIANA[11]	Tisa-cel	77%	47% ICU	40%	13%
ZUMA-3[12]	Brexu-cel	89%	24%	60%	25%
Multiple myeloma					
KaRMMA[13]	Ide-cel	84%	6%	18%	3%
CARTITUDE-1[14]	Cilta-cel	95%	5%	21%	9%

* Interstudy comparisons of CRS grading is difficult due to variations in the grading systems used

Frequency of CRS and ICANS in Alberta

Among the 23 patients treated with standard of care CAR-T cell therapy in Alberta up to December 2022, 19 (83%) patients developed CRS and 8 (35%) developed ICANS. Most events were mild-to-moderate but 2 (9%) patients required ICU transfer for grade 3 CRS (n=1) and grade 4 ICANS (n=1). Tocilizumab was given to 18 (78%) patients who received a median of 2 doses (range 1-3). Dexamethasone was given to 10 (43%) patients who received a median cumulative dose of 25mg (range 10-270mg). The risk of grade 2-4 CRS or ICANS in Alberta can be predicted by the modified EASIX score proposed by Greenbaum et al.[15], which incorporates the EASIX score ([Creatinine/88 × LDH]/platelets), ferritin, and CRP measured at the start of lymphodepleting chemotherapy:





Alberta CAR-T recipients	Grade 2-4 CRS
Low EASIX-F (n=6)	16%
Int./high EASIX-F (n=17)	65%

Alberta CAR-T recipients	Grade 2-4 ICANS
Low EASIX-FC (n=7)	14%
Int./high EASIX-FC (n=16)	31%

Clinical Features of Cytokine Release Syndrome

Cytokine release syndrome is observed in 50-95% of patients treated with CAR T-cells. Risk factors for CRS include disease burden at the time of administration, baseline inflammatory state, the dose of CAR T-cells administered and the CAR construct. Higher rates of CRS are observed in patients treated with CAR T-cells bearing a CD28 costimulatory domain than those bearing 4-1BB constructs. Higher rates of CRS are also reported among patients with recent viral infection or with bacterial infections at the time of treatment.

The majority of patients with CRS present with fever. The median onset of CRS was 2 days after axi-cel infusion, 3 days after tisa-cel infusion, and 5 days after liso-cel infusion in the ZUMA-1, JULIET, and TRANSFORM trials. Median duration of CRS was 5-8 days. Fevers are often as high as 40°C and are associated with systemic symptoms such as malaise, myalgias and nausea or vomiting. Severe CRS is almost always associated with hypotension and vasoplegic shock. Early use of vasopressors in this situation is associated with improved outcomes. Severe CRS may progress to multi-organ dysfunction or HLH and can be fatal.

In addition to the systemic symptoms described above, patients with CRS may experience direct toxicity to a range of organ systems. This includes cardiac toxicity in the form of tachycardia and arrhythmias. Grade 3-4 hypotension occurs in 22-38% of patients with CRS. Stress cardiomyopathy

may be observed in this population. This may remain occult until the patient receives fluid challenges for hypotension. Pulmonary edema may occur in the context of cardiomyopathy but non-cardiogenic pulmonary edema may also occur. Hypoxia, cough and pneumonitis may also develop. Grade 3-4 hypoxia is noted in 6-15% of patients and BiPAP or mechanical ventilation may be required. Renal impairment is almost always due to hypoperfusion in the context of shock or low cardiac output. Electrolyte abnormalities are not uncommon. Tumor lysis syndrome may occur in patients with significant tumor burden at the time of treatment. Elevated liver enzymes and bilirubin may be seen in patients who develop CRS. Patients may develop nausea, vomiting, diarrhea and abdominal pain.

Cytopenias are also common after CRS. These may persist for weeks or months after treatment and should be treated supportively with transfusion and close monitoring for fever in neutropenia. It has been suggested that G-CSF should be avoided early after CAR-T cell infusion due to the potential risk of exacerbating CRS, but it can be given >14 days after CAR-T cell infusion once CRS has resolved[16]. Patients may also develop coagulopathy similar to DIC. It can often be difficult to distinguish fever from infection in this context and it is recommended that patients with CRS and clinical features of infection, including hypotension, should undergo careful screening for infection and receive treatment with antibiotics appropriate to their clinical presentation.

General Care of the CAR T-Cell Recipient

Frequent and careful evaluation by physician and nursing staff of CAR T-cell recipients is the cornerstone of safe management of these patients. The majority of patients destined to develop CRS will do so within the first two weeks after treatment. In Calgary we plan to administer CAR T-cells in hospital. Patients will remain in hospital at the discretion of the treating physician. During this time, vital signs should be obtained frequently and medical staff should be advised of any new fever (≥38° C), hypotension (SBP ≤ 90 mmHg), tachycardia (HR ≥ 120 bpm), hypoxia (SpO2 ≤ 90%) or organ toxicity. Patients with bulky disease should receive prophylaxis and monitoring for tumor lysis syndrome. Patients should have a physical exam and complete review of systems performed daily. Screening for ICANS should be completed at minimum every 12 hours using an accepted neurological scoring system (ICE, outlined below). Laboratory testing (which should include CBC, electrolytes, creatinine, serum calcium, magnesium, phosphate, uric acid, liver enzymes, PTT, INR, fibrinogen, C-reactive protein and ferritin) should be sent daily, but may need to be repeated more often if patients develop new findings. The physician should be advised of changes in the neurological status of the patient, including changes in the ICE score, uncoordinated or jerky movements in the extremities, changes in alertness (drowsiness, agitation or confusion) or visual disturbance. Physicians will document CRS and ICANS grade once daily in the medical record.

Grading Cytokine Release Syndrome

Several CRS grading systems have been used in the clinical management of CAR T-cell recipients. The ASTCT grading system described by Lee et al[17] (Table 2) appears to be most suitable, and is gradually becoming the industry standard. Legacy grading systems are largely of historical interest but are still being used in some active clinical trials. These systems are compared in Appendix B.

Table 2. ASTCT cytokine release syndrome grading (per Lee et al.[17]).

	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Yes, ≥38 ^{O}	Yes, ≥ 38 ^{O}	Yes, ≥ 38 ^{O}	Yes, ≥ 38 ^{O}
		with		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		with		
Hypoxia**	None	Requiring low-flow nasal cannula (≤6 LPM) or blow-by	Requiring high-flow nasal cannula (>6 LPM), facemask, non-rebreather, or Venturi mask	Requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicity may be graded according to CTCAE Version 5.0 (2017)
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm but does not change grade.

* Fever is defined as temperature ≥ 38 degrees not attributable to other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade CRS. In this case CRS grading is driven by hypotension and/or hypoxia.
** Hypoxia should not be explained by other causes i.e. rigors or sedation in order to meet the definition of hypoxia in CRS.
*** Low-flow is defined as oxygen delivered at ≤ 6 LPM. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 LPM.

Management of Cytokine Release Syndrome

Cytokine release syndrome should be suspected in patients who develop new fever (≥ 38°C), hypotension (SBP ≤ 90 mmHg), hypoxia (SpO2 ≤ 90%) or organ toxicity. Careful clinical evaluation, including blood cultures, viral studies (respiratory virus panel, CMV and EBV PCR) and imaging tests should be carried out as appropriate to assess for other causes of these findings. Infection, septic or cardiogenic shock, venous thromboembolism, alveolar hemorrhage, tumor lysis syndrome and other syndromes may resemble CRS in their initial presentations and these diagnoses should be either treated empirically or excluded through appropriate investigations. The CRS grade should be determined at least twice per day and with changes in patient status. The syndrome should be

managed according to grade as described in Table 3, which is a harmonized summary of the management guidelines proposed by EBMT, ASCO, CARTOX groups and ZUMA-1 safety cohorts 4 and 6[16, 18, 19, 20, 21].

Principles of CRS management include the following:

1. The onset of CRS corresponds to the period of most rapid expansion of the CAR T-cell population. During this time, high levels of cytokines are elaborated leading to the clinical manifestations of the syndrome. Importantly, IL6 levels correlate with the severity of CRS and the anti-IL6 receptor antibody tocilizumab has been shown to rapidly reverse the course of CRS.
2. Hypotension that persists after 1-2 liters of 0.9% normal saline is unlikely to respond to further fluid resuscitation. The reasons for this are unclear but include the presence of vascular leak, vasoplegia and occult stress cardiomyopathy. Hypotension that fails to respond to two fluid challenges and tocilizumab should be treated with vasopressors.
3. Although we recommend corticosteroids for patients with severe CRS, the use of these agents for reasons beyond the management of CRS, for instance as premedication prior to blood transfusion or for minor allergic symptoms, should be avoided.
4. In general CRS that develops shortly (< 72 hours) after CAR T-cell infusion has a more aggressive course and requires more intensive treatment than that arising more gradually (≥72 hours after infusion). In addition, patients with comorbid medical conditions may experience a more complicated course with CRS and so early initiation of anticytokine therapy is justifiable in this population.
5. In general the use of tocilizumab and steroids have moved earlier in the course of CRS treatment. Recent evidence suggests that the use of tocilizumab and steroids do not impact important outcomes of CAR T-cell therapy such as progression-free and overall survival[19, 20, 22, 23]. However, high-dose or prolonged corticosteroid use has been associated with poor outcomes in some studies[24], hence corticosteroids should be rapidly tapered upon improvement and discontinued upon resolution of CRS.
6. The results of ZUMA-1 safety cohort 6 showed that low-dose corticosteroid prophylaxis may reduce the risk of severe CRS and severe ICANS compared to historical controls[20]. However, interpretation of this study is limited by its small sample size, single-arm design, and baseline differences in tumor burden and inflammatory state. Nevertheless, corticosteroid prophylaxis may be reasonably considered for patients who have ≥2 risk factors for severe CRS or ICANS, such as receiving axi-cel or brexu-cel, age >65, high tumor burden, and/or elevated baseline inflammatory markers.

Table 3. Management of CRS after CAR T-cell therapy.

Grade	Recommendations
Prophylaxis	▪ Consider dexamethasone 10mg on morning of infusion and on days +1 and +2 if high risk for severe CRS or ICANS (e.g. ≥2 risk factors: axi-cel or brexu-cel, age >65, int/high modified EASIX, high tumor burden)
Supportive care	▪ Anti-pyretics (e.g. acetaminophen, NSAID, external cooling) as needed ▪ Order infectious work-up and start antibiotics if neutropenic, unstable, or infection suspected ▪ Provide supplemental oxygen for hypoxia and IV fluids for hypotension with early consideration for vasopressors if hypotension persists after 1-2L
Grade 1	▪ Consider tocilizumab x1 dose if fever lasting >24-72 hours, especially if early onset CRS, comorbidities, or high risk for severe CRS
Grade 2	▪ Tocilizumab x1 dose → repeat up to 3 doses per day PRN for up to 4 total doses ▪ Dexamethasone 10mg x1 dose if high risk and/or refractory to tocilizumab → re-assess in 6 hours
Grade 3	▪ Tocilizumab up to 3 doses per day PRN for up to 4 total doses ▪ Dexamethasone 10mg q6h → 20mg q6h if refractory
Grade 4	▪ Tocilizumab up to 3 doses per day PRN for up to 4 total doses ▪ Methylprednisolone 1-2g daily for 3 days then rapid taper ▪ Consider anakinra (preferred), siltuximab, ruxolitinib, cyclophosphamide, or ATG if refractory

Pharmacotherapy of CRS

- Tocilizumab
  - Anti-IL6 receptor antibody with most extensive track record in CRS
  - Dose 8 mg/kg (not to exceed 800 mg per dose) IV over one hour
  - Half-life of tocilizumab is 13 days in rheumatoid arthritis. Some guidelines suggest repeat dosing q4-6 hours based on response, up to 3 doses in 24 hours and 4 doses in total
  - May premedicate with Benadryl or Tylenol if not recently given. NO STEROID PREMEDS.
- Steroids
  - Dexamethasone 10 mg IV may be given for grade 2 CRS especially if high risk and/or refractory to tocilizumab
  - Higher doses of dexamethasone (e.g. 10mg IV q6h) are used for grade 3 CRS
  - If life-threatening and no response to tocilizumab may give up to MP 1 gm IV daily x 3
- Other monoclonal antibodies for steroid refractory toxicities
  - Anakinra (preferred for steroid-refractory CRS/ICANS or overlap with HLH/MAS)
  - Siltuximab

- Treatments of last resort for life-threatening toxicities:
  - ATG Thymoglobulin if life-threatening and no response to steroids and tocilizumab
  - Cyclophosphamide 1.5 gm/m2 may be given if CRS fails to respond to repeated doses of tocilizumab and steroids.
  - Need to balance risk of death from CRS with loss of CAR T-cells (and likely relapse of underlying cancer) if using high-dose steroids, ATG, Campath or cyclophosphamide.

Management of Immune Effector Cell-Associated Neurological syndrome (ICANS)

Neurological abnormalities are relatively common among recipients of CAR T-cells. Risk factors for ICANS include age >65, CD28-costimulatory domain, higher CAR-T cell doses, higher tumor burden, elevated baseline inflammatory state, and early onset or severe CRS. Early findings of ICANS include tremor, impaired attention, dysgraphia, mild difficulty in expressive speech (especially difficulty naming objects) and somnolence. More profound derangements include ataxia, aphasia, encephalopathy and seizures. Severe ICANS is characterized by motor weakness, obtundation, increased intracranial pressure and cerebral edema. Although rare, cerebral edema may have a very rapid course, progressing to brain death within 24 hours. ICANS usually occurs a few days following the onset of CRS. The median onset of ICANS was 5 days after axi-cel infusion, 6 days after tisa-cel infusion, and 9 days after liso-cel infusion in the ZUMA-1, JULIET, and TRANSFORM trials. Median duration of ICANS was 11-17 days. It is important to note that ICANS may exhibit a biphasic pattern, with symptoms appearing and resolving within the first 1 to 2 weeks but reemerging as late as the third or fourth week after CAR T-cell infusion.

Early detection of ICANS has been facilitated by the development of scoring systems capable of detecting early changes in neurological function. One such system, the ASTCT Immune Effector Cell-associated Encephalopathy (ICE) tool (below) can be administered several times per day by medical or nursing staff with minimal training. The tool gives the patient one point for each of 10 items, so the ICE score ranges from 0 (worst) to 10 (best)

ICE tool:

- Orientation to
  - Year – *1 point*
  - Month – *1 point*
  - City – *1 point*
  - Hospital – *1 point*
- Naming 3 objects – *up to 3 points*
- Following Commands (eg, Show me two fingers) – *1 point*
- Writing a short sentence – *1 point*
- Attention: Count backwards from 100 by ten – *1 point*

The ICE tool is reproducible and prognostic, and has been integrated into a comprehensive ASTCT ICANS grading system (Table 4). ICANS management according to grade is outlined in Table 5. The mainstay of treatment is supportive care along with corticosteroids. Tociluzumab does not appear to have a significant role in the treatment of ICANS but can be considered if there is concurrent CRS.

Table 4. ASTCT Grading Immune Effector Cell-Associated Neurological Syndrome[17]

Symptom or sign	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9 (mild)	3-6 (moderate)	0-2 (severe)	Unable to perform
Level of Consciousness	Awakens spontaneously	Awakens to voice	Awakens to touch	Unarousable or requires vigorous or repeated stimuli to arouse. Stupor or coma
Seizure	NA	NA	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizure that resolves with intervention	Life-threatening or prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline between
Motor Findings	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/Cerebral edema	NA	NA	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or CN VI palsy; or papilledema or Cushing's

Table 5. Management of ICANS

Prophylaxis • Consider dexamethasone 10mg on morning of infusion and on days +1 and +2 if high risk for severe CRS or ICANS (e.g. ≥2 risk factors: axi-cel or brexu-cel, age >65, int/high modified EASIX, high tumor burden) • Consider levetiracetam 500mg BID prophylaxis from day 0 to +14 for patients receiving axi-cel or brexu-cel or who have other risk factors for ICANS. Duration of levetiracetam should be extended for patients who develop seizures or have ongoing ICANS, in conjunction with the neurology service.
Grade 1 • Aspiration precautions, intravenous hydration • Withhold oral intake of food, medicines, and fluids and assess swallowing • Convert all medications and nutrition to IV if swallowing is impaired • Avoid sedating medications • Low-dose lorazepam (0.25-0.5 mg IV q8h) or haloperidol (0.5 mg IV q6h) for agitated patients • Neurology consultation • Fundoscopic exam for papilledema • MRI of the brain with and without contrast, MRI spine if focal neurological deficits • Consider diagnostic LP if other causes of encephalitis suspected • Consider tocilizumab 8 mg/kg IV if ICANS occurs in setting of CRS • Dexamethasone 10 mg IV x 1 dose and reassess in 6 hours • Start levetiracetam 500 mg bid prophylaxis if not already given
Grade 2 • Workup and supportive care as described above • Tocilizumab 8 mg/kg IV if ICANS occurs in setting of CRS • Dexamethasone 10 mg IV q6-12h. Once ICANS improves to grade 1 or less taper and/or discontinue steroids if clinically appropriate • Consider ICU transfer if associated with grade ≥ 2 CRS • Start levetiracetam 500 mg bid prophylaxis if not already given
Grade 3 • Workup and supportive care as described above • ICU transfer • Tocilizumab 8 mg/kg IV if ICANS occurs in setting of CRS, if not administered previously • Dexamethasone 10-20 mg IV q6h for most patients. Consider treating focal brain edema with methylprednisolone 1 gm IV daily x 1-3 days • Increased intracranial pressure should be treated according to standard guidelines with acetazolamide 1000 mg IV followed by 250-1000 mg q12h (based on renal function and acid/base balance), elevate HOB. • Diagnostic LP if no improvement with treatment or if other causes of encephalitis suspected • Consider repeat neuroimaging every 2-3 days • Antiepileptic drugs as prescribed by neurology (avoid phenytoin and lacosamide due to cardiotoxicity)
Grade 4 • Supportive care and workup as described above • ICU monitoring and mechanical ventilation for airway protection • Tocilizumab 8 mg/kg IV if ICANS occurs in setting of CRS, if not administered previously • Treat with methylprednisolone 1 to 2 g IV daily x 3 days followed by rapid taper • Consider anakinra, intrathecal hydrocortisone/methotrexate, or siltuximab if steroid refractory. Cyclophosphamide or ATG may be considered as treatments of last resort. • For convulsive status epilepticus treat according to established guidelines • Cerebral edema should be treated as per established guidelines, including hyperventilation, hyperosmolar therapy, frequent metabolic profiling and neurosurgical or anesthesia consultation for burst-suppression pattern EEG • Antiepileptic drugs as prescribed by neurology (avoid phenytoin and lacosamide due to cardiotoxicity)

References

1. Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR T-cell therapy. Mol Ther Oncolytics. 2016;3:16011.
2. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-44.
3. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.
4. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-52.
5. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2021.
6. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386(7):629-39.
7. Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399(10343):2294-308.
8. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020;382(14):1331-42.
9. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.
10. Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325-32.
11. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-48.
12. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;398(10299):491-502.
13. Munshi NC, Anderson LD, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-16.
14. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-24.
15. Greenbaum U, Strati P, Saliba RM, Torres J, Rondon G, Nieto Y, et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. Blood Adv. 2021;5(14):2799-806.
16. Hayden PJ, Roddie C, Bader P, Basak GW, Bonig H, Bonini C, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022;33(3):259-75.
17. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.
18. Santomasso BD, Nastoupil LJ, Adkins S, Lacchetti C, Schneider BJ, Anadkat M, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol. 2021;39(35):3978-92.
19. Topp MS, van Meerten T, Houot R, Minnema MC, Bouabdallah K, Lugtenburg PJ, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;195(3):388-98.
20. Oluwole OO, Bouabdallah K, Muñoz J, De Guibert S, Vose JM, Bartlett NL, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;194(4):690-700.
21. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.

22. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. J Clin Oncol. 2020;38(27):3119-28.
23. Gardner RA, Ceppi F, Rivers J, Annesley C, Summers C, Taraseviciute A, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood. 2019;134(24):2149-58.
24. Strati P, Ahmed S, Furqan F, Fayad LE, Lee HJ, Iyer SP, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. Blood. 2021;137(23):3272-6.

Management of Transfusion and Cytopenias Post-Hematopoietic Cell Transplant

Presented by: Jason Tay and Sadaf Ekhlas

Summary

1. The Alberta Bone Marrow and Blood Cell Transplant Program will utilize irradiated cellular blood products from the Canadian Blood Services (universally leukoreduced and CMV Safe) for patients who have received a Hematopoietic Cell Transplant (HCT).

2. We recommend the provision of 1 unit of red cells based on daily CBC demonstrating a hemoglobin <70g/L (15 mL/kg to a maximum of 1 unit for pediatrics). The use of a higher red cell transfusion threshold would be at the discretion of the clinician based on clinical judgement such as symptoms of anemia.

3. We recommend the provision of 1 unit of pooled platelets based on daily CBC demonstrating platelets < 10×10^9/L (10 mL/kg, maximum of 1 unit for pediatrics). The use of a higher platelet transfusion threshold would be at the discretion of the clinician based on clinical judgement such as active bleeding.

4. We do NOT recommend the routine use of therapeutic platelet transfusions or prophylactic tranexamic acid instead of prophylactic platelets. It may be reasonable to consider their use in exceptional circumstances e.g., Jehovah's Witness.

5. We do NOT recommend choosing blood products based on duration of storage.

6. We recommend the routine use of G-CSF post-autologous HCT starting on Day 7 until ANC>0.5.

7. We do NOT recommend the routine use of G-CSF post-allogeneic HCT (excepting non-malignant pediatric disorders).

8. We do NOT recommend the routine use of erythropoietin post-HCT. It may be reasonable to consider its use in exceptional circumstances e.g., Jehovah's Witness.

9. It is reasonable to consider on a case-by-case basis, the use of Thrombopoietin receptor agonists (e.g., eltrombopag) in circumstances of prolonged isolated thrombocytopenia post-HCT or secondary failure of platelet recovery.

10. In general, the management of cytopenias post Chimeric antigen receptor T-cell therapy (CAR-T) will follow similar principles of care.

Background

High dose chemotherapy with or without radiation followed by hematopoietic stem cell (HSC) rescue, typically suppress the production of blood cells by the bone marrow for 7 to 14 days. This results in aplasia, during which the patient is likely to require prophylactic or therapeutic transfusions of red cells and platelets. This is particularly salient in the allogeneic setting where longer periods of transfusion support may be required, when recovery is complicated by delayed engraftment, acute graft-versus-host disease (GvHD) or severe sepsis.

There is a paucity of randomized controlled trial data to guide transfusion practice in the HCT setting[1]. Indeed, guidelines for transfusion support are often extended to the hematopoietic cell transplant (HCT) setting from general oncology/medicine despite the lack of strong clinical trial evidence (insert guidelines)[2-6].

Transfusion Utilization

It has been estimated that up to 39% of the total blood transfused in the USA in 2017 was used by inpatient medicine (including hematology/oncology) patients[7], while an estimate of 27.1% in hematology/oncology was noted in the UK in 2014[8]. The frequency of transfusion support is the highest post-conditioning chemoradiotherapy and decreases significantly after the 1st 30 days consistent with the timing of stem cell engraftment. For instance, Xenocostas et al. reported that the mean number of red cell units transfused per patient from 0 to 60 days was 6.8 +/- 6.4; 61 to 120 days, 3.2 +/- 5.5; and 121 to 180 days, 2.0 +/- 4.6[9]. Factors that are associated with avoidance of transfusion after HCT include male sex ($p = 0.0013$), diagnosis, specifically plasma cell dyscrasias ($p < 0.0001$), early-stage disease ($p = 0.006$), and higher baseline hemoglobin (Hb) at time of transplant ($p < 0.0001$)[10]. The following table summarizes selected clinical studies reviewing transfusion utilization in the HCT setting.

Table 1: Selected clinical studies reviewing transfusion utilization in the HCT setting

	Setting	Timeline	Red Cell Utilization (units)	Platelet Utilization (units)
			Mean (SD)	*Mean (SD)*
Observational Studies				
Xenocostas 2003	Allo	Day 0 to 60	6.8 ± 6.4	
Sohl 2011	Allo	Day 0 to 60	5.2 (95% CI 3.7-6.7)	12.9 (95% CI 9.4-16.4)
	Cord Allo	Day 0 to 60	7.8 (95% CI 6.7-8.9)	25.2 (95% CI 22.1-28.2)
Kekre 2012	Auto & Allo	Day 0 to 30	4.7± 4.5	
Christou 2015	Auto & Allo	Day 0 to 60		7.5 (95% CI 6.7-8.4)
LeViellez 2015	Allo	Day 0 to 60	Median 4	Median 4
Leahy 2017	Induction AML or Allo	Day	3.7	4.1
Gastecki 2019	Allo	Day	Median 19	
Konuma 2019	Cord Allo only	Day 0 to 30	Median 12 (range 4-66)	
Randomized Controlled Trials				
Wandt 2012	Induction AML or Auto	Day 0 to 30	2.85 (95% CI 2.58-3.12) in St. Arm	2.44 (95%CI 2.22-2.67) in St. arm
			3.14 (95% CI 2.81-3.46) in Exp arm	1.63 (95% CI 1.42-1.83) in Exp arm
Stansworth 2013	Chemotherapy or HCT	Day 0 to 30	3.0 ±3.4 in St. arm	1.7 ± 2.6 in St. arm
			2.8 ±3.1 in Exp. arm	3.0 ±3.2 in Exp. arm
Tay 2020	Auto & Allo	Day 0 to 100	5.02 ± 6.13 in St. arm	
			2.73 ± 4.81 in Exp. arm	

Association with post-HCT Outcomes

While confounded by indication, lower hemoglobin levels and/or transfusion support have been associated with various negative post-HCT outcomes. However, it remains unclear if such “risk factors” are modifiable and whether they would lead to improved post-HCT outcomes.

For instance, Xenoscosta et al. in a retrospective study of 519 consecutive patients receiving allogeneic HCT between January 1995 and March 2000 demonstrates an increased mortality during the 6-month period after HCT was associated with lower pre-HCT hemoglobin levels. Similar findings have been reported in the cord blood HCT setting where RBC transfusion >/=18 units by day 30 was significantly associated with higher overall mortality (hazard ratio, 1.86; P = 0.018)[11]. A more recent retrospective study by Hosoba et al. of 322 consecutive patients receiving an allogeneic bone marrow or granulocyte colony-stimulating factor-mobilized blood stem cell graft for a hematologic malignancy[12]. This study demonstrated that transfusion of more than the median number of RBC units (HR, 2.1; 95% CI, 1.1 to 3.7; P = .02) were independently associated with greater risk of grade III-IV acute GVHD in a multivariable analysis model and transfusion of more than the median number (5 units within 27 days) of RBC units (HR, 1.4; 95% CI, 1.0 to 2.0; P = .054) was associated with inferior overall survival.

Vande Vusse et al. examined the associations between platelet transfusions and idiopathic pneumonia syndrome (IPS) among 914 individuals who underwent myeloablative allogeneic HCT between 1997 and 2001. They identified 77 IPS cases (8.4%), where each additional platelet unit transfused in the prior week was associated with 16% higher IPS risk with a HR 1.16; 95%CI (1.09-1.23)[13]. Likewise, Christou et al. confirmed that the number of platelet transfusion events was associated with increased 100-day non relapse mortality ($p < 0.01$), post-HCT length of hospital stay ($p < 0.01$), need for intensive care unit admission ($p < 0.01$), and number of organs affected by severe toxicity ($p < 0.01$)[14].

Blood Products

The Alberta Bone Marrow and Blood Cell Transplant Program relies on the Canadian Blood Services for transfusion products. The collection, testing, processing, contents and distribution of these blood products will follow the Canadian Blood Services procedures[15]. Blood products are issued by Transfusion Medicine, Alberta Precision Laboratories.

Red Cell Transfusion

Threshold:
Different strategies have been developed for RBC transfusions. A restrictive transfusion strategy seeks to maintain a lower hemoglobin level (usually between 70 g/L to 90 g/L) with a trigger for transfusion when the hemoglobin drops below 70 g/L), whereas a liberal transfusion strategy aims to maintain a higher hemoglobin (usually between 100 g/L to 120 g/L, with a threshold for transfusion when hemoglobin drops below 100 g/L). There are very few randomized studies examining red cell transfusion thresholds in the oncology setting as summarized by a recent Cochrane review in 2017[16]. The review suggests that a restrictive RBC transfusion policy has little or no effect on mortality at 30 to 100 days, bleeding, or hospital stay. However, there is absence of data on health-related quality of life, arterial or venous thromboembolic events, length of intensive care admission or readmission to hospital.

A recent noninferiority randomized controlled trial in four different Canadian centers evaluated 300 patients with hematologic malignancies requiring HCT between 2011 and 2016[17]. Patients were randomly assigned to either a restrictive (hemoglobin [Hb] threshold < 70 g/L) or liberal (Hb threshold < 90 g/L) RBC transfusion strategy between day 0 and day 100 with a primary outcome of health-related quality of life measured by FACT-BMT. Clinical outcomes of transplantation-related mortality, length of hospital stay, intensive care unit admissions, acute graft-versus-host disease, Bearman toxicity score, sinusoidal obstruction syndrome, serious infections, WHO Bleeding Scale, transfusion requirements and reactions to therapy were collected. The authors demonstrate that the number of RBC units transfused was lower in the restrictive-strategy group than in the liberal-strategy group (mean, 2.73 units [standard deviation, 4.81 units] v 5.02 units [standard deviation, 6.13 units]; P =

.0004). After adjusting for transfusion type and baseline FACT-BMT score, the restrictive-strategy group had a higher FACT-BMT score at day 100 (difference of 1.6 points; 95% CI, −2.5 to 5.6 points), which was noninferior compared with that of the liberal-strategy group. Additionally, there were no significant differences in clinical outcomes between the transfusion strategies. Another Canadian Blood and Marrow Transplant Group trial compared red blood cell transfusion thresholds of 120 g/L in the experimental arm and 70 g/L in the control arm. The study was stopped early due to excess sinusoidal obstructive syndrome in the experimental group[18].

Number of Red Cell Units per Transfusion:
With the advent of the Choosing Wisely initiatives[19], many clinicians are using one-unit transfusions as opposed to using two units at a time. Observational studies support this safe strategy with decreases in the use of red cell units[20-22] although the results are inconsistent[23]. Moreover, it remains unclear if a one-unit transfusion leads to better patient satisfaction or improved health care utilization beyond the number of units transfused.

Duration of Storage of Red Cell Products:
Laboratory evidence coupled with early clinical observational studies suggest that there might be concerns of using older red cell products*, i.e.,* storage lesion[24]. However, numerous randomized studies in a varied clinical setting, summarized by systematic reviews have found no convincing evidence that the age of red blood cells have an adverse effect on patient outcomes[25-29]. Moreover, retrospective reviews in the general cancer[30] and HCT[31] settings would further affirm this absence of association.

Red Cell Transfusion- Summary:
Taken together, the clinical evidence supports the use of a restrictive red cell transfusion threshold in patients undergoing HCT. However, it is reasonable to consider an individualized higher red cell threshold depending on clinical judgement such as the presence of symptoms of anemia. There is no evidence to support preference for “younger” red cell units over “older” units. It is reasonable and practical to provide 1-unit red cell unit per transfusion.

Platelet Transfusion

Thresholds:
Clinically significant bleeding related to thrombocytopenia occurs in nearly 50% of all patients undergoing HCT. Over the last 2 decades, there have been randomized controlled trials examining platelet transfusion thresholds (where the primary endpoint is WHO grade 2 or higher bleeding), summarized by the following table:

Table 2: RCTs examining platelet transfusion thresholds

RCT	Setting	Patients (N)	Interventions	Key findings
Heckman 1997[32]	Induction therapy for acute leukemia	78	<10 vs. <20	1. <10 group received more platelet transfusions for bleeding. 2. <20 group arm received more platelet transfusions for prophylactic indications. 3. No difference in RBC transfusion requirements, febrile days, days hospitalized, days thrombocytopenic, need for HLA-matched platelets, remission rate, or death.
Rebulla 1997[33]	Induction for acute myeloid leukemia	255	<10 vs. <20	1. <10 group had 21.5 percent fewer platelet transfusions. 2. No difference in risk of major bleeding. 3. No difference in survival, absence of major bleeding or length of stay
Zumberg 2002[34]	Autologous or Allogeneic HCT	159	<10 vs. <20	1. No differences in bleeding incidence or severity. 2. More transfusions were given above the assigned transfusion threshold. 3. No difference in transfusion utilization.
Diedrich 2005[35]	Allogeneic HCT	166	<10 vs. <30	4. <10 group had fewer platelet transfusions. 5. No difference in bleeding, bacteremia, engraftment, GVHD, hospital stay, death, and survival. 6. No difference in RBC transfusions.

The results from these studies have informed the care of patients with hematologic malignancies receiving high dose chemotherapy, where the current standard practice is to transfuse platelets prophylactically when the daily platelet count is < 10 x 10^9/L to prevent bleeding[3,6,36-38].

Platelet Dose:

Additionally, there have been 5 RCTs evaluating the efficacy of different platelet doses[39-43] summarized by a Cochrane review[44]. For instance, the more recent and adequately powered study by Slichter et al. randomized (n=1,272) patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumors to receive prophylactic platelet transfusions at a low dose, a standard dose, or a high dose (1.1×10^{11}, 2.2×10^{11}, or 4.4×10^{11}) platelets per square meter of body-surface area, respectively[43]. They demonstrate that low doses of platelets administered as a prophylactic transfusion led to fewer platelets transfused per patient, but an increased number of

transfusions given. At doses between 1.1×10^{11} and 4.4×10^{11} platelets per square meter, the number of platelets in the prophylactic transfusion had no effect on the incidence of bleeding.

Taken together, there is no evidence to suggest that a low-dose platelet transfusion policy is associated with an increased bleeding risk compared to a standard-dose or high-dose policy, or that a high-dose platelet transfusion policy is associated with a decreased risk of bleeding when compared to a standard-dose policy[44]. However, a low-dose platelet transfusion strategy leads to an increased number of transfusion episodes compared to a standard-dose strategy. A high-dose platelet transfusion strategy does not decrease the number of transfusion episodes per participant compared to a standard-dose regimen, and it may increase the number of transfusion-related adverse events.

Duration of Storage of Platelets:
Platelets are usually stored for up to 5 days prior to transfusion, although in some blood services the storage period is extended to 7 days. During storage, changes occur in both platelets and storage medium, which may lead to platelet activation and dysfunction. There have been several observational studies, mostly in the critical care setting that evaluated the potential impact of platelet storage and clinical outcomes. A recent systematic review of such studies suggests that storage time does not appear to be associated with clinical outcomes, including bleeding, sepsis or mortality[27]. However, the freshest PLTs (less than 3 days) were associated with a better CCI, although there was no impact on bleeding events. Taken together, the duration of storage of transfused platelets likely has no appreciable impact on post-HCT outcomes.

Platelet Transfusion Alternatives:
However, the true benefit of prophylactic platelet transfusions in the autologous HCT setting is unclear; subgroup analyses from 2 recent studies suggest that a therapeutic strategy (transfusing platelets only to treat bleeding) may be as effective as a prophylactic transfusion strategy[45,46]. There has been interest in the use of prophylactic TXA to prevent bleeding in patients with chemotherapy-related hypoproliferative thrombocytopenia[47,48]. Gernshiemer et al. in the a-TREAT Trial evaluated the effects of prophylactic TXA in addition to routine transfusion therapy on bleeding and transfusion requirements in a multicenter, double-blind placebo controlled randomized clinical trial in patients undergoing treatment for hematologic malignancy. 330 patients were activated and evaluable; 327 received at least one dose of study drug. The adjusted odds ratio of grade 2+ bleeding was 0.86 (95% CI: 0.52, 1.38; p-value=0.74). The difference in mean number of transfusions was 0.1 (95% CI: -1.9, 2.0; p-value=0.94), while the average difference in days alive without grade 2+ bleeding was 0.1 (95% CI: -1.4, 1.5; p-value=0.94). As such, the authors conclude that Prophylactic TXA has no effect on the incidence of WHO Grade 2+ bleeding when given in addition to routine plt transfusions to severely thrombocytopenic patients undergoing therapy for hematologic malignancy[114].

Additionally, there are 2 ongoing RCTs, with another examining the addition of prophylactic TXA to prophylactic platelet transfusions in patients with in patients with hematological malignancies with

severe thrombocytopenia[49] and another examining prophylactic tranexamic acid instead of prophylactic platelets in patients undergoing autologous HCT[118].

Platelet Transfusion-Summary:
Taken together, the clinical evidence supports the use of < 10 x 10^9/L as a platelet transfusion threshold. However, it is reasonable to consider an individualized higher platelet threshold and/or dose, depending on clinical judgement such as the presence of persistent bleeding. There is a paucity of high-quality evidence to routinely use therapeutic over prophylactic platelet transfusions. There is no evidence to support preference for "younger" platelet units over "older" units.

Platelet Refractoriness:
Platelet transfusion refractoriness is defined as the repeated failure to achieve satisfactory responses to platelet transfusions from random donor[51]. There have been various formulae that have been proposed to determine platelet refractoriness[52]. However, it is argued that such calculations are not clinically useful. Instead, a pragmatic definition of failure of the immediate post-transfusion (10 to 60 minutes) platelet increment to exceed the transfusion trigger or a rise of less than 10×10^9/L 20 to 24 hours after transfusion with unsatisfactory responses to two or more transfusions[53]. The following table summarizes some potential causes for platelet refractoriness:

Table 3: Potential causes for platelet refractoriness

Immune	Non-Immune
Platelet alloantibodies: HLA, ABO, HPA	Infection
Other antibodies: Platelet autoantibodies, Drug dependent antibodies	Fever
Immune complexes	Anti-microbials (vancomycin, fluroquinolones, Ampho B)
	Graft versus host Disease
	Veno-occlusive Disease
	Splenomegaly
	Disseminated Intravascular Coagulation

While universal leukoreduction has decreased the incidence of platelet refractoriness from HLA antibodies[54], it does not address other causes. It is likely that there are multiple competing etiologies for platelet refractoriness. Moreover, it would be impossible to determine their relative contributions to platelet refractoriness. Beyond, optimizing specific and potential etiologies, it is practical to consider the following 2 measures where the risk of bleeding is considered high or unacceptable. These measures should be continued until the risk of bleeding is deemed low.

1. Prophylactic HLA matched platelets
    a. Antibodies against HLA-A and –B antigens are the only clinically relevant HLA antibodies that cause platelet refractoriness.
2. Prophylactic Tranexamic acid 1gram TID PO/IV

The following are additional considerations:

1. It is reasonable to provide both prophylactic standard daily prophylactic non-HLA matched platelets and tranexamic acid measures in the absence of a satisfactory response with HLA matched platelets or if HLA matched platelets are not available.
2. In cases where the risk of bleeding is deemed low, it is reasonable to solely provide prophylactic tranexamic acid.
3. There are advocates for platelet cross-matching, but it is not routinely available in Canada and not recommended over HLA matched platelets.
4. Intravenous immunoglobulin is not effective in the management of platelet refractoriness.

Prevention of Transfusion- Associated GVHD

While recipient anti-donor responses are usually able to eliminate donor leukocytes, settings in which the recipient anti-donor responses are impaired permits unabated donor anti-recipient responses (which can occur in the HCT setting), resulting in transfusion-associated graft-versus-host disease (TA-GVHD)[55]. There are 2 standard complimentary approaches to reduce the risk of TA-GVHD: 1) Leukoreduction, and 2) Irradiation of the blood product.

The ability to deplete leukocytes from the blood product reduces the incidence of TA-GVHD[56,57]. Blood products from the Canadian Blood Services are universally leukodepleted, a practice that is supported by randomized trial data[54,58,59]. However, leukodepletion may not be fully protective[60]. The results of *in vitro* studies led to the adoption of a dose of 25–30 Gy γ-irradiation as a standard for the inactivation of T lymphocytes in blood products[61,62]. This led to routine irradiation of blood products, especially in settings in where patients are at risk for developing TA-GVHD. Reports from Japan (population at higher risk of TA-GVHD) indicate that no further cases of TA-GVHD were detected once universal irradiation was implemented[63,64].

It should be kept in mind that prolonged storage of pre-irradiated red blood cells has been associated with high potassium levels, in vitro hemolysis and decreased post-transfusion recovery[65]. Irradiation of red blood cell products should occur as near as possible to the time of transfusion, and no longer than 14 days prior to transfusion. This is particularly important in infants, where life threatening hyperkalemia can occur following transfusion of irradiated RBC. In patients at risk of hyperkalemia, it is recommended red cells be transfused within 24 hours of irradiation. If freshly irradiated RBC are not available, the product should undergo centrifugation and supernatant plasma removal prior to transfusion.

There are other laboratory techniques such as psoralen/UVA light treatment (primary purpose of pathogen reduction) that can inactivate T cells in blood products and potentially reduce the risk of transfusion-associated graft-versus-host disease (TA-GVHD), but this has not been routinely adopted by Canadian Blood Services. Importantly, pathogen reduced platelets increase the risk of platelet refractoriness and the platelet transfusion requirement[66].

Prevention of CMV Transmission

Cytomegalovirus (CMV) infection continues to be a serious complication following HSCT[67,68]. Most CMV infections may be due to a reactivation of the virus from a previous infection rather than due to the acquisition of a new strain[69]. However, CMV antibody-negative persons are at risk for developing a transfusion-transmitted *de novo* CMV infection. There are 2 standard complimentary approaches to reduce this risk: 1) Use of CMV-antibody negative blood, and 2) leukoreduced components.

As discussed, blood products from the Canadian Blood Services undergo universal leukoreduction. This practice is further supported by studies demonstrating that leukoreduced components are as effective as antibody-negative components in the prevention of transfusion-transmitted CMV infection[70-73]. However, early consensus guidelines supported the use of both leukoreduction and provision of CMV-antibody negative blood in at risk population (belt and suspenders approach)[74,75].

However, this practice has been challenged[71,76]. For instance, a single Canadian HCT institution before-after study reviewed 186 patients who were CMV negative and received an allogeneic HCT from a CMV-negative donor between October 1, 1999 and June 30, 2012[77]. Of these, 89 patients received an HCT before January 2007, during the time when patients received leukoreduced and CMV-negative blood products. Seventy-seven patients received an HCT after this time, receiving only leukoreduced blood products. CMV viremia was detected in 3 patients who received CMV-negative leukoreduced blood products (3.37%) and in 1 patient who received only leukoreduced blood products (1.30%, P = .6244). Of the patients who developed CMV viremia, 2 developed suspected CMV disease. Both of these patients were transfused with CMV-negative blood products.

This suggests that in the era of universal leukoreduction of blood products, that testing for CMV-negative blood products is not needed for HCT recipients. Indeed, the Canadian National Advisory Committee on Blood and Blood Products (NAC) subcommittee has deemed that CMV-safe leukoreduced cellular blood products are equivalent in safety to CMV-seronegative and leukoreduced blood products for transfusion in all patient populations except for intrauterine transfusion.

Transfusion in ABO- or RhD-Incompatible HCT

Please refer to Chapter entitled ABO Incompatible Graft and Recipient in the Alberta Bone Marrow and Blood Cell Transplant Program: BMT Standard Practice Manual.

Growth Factor Support

Granulocyte colony-stimulating factor:

The use of G-CSFs post-HCT is supported by decreased time to engraftment ranging between 1–6 days, with some studies demonstrating savings in duration of hospitalization, infections and survival[78]. The timing of administration of G-CSF has been the subject of investigation – early or delayed approaches. Such studies have not demonstrated any clear disadvantage of delaying G-CSF for up to 10 days post-HCT in the autologous setting[79-92]. G-CSF has been used in the allogeneic setting,

but there is theoretical concern that T cell reconstitution may be impaired by G-CSF, and GVHD may be induced or worsen with its use. Although G-CSF is often administered post-HCT to accelerate neutrophil recovery, there appears to be no long-term benefit or disadvantage of giving G-CSF after HCT to promote hematopoietic recovery[93].

Taken together, it is reasonable to provide routine post-autologous HCT G-CSF starting on Day 7 (until ANC >0.5) to accelerate neutrophil recovery which in principle may improve infectious complications and assist with earlier hospital discharge. We do not recommend the routine use of G-CSF in the allogeneic setting. This recommendation does not apply to most pediatric non-malignant conditions.

Erythropoiesis-stimulating agents:

The use of erythropoiesis-stimulating agents to manage anemia raises hemoglobin levels, reduces the need for RBC transfusions, but increases the risk of thromboembolic events[94]. In the setting of HCT, there have been 6 randomized studies addressing the utility of erythropoietin. The most recent study, which might inform current practice, was conducted by Jaspers et. al in 2014[95]. The authors randomized 131 patients between no treatment (control arm) or erythropoietin at 500 U/kg per week. They demonstrate that erythropoietin results in a higher proportion (63.1%) of hemoglobin ≥13 g/dL before Day 126 as compared with 8.1% in the control arm. Additionally, Hb levels were higher and transfusion requirements decreased in the erythropoietin arm. There was no difference in rates of thromboembolic events or other complications between the 2 arms. There was no impact on long term survival[96].

The following table from Christou et al. summarizes and provides a scoping review of the 6 randomized trials evaluating the use of erythropoietin post-HCT[1].

Table 4: 6 RCTs evaluating the use of erythropoietin

Reference	Year of Publication	Sample Size	EPO treatment arm	Control arm	Hb level	Bleeding	Days to PLT engraftment	Days to neutrophil engraftment	RBC utilization	PLT utilization	Hospital LOS	GVHD	Infection	Transfusion reaction	Overall survival
Steegmann et al.	1992	27	100 U/kg/day IV Day 0-Day 7 then 150 U/kg/day IV Day7-Day30	No injection	↔		↓	↔	↓	↓					↔
Link et al.	1994	329	150 U/kg/day IV continuous infusion Day 0-Day 42 or transfusion independence	Placebo		↔	↔	↔	↓	↔		↔			
Klaesson et al.	1994	50	200 U/kg/day IV Day 0-Day 28, then 2X/week IV Day 29-Day 48	Placebo	↑	↔	↔	↔	↓	↔	↔		↔		↔
Biggs et al.	1995	91	300 U/kg/day IV 3x/week Day 0- Day 42	No injection	↑		↔	↔	↔	↔	↔	↔	↔		↔
Vanstraelen et al.	2006	60	500 U/kg/day SC weekly starting at Day 0 or Day 30	No injection	↑		↔	↔	↓						
Jaspers et al.	2014	131	500 U/kg SC weekly starting at Day 0 or Day 28	No injection	↑		↔	↔	↓			↔	↔		↔

* arrows indicate whether any significant increase (↑), decrease (↓), or no change (↔) was reported for the outcomes listed in the table. LOS=Length of stay; SC= subcutaneously

Taken together, the use of erythropoietin post-HCT can improve hemoglobin levels and assist with red cell utilization. However, the absence of quality of life data from the available trials tempers its use. Moreover, enthusiasm for the use of erythropoietin in the HCT setting has waned, especially with the recognition of serious adverse events in several patient populations[97,98].

Thrombopoietin receptor agonists:

Prolonged thrombocytopenia after HCT is a strong risk factor for transplantation-related mortality, and efforts to improve platelets may lead to improve post-HCT outcomes and decrease platelet utilization[99,100]. The literature categorizes these patients into 2 types—prolonged isolated thrombocytopenia (PIT) and secondary failure of platelet recovery (SFPR)—according to the timeline of presentation.

Prolonged isolated thrombocytopenia (PIT) can be attributed to:

1. Delayed platelet engraftment, often defined as persistent severe thrombocytopenia with a platelet count <20 × 109/L beyond 35 days after HSCT,
2. Primary graft failure, defined as failure to achieve initial engraftment by day + 28 post-HSCT or
3. Poor graft function, usually defined as persistent thrombocytopenia (platelet count ≤20 × 109/L) with neutropenia (absolute neutrophil count ANC ≤.5 × 10^9/L) and/or hemoglobin <7

g/dL for at least 3 consecutive days by 28 days after HSCT, with transfusion dependence associated with hypoplastic-aplastic bone marrow and complete donor chimerism without concurrent GVHD or disease relapse.

Secondary failure of platelet recovery (SFPR) refers to thrombocytopenia that develops after initial platelet engraftment and is not due to graft rejection or relapse. SFPR is defined as a decline in platelet count of <20 × 10^9/L for 7 consecutive days or requiring transfusion support after achieving a sustained platelet count ≥50 × 10^9/L without transfusion for 7 consecutive days after HCT[101].

Thrombopoietin receptor agonists (TPOs) are novel treatments for patients with chronic ITP aimed at increasing platelet production through interactions with the TPO receptor on megakaryocytes[102]. Beyond potential improvements in platelet counts, there is laboratory and clinical evidence to support the use of TPO to overcome depletion of HSCs and progenitor cells in aplastic anemia[103]. Invariably, these observations and experiences have led to the use of TPOs in patients with either persistent thrombocytopenia or general hypoplasia post-HCT[104,105].

A recent systematic review comprising of 25 reports (case series and reports) suggests that patients with prolonged post-HCT thrombocytopenia may respond to both eltrombopag (overall response rate [ORR], 70%) and romiplostim (ORR, 82%), with no evidence of serious adverse effects[106]. The authors note that most of the studies reported initiating treatment at a lower dosage range and escalating the dosage based on the response to treatment. Patients were treated for variable durations, ranging from 2 weeks to 1 year, depending on the severity of thrombocytopenia and the response to treatment.

Taken together, it is reasonable to initiate the use of eltrombopag starting at 25 to 50mg, increasing to 150mg. Start at a maximum dose of 25 mg daily in patients of East Asian ethnicity (Pediatric dosing: initiate at 25 mg/day, increase weekly by 25 mg to a maximum of 75 mg daily based on platelet count. Not licensed for patients under 1 year of age.) for prolonged isolated thrombocytopenia (PIT) or secondary failure of platelet recovery. It is reasonable to gradually wean off TPO over weeks once stable hematic parameters are achieved.

Cytopenias after CAR-T cell therapy

Chimeric antigen receptor T-cell therapy (CAR-T) is increasingly used in practice for the management for B cell lymphoma, B-cell ALL and symptomatic myeloma. Cytopenia in ≥1 cell lineage often occurs, and the following table summarizes the prevalence of cytopenias in Phase 3 studies.

Table 5: RCTs showing the effectiveness of Car T cell treatment in multiple myeloma, lymphoma, and leukemia.

Disease	Ref	Year of Pub	Sample Size	Product	Anemia	Thrombocytopenia	Neutropenia	Leukopenia	Comments
Myeloma	Berdeja et al.	2021	113 (enrolled); 97 (infused cohort)	Ciltacabtageneautoleucel (Carvykti)	Grade 3-4: 68% after day 1 of cilta-cel	Grade 3-4: after day 1 of cilta-cel →reduced to grade 2 or lower by day 30 in (59%)	Grade 3-4: 95% after day 1 of cilta-cel →reduced to grade 2 or lower by day 30 in (70%)	Grade 3-4: 61% after day 1 of cilta-cel	Pts received supportive measures to treat cytokine release syndrome or associated symptoms, most commonly tocilizumab, corticosteroids and anakinra
	Munshi et al.	2021	140 (enrolled); 129 (infused cohort)	Idecabtagene vicleucel (Abecma)	Grade 3-4: 60% within 8 weeks after infusion	Grade 3-4: 52% within 8 weeks after infusion →recovery to grade 2 or lower occurred at a median of 2.1 months	Grade 3-4: 89% within 8 weeks after infusion →recovery to Grade 2 or lower occurred at a median of 1.9 months	Grade 3-4: 39% within 8 weeks after infusion	Pts received supportive measures to treat cytokine release syndrome or associated symptoms, most commonly tocilizumab and corticosteroids
Lymphoma	Neelapu et al.	2017	111 (total cohort); 101 (infused cohort)	Axicabtagene cilo-leucel (Yescarta)	Grade 3-4: 43% (unspecified duration) →at 3 months, grade 3 or higher was reported (3%)	Grade 3-4: 38% (unspecified duration) →at 3 months, grade 3 or higher was reported (7%)	Grade 3-4: 78% (unspecified duration) →at 3 months, grade 3 or higher was reported (11%)	Grade 3-4: 29% (unspecified duration)	Pts received tocilizumab and glucocorticoids for supportive measures to treat cytokine release syndrome, neurologic events, or both.
	Schuster et al.	2022	167 (total cohort); 115 (infused cohort)	Tisagenlecleu-cel (Kymriah)	Grade 3-4: 39% after infusion (unspecified duration)	Grade 3-4: 28% after infusion (unspecified duration) →unresolved grade 3-4 at day 28 in 41% of pts →unresolved grade 3-4 at 3 months in 38% of pts	Grade 3-4: 33% after infusion (unspecified duration) →unresolved grade 3-4 at day 28 in 24% of pts →At 3 months, no patients had unresolved grade 3-4	Grade 3-4: 31% after infusion (unspecific duration)	17% of pts received systemic anti-cytokine therapy, 16% received tocilizumab, and 10% received corticosteroids
	Abramson et al.	2020	344 (total cohort); 269 (infused cohort)	Lisocabtagene maraleucel (breyanzi)	Grade 3-4: 37% after 29 days →after 90 days recovery to grade 2 occurred in 82%	Grade 3-4: 27% after 29 days →after 90 days, recovery to grade 2 occurred in 62 %	Grade 3-4: 60% after 29 days →After 90 days, recovery to grade 2 occurred in 84%	Grade 3-4: 14% after 29 days	Pts received tocilizumab, corticosteroids, vasopressors, siltuximab, and anakinra for supportive measure of cytokine release
Leukemia	Maude et al.	2018	75 (infused cohort)	Tisacel (Kymriah)	Grade 3-4: 4% (unspecified duration)	Grade 3-4: 7% (unspecified duration) →By last assessment, 71% of pts has Grade 2 or lower	Grade 3-4: 11% (unspecified duration) →By last assessment, 80% of patients has Grade 2 or lower	Grade 3-4: 9% (unspecified duration)	Tocilizumab was given to pts experiencing cytokine release syndrome
	Shah et al.	2021	54 (enrolled); 45 (infused cohort)	Brexu-cel (Tecartus)	Grade 3-4: 49% with median duration of 9 days →At day 30, grade 3 or higher was reported by 7% of pts	Grade 3-4: 30% with median duration of 9 days →At day 30, grade 3 or higher was reported by 18% of pts	Grade 3-4: 27% with median duration of 9 days →At day 30, grade 3 or higher was reported by 25% of pts	Grade 3-4: 23% with median duration of 9 days	Steroids and tocilizumab were used fir cytokine release syndrome and neurologic events

Table 6:

Lineage	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils	<LLN to 1,500/mm^3	1,000-1,500/mm^3	500-1,000/mm^3	<500/mm^3
Platelets	<LLN to 75,000/mm^3	50,000-75,000/mm^3	25,000-50,000/mm^3	<25,000/mm^3
Hemoglobin	<LLN to 10 g/dL	8.0-10.0 g/dL	<8.0 g/dL	Life-threatening consequences
Lymphocytes (total)	<LLN to 800/mm^3	500-800/mm^3	200-500/mm^3	<200/mm^3

Neutropenia, thrombocytopenia, anemia, and lymphopenia were determined from the complete blood count after chemotherapy, and the lowest count was used for calculating grade of toxicity. All patients with sustained fever of >100.4ºF in the midst of chemotherapy-induced grade 4 neutropenia received a first course of IV antibiotics in hospital. Taken from National Cancer Institute Common terminology Criteria for Adverse Events (NCI CTCAE, version 3.0). LLN, lower limit of normal.

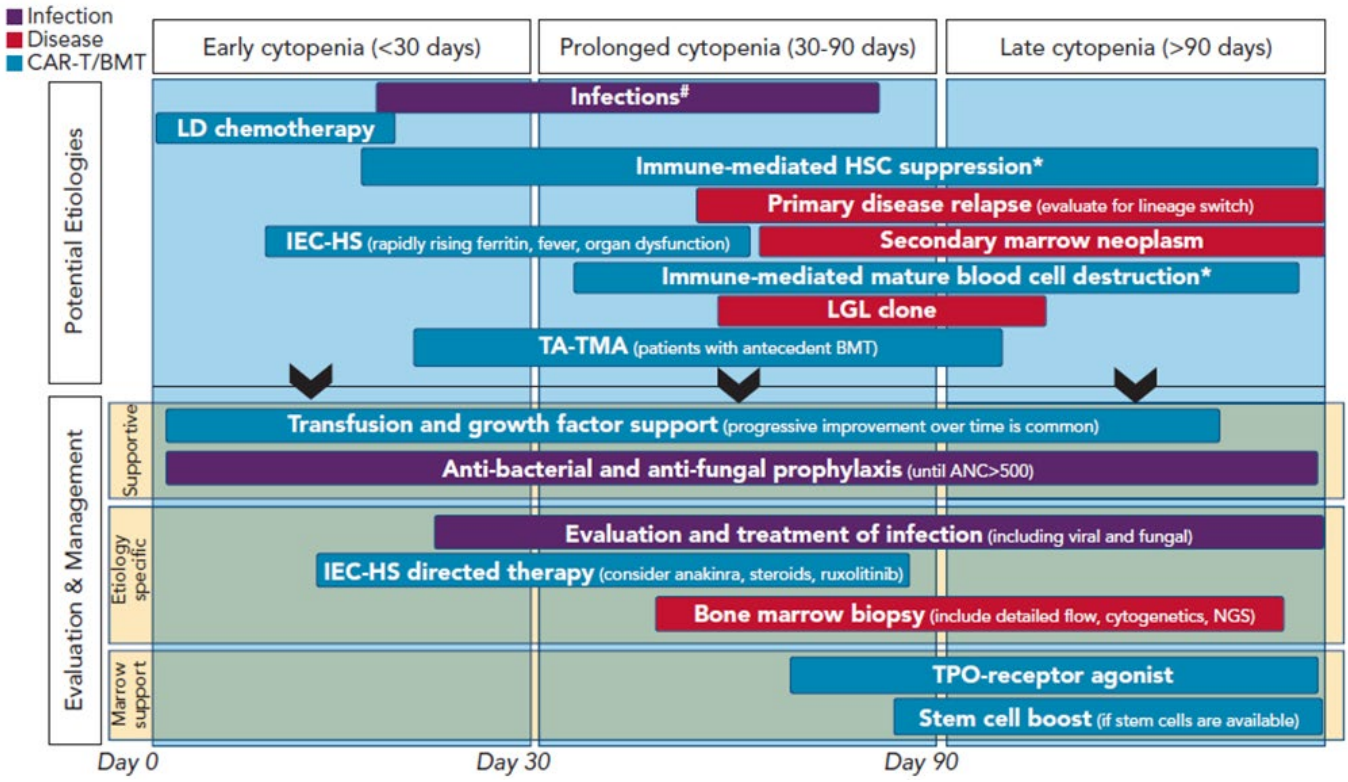
Prediction of Cytopenias after CAR-T

Rejeski et al. created the CAR-HEMATOTOX model, which included markers associated with hematopoietic reserve (eg, platelet count, hemoglobin, and ANC) and baseline inflammation (eg, C-reactive protein and ferritin)[115]. A high CAR-HEMATOTOX score resulted in a longer duration of neutropenia (12 vs 5.5 days; P < .001) and a higher incidence of severe thrombocytopenia (87% vs 34%; P < .001) and anemia (96% vs 40%; P < .001). Additionally, high CAR-HEMATOTOX score patients more frequently developed severe infections (40% vs 8%, p<0.0001)—particularly severe bacterial infections (27% vs 0.9%, p<0.0001). Further, they experienced worse median progression-free (3.4 vs 12.6 months) and overall survival (9.1 months vs not-reached), and were hospitalized longer (median 20 vs 16 days)[116].

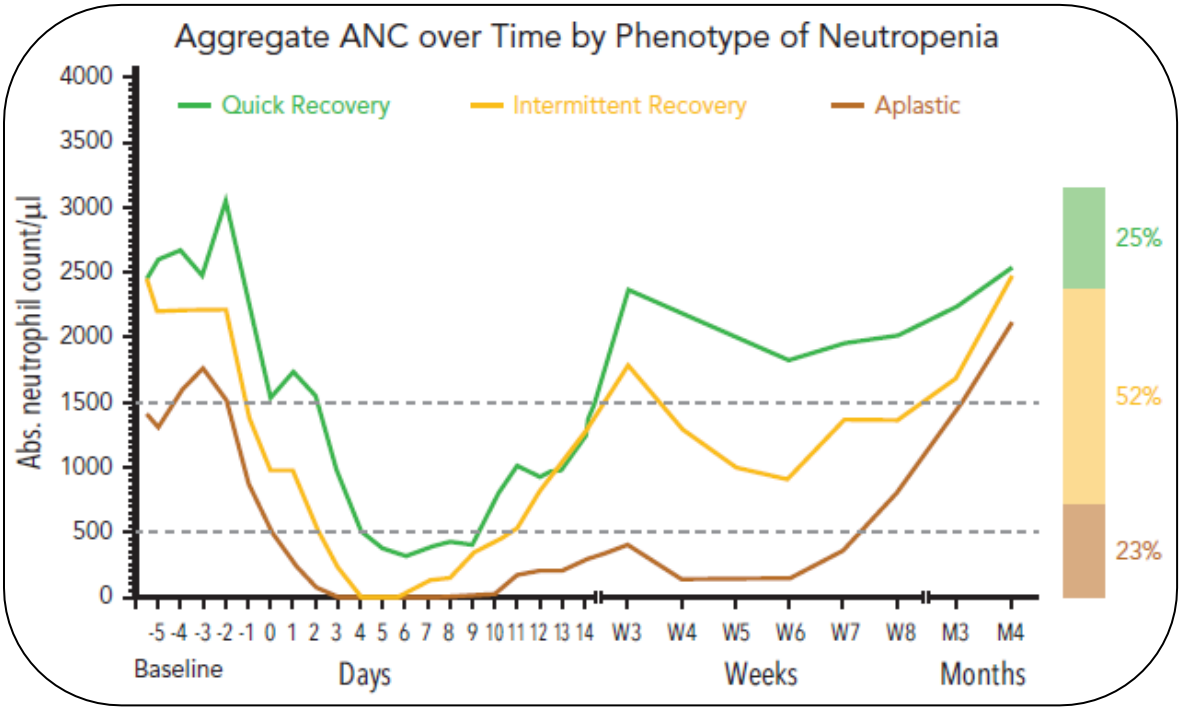
Table 7:

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	>175,000/ µl	75,000-175,000/ µl	<75,000/ µl
Absoulte Neutrophil Count (ANC)	>1200/µl	<1200/ µl	-
Hemoglobin	>9.0 g/ dl	< 9.0 g/dl	-
C-reactive protein (CRP)	<3.0 mg/ dl	> 3.0 mg/dl	-
Ferritin	<650 ng/ ml	650-2000 ng/ ml	>2000 ng/ ml
Low: 0-1	High: ≥2		

The literature often describes cytopenias based on timing: 1) early (<30 days after infusion), 2) prolonged (30-90 days after infusion), and 3) late (>90 days after infusion), suggesting potential different (perhaps overlapping) mechanisms and different management strategies. The following figure summarizes these concepts[117]:



Patterns of ANC recovery[115]



Considerations - Early Cytopenias (<30 days)[117]

1. Mechanism – presumed LD chemotherapy related.
2. Supportive Transfusion as per standard transplant practice (see above).
3. Evaluation and management of infections including viral and fungal.
4. Consider G-CSF if ANC not recovered by Day 7-10
    a. Data inconclusive if G-CSF worsens CRS and ICANS
    b. Avoid in the presence of active CRS.

Considerations - Prolonged Cytopenias (>30 and <90 days)[117]

1. Mechanism – unclear/complex.? Immune driven suppression of the HSC and marrow microenvironment changes.
    a. Severe cytopenia associated with peak levels of inflammatory cytokines.
    b. Prolonged cytopenia associated with Grade 3 and 4 CRS and ICANS
    c. Preceding cytopenia associated with prolonged cytopenias (marrow reserve and residual disease)
2. Evaluation and management of infections including viral and fungal.
3. Consider immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS).
    a. Resolved CRS, but rapid increase in Ferritin levels.
    b. Anakinra and high dose steroids
4. Growth Factor use – G-CSF and Eltrombopag
    a. Transient responses (ANC) are common and suggest gradual improvement over weeks and decreased dependence on G-CSF
    b. Lack of responsiveness should prompt bone marrow biopsy.
    c. Eltrombopag for transfusion dependence (red cells and platelets)

Considerations - Late Cytopenias (>90 days)[117]

1. Avoidance of marrow suppression medications
2. Marrow evaluation -? hypoplasia/dysplasia/CHIP/secondary cancers. Does CAR-T inflammation promote therapy related myeloid cancers?
3. Autologous stem cell boost
    a. Unclear if a rainy-day harvest should be done for this possibility
    b. ?CD34 selection to avoid tumor contamination

References

1. Christou G, Iyengar A, Shorr R, et al. Optimal transfusion practices after allogeneic hematopoietic cell transplantation: a systematic scoping review of evidence from randomized controlled trials. *Transfusion.* 2016;56(10):2607-2614.
2. Estcourt LJ, Birchall J, Allard S, et al. Guidelines for the use of platelet transfusions. *British Journal of Haematology.* 2017;176(3):365-394.
3. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2015;162(3):205-213.
4. Schiffer CA, Bohlke K, Delaney M, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36(3):283-299.
5. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. *JAMA.* 2016;316(19):2025-2035.
6. Nahirniak S, Slichter SJ, Tanael S, et al. Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia. *Transfus Med Rev.* 2015;29(1):3-13.
7. Jones JM, Sapiano MRP, Savinkina AA, et al. Slowing decline in blood collection and transfusion in the United States – 2017. *Transfusion.* 2020;60(S2):S1-S9.
8. Tinegate H, Pendry K, Murphy M, et al. Where do all the red blood cells (RBCs) go? Results of a survey of RBC use in England and North Wales in 2014. *Transfusion.* 2016;56(1):139-145.
9. Xenocostas A, Yee A, Wong CJ, et al. RBC transfusion requirements after allogeneic marrow transplantation: impact of the before-transplant Hb level on transfusion and early survival. *Transfusion.* 2003;43(3):373-382.
10. Kekre N, Christou G, Mallick R, et al. Factors associated with the avoidance of red blood cell transfusion after hematopoietic stem cell transplantation. *Transfusion.* 2012;52(9):2049-2054.
11. Konuma T, Oiwa-Monna M, Mizusawa M, et al. Red blood cell transfusion burden by day 30 predicts mortality in adults after single-unit cord blood transplantation. *Bone Marrow Transplant.* 2019;54(11):1836-1846.
12. Hosoba S, Waller EK, Shenvi N, et al. Peritransplantation Red Blood Cell Transfusion Is Associated with Increased Risk of Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2018;24(5):973-982.
13. Vande Vusse LK, Madtes DK, Guthrie KA, Gernsheimer TB, Curtis JR, Watkins TR. The association between red blood cell and platelet transfusion and subsequently developing idiopathic pneumonia syndrome after hematopoietic stem cell transplantation. *Transfusion.* 2014;54(4):1071-1080.
14. Christou G, Kekre N, Petrcich W, et al. Impact of platelet transfusion on toxicity and mortality after hematopoietic progenitor cell transplantation. *Transfusion.* 2015;55(2):253-258.
15. Services CB. Circular of Information. https://www.blood.ca/en/hospital-services/products/component-types/circular-information. Published 2020. Accessed 08 July 2020, 2020.
16. Estcourt LJ, Malouf R, Trivella M, Fergusson DA, Hopewell S, Murphy MF. Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support. *Cochrane Database of Systematic Reviews.* 2017(1).
17. Tay J, Allan DS, Chatelain E, et al. Liberal Versus Restrictive Red Blood Cell Transfusion Thresholds in Hematopoietic Cell Transplantation: A Randomized, Open Label, Phase III, Noninferiority Trial. *J Clin Oncol.* 2020;38(13):1463-1473.
18. Robitaille N, Lacroix J, Alexandrov L, et al. Excess of veno-occlusive disease in a randomized clinical trial on a higher trigger for red blood cell transfusion after bone marrow transplantation: a canadian blood and marrow transplant group trial. *Biol Blood Marrow Transplant.* 2013;19(3):468-473.
19. Hematology ASo. Choosing Wisely https://www.hematology.org/education/clinicians/guidelines-and-quality-care/choosing-wisely. Published 2020. Accessed 08 July 2020, 2020.
20. Leahy MF, Trentino KM, May C, Swain SG, Chuah H, Farmer SL. Blood use in patients receiving intensive chemotherapy for acute leukemia or hematopoietic stem cell transplantation: the impact of a health system-wide patient blood management program. *Transfusion.* 2017;57(9):2189-2196.
21. Berger MD, Gerber B, Arn K, Senn O, Schanz U, Stussi G. Significant reduction of red blood cell transfusion requirements by changing from a double-unit to a single-unit transfusion policy in patients receiving intensive chemotherapy or stem cell transplantation. *Haematologica.* 2012;97(1):116-122.
22. Bowman Z, Fei N, Ahn J, et al. Single versus double-unit transfusion: Safety and efficacy for patients with hematologic malignancies. *European journal of haematology.* 2019;102(5):383-388.

23. Gastecki K, Shanley R, Welbig J, Cohn C, Brunstein CG. Red blood cell product utilization in patients undergoing allogeneic stem cell transplantation. *Transfusion.* 2019;59(7):2301-2307.
24. Sut C, Tariket S, Chou ML, et al. Duration of red blood cell storage and inflammatory marker generation. *Blood Transfus.* 2017;15(2):145-152.
25. Shah A, Brunskill SJ, Desborough MJR, Doree C, Trivella M, Stanworth SJ. Transfusion of red blood cells stored for shorter versus longer duration for all conditions. *Cochrane Database of Systematic Reviews.* 2018(12).
26. Lelubre C, Vincent JL. Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: a systematic review. *Crit Care.* 2013;17(2):R66.
27. Aubron C, Flint AWJ, Ozier Y, McQuilten Z. Platelet storage duration and its clinical and transfusion outcomes: a systematic review. *Critical Care.* 2018;22(1):185.
28. Trivella M, Stanworth SJ, Brunskill S, Dutton P, Altman DG. Can we be certain that storage duration of transfused red blood cells does not affect patient outcomes? *BMJ.* 2019;365:l2320.
29. Chai-Adisaksopha C, Alexander PE, Guyatt G, et al. Mortality outcomes in patients transfused with fresher versus older red blood cells: a meta-analysis. *Vox Sang.* 2017;112(3):268-278.
30. Kekre N, Mallick R, Allan D, Tinmouth A, Tay J. The impact of prolonged storage of red blood cells on cancer survival. *PLoS One.* 2013;8(7):e68820.
31. Kekre N, Chou A, Tokessey M, et al. Storage time of transfused red blood cells and impact on clinical outcomes in hematopoietic stem cell transplantation. *Transfusion.* 2011;51(11):2488-2494.
32. Heckman KD, Weiner GJ, Davis CS, Strauss RG, Jones MP, Burns CP. Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/microL versus 20,000/microL. *Journal of Clinical Oncology.* 1997;15(3):1143-1149.
33. Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. *N Engl J Med.* 1997;337(26):1870-1875.
34. Zumberg MS, del Rosario ML, Nejame CF, et al. A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10,000/L versus 20,000/microL trigger. *Biol Blood Marrow Transplant.* 2002;8(10):569-576.
35. Diedrich B, Remberger M, Shanwell A, Svahn BM, Ringden O. A prospective randomized trial of a prophylactic platelet transfusion trigger of 10 x 10(9) per L versus 30 x 10(9) per L in allogeneic hematopoietic progenitor cell transplant recipients. *Transfusion.* 2005;45(7):1064-1072.
36. Crighton GL, Estcourt LJ, Wood EM, Trivella M, Doree C, Stanworth S. A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. *Cochrane Database Syst Rev.* 2015(9):CD010981.
37. Kumar A, Mhaskar R, Grossman BJ, et al. Platelet transfusion: a systematic review of the clinical evidence. *Transfusion.* 2015;55(5):1116-1127; quiz 1115.
38. Committee TCG. Platelet Transfusion Thresholds. http://www.c17.ca/index.php?cID=86. Published 2011. Accessed 20 October 2020, 2020.
39. Roy AJ, Jaffe N, Djerassi I. Prophylactic platelet transfusions in children with acute leukemia: a dose response study. *Transfusion.* 1973;13(5):283-290.
40. Heddle NM, Cook RJ, Tinmouth A, et al. A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. *Blood.* 2009;113(7):1564-1573.
41. Tinmouth A, Tannock IF, Crump M, et al. Low-dose prophylactic platelet transfusions in recipients of an autologous peripheral blood progenitor cell transplant and patients with acute leukemia: a randomized controlled trial with a sequential Bayesian design. *Transfusion.* 2004;44(12):1711-1719.
42. Sensebe L, Giraudeau B, Bardiaux L, et al. The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: results of a prospective, randomized, open, blinded end point (PROBE) study. *Blood.* 2005;105(2):862-864.
43. Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med.* 2010;362(7):600-613.
44. Estcourt LJ, Stanworth S, Doree C, et al. Different doses of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. *Cochrane Database Syst Rev.* 2015(10):CD010984.
45. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med.* 2013;368(19):1771-1780.

46. Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet.* 2012;380(9850):1309-1316.
47. Avvisati G, ten Cate JW, Buller HR, Mandelli F. Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia. *Lancet.* 1989;2(8655):122-124.
48. Shpilberg O, Blumenthal R, Sofer O, et al. A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukemia. *Leuk Lymphoma.* 1995;19(1-2):141-144.
49. Estcourt LJ, McQuilten Z, Powter G, et al. The TREATT Trial (TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia): safety and efficacy of tranexamic acid in patients with haematological malignancies with severe thrombocytopenia: study protocol for a double-blind randomised controlled trial. *Trials.* 2019;20(1):592.
50. Tay J, Allan D, Beattie S, et al. Rationale and design of platelet transfusions in haematopoietic stem cell transplantation: the PATH pilot study. *BMJ Open.* 2016;6(10):e013483.
51. Murphy MF. Managing the platelet refractory patient. *ISBT Science Series.* 2014;9(1):234-238.
52. Stanworth SJ, Navarrete C, Estcourt L, Marsh J. Platelet refractoriness--practical approaches and ongoing dilemmas in patient management. *Br J Haematol.* 2015;171(3):297-305.
53. Norfolk D. Transfusion in haemato-oncology. In: Norfolk D, ed. *Handbook of Transfusion Medicine.* 5th ed.: TSO; 2013.
54. Bianchi M, Vaglio S, Pupella S, et al. Leucoreduction of blood components: an effective way to increase blood safety? *Blood Transfus.* 2016;14(2):214-227.
55. Prokopchuk-Gauk OS, Z. CMV Seronegative, Irradiated and Washed Blood Components. In: Clarke GC, S, ed. *Clinical Guide to Transfusion.* Vol 2020. Canadian Blood Services; 2017.
56. Hayashi H, Nishiuchi T, Tamura H, Takeda K. Transfusion-associated graft-versus-host disease caused by leukocyte-filtered stored blood. *Anesthesiology.* 1993;79(6):1419-1421.
57. Stainsby D, Jones H, Asher D, et al. Serious hazards of transfusion: a decade of hemovigilance in the UK. *Transfus Med Rev.* 2006;20(4):273-282.
58. Dzik WH, Anderson JK, O'Neill EM, Assmann SF, Kalish LA, Stowell CP. A prospective, randomized clinical trial of universal WBC reduction. *Transfusion.* 2002;42(9):1114-1122.
59. Fergusson D, Khanna MP, Tinmouth A, Hebert PC. Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials. *Can J Anaesth.* 2004;51(5):417-424.
60. Akahoshi M, Takanashi M, Masuda M, et al. A case of transfusion-associated graft-versus-host disease not prevented by white cell-reduction filters. *Transfusion.* 1992;32(2):169-172.
61. Luban NL, Drothler D, Moroff G, Quinones R. Irradiation of platelet components: inhibition of lymphocyte proliferation assessed by limiting-dilution analysis. *Transfusion.* 2000;40(3):348-352.
62. Pelszynski MM, Moroff G, Luban NL, Taylor BJ, Quinones RR. Effect of gamma irradiation of red blood cell units on T-cell inactivation as assessed by limiting dilution analysis: implications for preventing transfusion-associated graft-versus-host disease. *Blood.* 1994;83(6):1683-1689.
63. Uchida S, Tadokoro K, Takahashi M, Yahagi H, Satake M, Juji T. Analysis of 66 patients definitive with transfusion-associated graft-versus-host disease and the effect of universal irradiation of blood. *Transfus Med.* 2013;23(6):416-422.
64. Otsubo H, Yamaguchi K. Current risks in blood transfusion in Japan. *Jpn J Infect Dis.* 2008;61(6):427-433.
65. Serrano K, Chen D, Hansen AL, et al. The effect of timing of gamma-irradiation on hemolysis and potassium release in leukoreduced red cell concentrates stored in SAGM. *Vox Sang.* 2014;106(4):379-381.
66. Estcourt LJ, Malouf R, Hopewell S, et al. Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database of Systematic Reviews.* 2017(7).
67. Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis.* 2019;19(8):e260-e272.
68. El Chaer F, Shah DP, Chemaly RF. How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients. *Blood.* 2016;128(23):2624-2636.
69. Marchesi F, Mengarelli A, Giannotti F, et al. High incidence of post-transplant cytomegalovirus reactivations in myeloma patients undergoing autologous stem cell transplantation after treatment with bortezomib-based regimens: a survey from the Rome transplant network. *Transpl Infect Dis.* 2014;16(1):158-164.
70. Bowden RA, Slichter SJ, Sayers M, et al. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. *Blood.* 1995;86(9):3598-3603.

71. Mainou M, Alahdab F, Tobian AAR, et al. Reducing the risk of transfusion-transmitted cytomegalovirus infection: a systematic review and meta-analysis. *Transfusion.* 2016;56(6pt2):1569-1580.
72. Nash T, Hoffmann S, Butch S, Davenport R, Cooling L. Safety of leukoreduced, cytomegalovirus (CMV)-untested components in CMV-negative allogeneic human progenitor cell transplant recipients. *Transfusion.* 2012;52(10):2270-2272.
73. Thiele T, Kruger W, Zimmermann K, et al. Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME). *Transfusion.* 2011;51(12):2620-2626.
74. Laupacis A, Brown J, Costello B, et al. Prevention of posttransfusion CMV in the era of universal WBC reduction: a consensus statement. *Transfusion.* 2001;41(4):560-569.
75. Blajchman MA, Goldman M, Freedman JJ, Sher GD. Proceedings of a consensus conference: prevention of post-transfusion CMV in the era of universal leukoreduction. *Transfus Med Rev.* 2001;15(1):1-20.
76. Heddle NM, Boeckh M, Grossman B, et al. AABB Committee Report: reducing transfusion-transmitted cytomegalovirus infections. *Transfusion.* 2016;56(6 Pt 2):1581-1587.
77. Kekre N, Tokessy M, Mallick R, et al. Is cytomegalovirus testing of blood products still needed for hematopoietic stem cell transplant recipients in the era of universal leukoreduction? *Biol Blood Marrow Transplant.* 2013;19(12):1719-1724.
78. Trivedi M, Martinez S, Corringham S, Medley K, Ball ED. Optimal use of G-CSF administration after hematopoietic SCT. *Bone Marrow Transplant.* 2009;43(12):895-908.
79. Demirer T, Ayli M, Dagli M, et al. Influence of post-transplant recombinant human granulocyte colony-stimulating factor administration on peritransplant morbidity in patients undergoing autologous stem cell transplantation. *Br J Haematol.* 2002;118(4):1104-1111.
80. Hornedo J, Solá C, Solano C, et al. The role of granulocyte colony-stimulating factor (G-CSF) in the post-transplant period. *Bone Marrow Transplant.* 2002;29(9):737-743.
81. Valteau-Couanet D, Faucher C, Aupérin A, et al. Cost effectiveness of day 5 G-CSF (Lenograstim) administration after PBSC transplantation: results of a SFGM-TC randomised trial. *Bone Marrow Transplant.* 2005;36(6):547-552.
82. Piccirillo N, Sica S, Laurenti L, et al. Optimal timing of G-CSF administration after CD34+ immunoselected peripheral blood progenitor cell transplantation. *Bone Marrow Transplant.* 1999;23(12):1245-1250.
83. Bolwell BJ, Pohlman B, Andresen S, et al. Delayed G-CSF after autologous progenitor cell transplantation: a prospective randomized trial. *Bone Marrow Transplant.* 1998;21(4):369-373.
84. Bence-Bruckler I, Bredeson C, Atkins H, et al. A randomized trial of granulocyte colony-stimulating factor (Neupogen) starting day 1 vs day 7 post-autologous stem cell transplantation. *Bone Marrow Transplant.* 1998;22(10):965-969.
85. de Azevedo AM, Nucci M, Maiolino A, et al. A randomized, multicenter study of G-CSF starting on day +1 vs day +5 after autologous peripheral blood progenitor cell transplantation. *Bone Marrow Transplant.* 2002;29(9):745-751.
86. Faucher C, Le Corroller AG, Chabannon C, et al. Administration of G-CSF can be delayed after transplantation of autologous G-CSF-primed blood stem cells: a randomized study. *Bone Marrow Transplant.* 1996;17(4):533-536.
87. Cox JE, Campos S, Wu J, et al. Efficacy of deferred dosing of granulocyte colony-stimulating factor in autologous hematopoietic transplantation for multiple myeloma. *Bone Marrow Transplant.* 2014;49(2):219-222.
88. Faber E, Pytlík R, Slabý J, et al. Individually determined dosing of filgrastim after autologous peripheral stem cell transplantation in patients with malignant lymphoma--results of a prospective multicentre controlled trial. *Eur J Haematol.* 2006;77(6):493-500.
89. Powles R, Smith C, Milan S, et al. Human recombinant GM-CSF in allogeneic bone-marrow transplantation for leukaemia: double-blind, placebo-controlled trial. *Lancet.* 1990;336(8728):1417-1420.
90. De Witte T, Gratwohl A, Van Der Lely N, et al. Recombinant human granulocyte-macrophage colony-stimulating factor accelerates neutrophil and monocyte recovery after allogeneic T-cell-depleted bone marrow transplantation. *Blood.* 1992;79(5):1359-1365.
91. Nemunaitis J, Rosenfeld CS, Ash R, et al. Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1995;15(6):949-954.
92. Himmelmann B, Himmelmann A, Furrer K, Halter J, Schanz U. Late G-CSF after allogeneic bone marrow or peripheral blood stem cell transplantation: a prospective controlled trial. *Bone Marrow Transplant.* 2002;30(8):491-496.
93. Khoury HJ, Loberiza FR, Jr., Ringden O, et al. Impact of posttransplantation G-CSF on outcomes of allogeneic hematopoietic stem cell transplantation. *Blood.* 2006;107(4):1712-1716.
94. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database of Systematic Reviews.* 2012(12).

95. Jaspers A, Baron F, Willems É, et al. Erythropoietin therapy after allogeneic hematopoietic cell transplantation: a prospective, randomized trial. *Blood.* 2014;124(1):33-41.
96. Jaspers A, Baron F, Servais S, et al. Erythropoietin therapy after allogeneic hematopoietic cell transplantation has no impact on long-term survival. *Am J Hematol.* 2015;90(9):E197-199.
97. Bohlius J, Bohlke K, Castelli R, et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. *Journal of Clinical Oncology.* 2019;37(15):1336-1351.
98. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *Blood advances.* 2019;3(8):1197-1210.
99. Kuzmina Z, Eder S, Bohm A, et al. Significantly worse survival of patients with NIH-defined chronic graft-versus-host disease and thrombocytopenia or progressive onset type: results of a prospective study. *Leukemia.* 2012;26(4):746-756.
100. Bolwell B, Pohlman B, Sobecks R, et al. Prognostic importance of the platelet count 100 days post allogeneic bone marrow transplant. *Bone Marrow Transplant.* 2004;33(4):419-423.
101. Bruno B, Gooley T, Sullivan KM, et al. Secondary failure of platelet recovery after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2001;7(3):154-162.
102. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. *Haematologica.* 2019;104(6):1112-1123.
103. Scheinberg P. Activity of eltrombopag in severe aplastic anemia. *Blood Adv.* 2018;2(21):3054-3062.
104. Reid R, Bennett JM, Becker M, et al. Use of eltrombopag, a thrombopoietin receptor agonist, in post-transplantation thrombocytopenia. *Am J Hematol.* 2012;87(7):743-745.
105. Tanaka T, Inamoto Y, Yamashita T, et al. Eltrombopag for Treatment of Thrombocytopenia after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant.* 2016;22(5):919-924.
106. Mahat U, Rotz SJ, Hanna R. Use of Thrombopoietin Receptor Agonists in Prolonged Thrombocytopenia after Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2020;26(3):e65-e73.
107. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021;398(10297):314–24.
108. Munshi NC, Anderson LD, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–16.
109. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene cilo- leucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-44.
110. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refrac- tory aggressive B-cell lymphomas (JULIET): a multicentre, open- label, single-arm, phase 2 study. Lancet Oncol 2021;22:1403-15.
111. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arna- son J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a mul- ticentre seamless design study. Lancet Lond Engl. 2020;396(10254): 839–52.
112. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lym- phoblastic leukemia. N Engl J Med. 2018;378(5):439–48.
113. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lym- phoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet 2021;398(10299):491–502.
114. Gernsheimer, Terry B., et al. “Effects of Tranexamic Acid Prophylaxis on Bleeding Outcomes in Hematologic Malignancy: The a-TREAT Trial.” *Blood*, vol. 136, no. Supplement 1, 2020, pp. 1–2, https://doi.org/10.1182/blood-2020-138920.
115. Rejeski, Kai, et al. “CAR-HEMATOTOX: a Model for CAR T-Cell–related Hematologic Toxicity in Relapsed/refractory Large B-Cell Lymphoma.” *Blood*, vol. 138, no. 24, 2021, pp. 2499–513, https://doi.org/10.1182/blood.2020010543.
116. Rejeski, Kai, et al. “The CAR-HEMATOTOX Risk-Stratifies Patients for Severe Infections and Disease Progression after CD19 CAR-T in R/R LBCL.” *Journal for Immunotherapy of Cancer*, vol. 10, no. 5, 2022, p. e004475–, https://doi.org/10.1136/jitc-2021-004475.
117. Jain, Tania, et al. “How I Treat Cytopenias after CAR T-Cell Therapy.” *Blood*, vol. 141, no. 20, 2023, pp. 2460–69, https://doi.org/10.1182/blood.2022017415.
118. *Platelet transfusions in Hematopoietic Stem Cell Transplantation (The PATH III Trial) (PATH)*. (n.d.). https://classic.clinicaltrials.gov/ct2/show/NCT04448184. https://classic.clinicaltrials.gov/ct2/show/NCT04448184.

Other Topics

Conditioning for HCT

Presented by: Jan Storek and R. Puckrin

Summary

- A uniform approach to pretransplant conditioning is a prerequisite for an academic HCT program wishing to produce consistent results.
- Intravenous busulfan is an integral component to many of the conditioning regimens used in Alberta. When combined with fludarabine and 4Gy TBI in a myeloablative regimen, total exposure of 15000 uM.min is targeted. When used in a myeloablative regimen without TBI, total exposure of 18000 uM.min is targeted.
- In alloHCT for hematologic malignancies, myeloablative conditioning (MAC) using fludarabine + busulfan + 4Gy TBI is preferred to reduced intensity conditioning (RIC), except for rare patients with significant hepatic or pulmonary comorbidities who are still thought to benefit from alloHCT, and except for patients with CLL, including Richter's.
- The recommended common conditioning regimens for common conditions treated by the ABMTP are listed in Table 1. Details of these regimens are included in Appendix A. For less frequently used regimens or rare conditions, see pertinent disease-specific chapters.

Introduction

High-dose chemotherapy +/- TBI is used in HCT to eliminate residual disease. In allogeneic HCT, pretransplant conditioning also induces an immunosuppressed state enabling engraftment.
High-intensity/myeloablative conditioning (MAC) with HCT has been shown to be superior to alternative treatments (e.g., consolidation chemotherapy for AML vs alloHCT, low-dose chemotherapy for lymphoma vs autoHCT). A multitude of MAC regimens have been studied and used. It is unlikely that, of commonly used MAC regimens, one is superior to others. It is prudent for centers to use regimens with which they have experience. In the 2010's and 2020's, regimens including fludarabine and an alkylator like busulfan have been increasingly used due to assumed lower toxicity and similar antileukemic activity compared to "conventional" MAC regiments like cyclophosphamide 120 mg/kg with TBI 12 Gy or cyclophosphamide 120 mg/kg with busulfan 12-16 mg/kg,[1] despite objective evidence for the assumption has been lacking.[2-4] In Alberta, fludarabine (250 mg/m2) + busulfan (~12.8 mg/kg, targeted to total busulfan AUC of 15000 uM.min) + TBI (4 Gy) has become the institutional standard for allogeneic HCT for hematologic malignancies in the 2000's/2010's. In combination with ATG-based GVHD prophylaxis, this regimen appears to result in better OS than CIBMTR average.[5]
Reduced-intensity conditioning (RIC) with allogeneic HCT is an option for patients who are thought not to tolerate MAC due to comorbidities or advanced age. For younger patients without significant comorbidities, RIC is inferior to MAC due to the advantage of lower NRM being outweighed by the disadvantage of higher relapse leading to inferior OS,[6] though similar OS has been shown in some

studies.[7,8] For the older patients or patients with comorbidities, it is clear that RIC is sufficient for durable stem cell engraftment and can lead to long-term relapse-free survival. However, whether RIC with alloHCT is superior to best available non-HCT treatment has not been documented in randomized studies. In Alberta, we prefer our MAC (Flu+Bu+TBI) to RIC, even in elderly patients, except for patients with significant hepatic or pulmonary comorbidities who are still thought to benefit from alloHCT. For the rare patients with significant comorbidities who are still thought to benefit from RIC-alloHCT, we will use fludarabine and treosulfan, because fludarabine + treosulfan (30 mg/m^2) was superior to fludarabine + busulfan (6.4 mg/kg) in a phase 3 study due to lower NRM and similar incidence of relapse.[9] In nonmalignant diseases like aplastic anemia, a lymphodepleting RIC (usually including cyclophosphamide, fludarabine, or low-dose TBI), is typically used. In addition, RIC is recommended for most patients with CLL (including Richter transformation) as of 2023 to reduce the risks of GVHD, toxicity, and NRM (see CLL chapter for more details).

Drugs Used for Conditioning

Busulfan

Busulfan is an alkylating agent believed to act through alkylation and cross-linking of DNA strands. Busulfan is cell-cycle non-specific and induces prolonged cytopenias when used alone or in combination with other agents. The liver converts busulfan to inactive metabolites, which are then excreted in the urine. Very little busulfan is excreted unchanged.

Busulfan is available as oral 2 mg tablets and as a 6 mg/mL solution for intravenous administration. When used in conditioning, the intravenous solution is preferred due to unpredictable absorption and metabolism of the oral form. When busulfan is administered for myeloablative conditioning within the ABMTP together with total body irradiation (TBI), an exposure (total AUC) of 15,000 uM.min is targeted due to the association of higher exposures with increased toxicity[10-12]. When busulfan is administered without TBI, an exposure of 18,000 uM.min is targeted[13]. Busulfan is administered at a constant rate of 80 mg/hour to facilitate PK modeling. The protocol for dosage adjustment is shown in Appendix B. If busulfan is used in a reduced intensity regimen, PK may be measured but dose adjustments are not made.

Common side effects of intravenous busulfan include nausea, vomiting, abdominal pain, anorexia, skin rash, hyperbilirubinemia (grade 3/4 in 30%), electrolyte disturbances, dizziness, headache and insomnia. Serious adverse reactions include hemorrhagic cystitis, male infertility, ovarian failure and venoocclusive disease of the liver. Seizures may also occur, and busulfan is always administered with anticonvulsant medications. The ABMTP uses lorazepam 1 mg po qid until 24 hours after the last dose of busulfan for seizure prophylaxis as other anticonvulsant medications show significant drug interactions.

Treosulfan
Treosulfan is an alkylating agent that is structurally and pharmacodynamically similar to busulfan. However, treosulfan may be less toxic than busulfan despite similar antileukemic activity. This has been documented only in the RIC setting. In a randomized study of treosulfan+fludarabine vs busulfan+fludarabine in >50-y-old patients with comorbidities who had AML or MDS, treosulfan at 30 mg/m^2 resulted in a higher 2-y OS than busulfan at 6.4 mg/kg (71% vs 56%).[9] NRM was lower in the treosulfan arm, whereas relapse incidence was similar. In this study, busulfan was administered at 0.8 mg/kg i.v. every 6 hours x 8 doses. No PK-adjustment was done.
Given the results of this study, we will adopt treosulfan for RIC. However, we will not adopt it for MAC, as it is unclear whether in combination with fludarabine and low-dose TBI, non-targeted treosulfan is superior to targeted busulfan given daily (not every 6 h as in the study). Also, the dose of treosulfan in the MAC setting is unknown. Of note, the above randomized study started with 42 mg/m^2 and was stopped due to "concerns about prolonged neutropenia and subsequent serious infectious complications in the treosulfan group".[9] On the other hand, the 42 mg/m^2 dose has been used with good results in some RIC regimens with fludarabine and 2Gy TBI.[14,15]
Treosulfan is currently non-formulary, STEDT approval is needed.

Fludarabine
Fludarabine phosphate (F-Ara-AMP) is a highly-immunosuppressive nucleoside analog with a profound impact on T-Lymphocytes. It is actively dephosphorylated to F-Ara-A in peripheral blood and rephosphorylated to F-Ara-ATP after intracellular transport. It inhibits DNA polymerase alpha, ribonucleotide reductase and DNA primase, thereby inhibiting DNA synthesis. It also interferes with RNA transcription and translation, and induces apoptosis.

Fludarabine is licensed for the treatment of chronic lymphocytic leukemia. Off-label indications include acute myelogenous leukemia, follicular lymphoma, certain T-cell lymphomas and membranous glomerulonephritis. Within the context of stem cell transplantation fludarabine is used for its immunosuppressive properties and is given in combination with high-dose busulfan or melphalan for myeloablation. Non-myeloablative regimens also feature fludarabine in combination with cyclophosphamide, TBI or lower-dose melphalan (70-90 mg/m2).

Side effects of fludarabine include nausea, vomiting, diarrhea and immune system dysfunction. The latter include incidents of autoimmune cytopenias, hemolysis, hemophagocytic syndrome and opportunistic infection (PJP, progressive multifocal leukoencephalopathy, cryptococcal infection). Herpes zoster, Cytomegalovirus and Epstein-Barr virus reactivations may occur. Overdosage may be associated with neurological effects, including blindness, coma, convulsions and death.

In the ABMTP the last dose of fludarabine is given at least 48 h prior to graft infusion, as the presence of residual fludarabine at the time of graft infusion is associated with a two-day difference in the time

to neutrophil engraftment[16]. Approximately 40% of fludarabine clearance is renal; dosage adjustments are recommended for patients with compromised renal function. Patients with normal renal function (creatinine clearance > 60 ml/minute) should receive full dose, while those with moderate renal impairment (creatinine clearance 45-60 ml/minute) should receive a 30% dose reduction. Patients with severely impaired renal function (creatinine clearance < 45 ml/minute) should receive a 70% dose reduction. This information is also contained in the BMT protocol data sheets maintained by pharmacy on Unit 57.

Etoposide (VP-16)

Etoposide is a topoisomerase-II inhibitor which acts at the premitotic phase to inhibit DNA synthesis. It is cell-cycle specific with maximum activity in the S and G2 phases of cell division. Etoposide has been licensed by the US FDA for treatment of small cell lung and testicular cancers. A long list of off-label uses includes acute myeloid and acute lymphoblastic leukemia and Hodgkin and non-Hodgkin lymphomas.

Etoposide is administered at concentrations no higher than 0.4 mg/mL as it may precipitate. It is given over 4 hours as hypotension may occur with more rapid infusions. Anaphylaxis should be treated with Solucortef 250 mg IV) +/- epinephrine 0.2-0.5 mg (0.2-0.5 mL of 1:1000 solution) subcutaneously or intramuscularly.

Common side effects of etoposide include nausea, vomiting, diarrhea and severe mucositis A rare but important side effect is anaphylaxis. Etoposide use in pretransplant conditioning is associated with severe cytopenias in 100% of treated patients.

Melphalan

Melphalan is an alkylating agent that acts primarily through the alkylation and cross-linking of DNA. It is not cell cycle dependant. Melphalan is detoxified by chemical hydrolysis in plasma. The primary metabolites are inactive and dosage adjustment is not required in renal failure.

The FDA has licensed melphalan for palliative treatment of multiple myeloma and ovarian carcinoma. A black box warning indicates that severe myelosuppression may occur with melphalan. Its use has also been associated with development of chromosomal damage and leukemia, although this effect has been only rarely observed with the use of single-agent melphalan conditioning.

In addition to severe cytopenias, high-dose melphalan causes severe mucositis in transplant recipients. See guidelines on Head and Neck Complications (including mucositis) for guidelines on prevention and treatment of this complication.

References

1. Jethava YS, Sica S, Savani B, et al. Conditioning regimens for allogeneic hematopoietic stem cell transplants in acute myeloid leukemia. Bone Marrow Transplant 2017;52:1504-11.
2. Liu H, Zhai X, Song Z, et al. Busulfan plus fludarabine as a myeloablative conditioning regimen compared with busulfan plus cyclophosphamide for acute myeloid leukemia in first complete remission undergoing allogeneic hematopoietic stem cell transplantation: a prospective and multicenter study. J Hematol Oncol 2013;6:15.
3. Rambaldi A, Grassi A, Masciulli A, et al. Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2015;16:1525-36.
4. Lee JH, Joo YD, Kim H, et al. Randomized trial of myeloablative conditioning regimens: busulfan plus cyclophosphamide versus busulfan plus fludarabine. J Clin Oncol 2013;31:701-9.
5. Ousia S, Kalra A, Williamson TS, et al. Hematopoietic cell transplant outcomes after myeloablative conditioning with fludarabine, busulfan, low-dose total body irradiation, and rabbit antithymocyte globulin. Clin Transplant 2020:e14018.
6. Scott BL, Pasquini MC, Fei M, et al. Myeloablative versus Reduced-Intensity Conditioning for Hematopoietic Cell Transplantation in Acute Myelogenous Leukemia and Myelodysplastic Syndromes-Long-Term Follow-Up of the BMT CTN 0901 Clinical Trial. Transplant Cell Ther 2021;27:483 e1- e6.
7. Fasslrinner F, Schetelig J, Burchert A, et al. Long-term efficacy of reduced-intensity versus myeloablative conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: retrospective follow-up of an open-label, randomised phase 3 trial. Lancet Haematol 2018;5:e161-e9.
8. Kroger N, Iacobelli S, Franke GN, et al. Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial). J Clin Oncol 2017;35:2157-64.
9. Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. Lancet Haematol 2020;7:e28-e39.
10. Russell JA, Tran HT, Quinlan D, et al. Once-daily intravenous busulfan given with fludarabine as conditioning for allogeneic stem cell transplantation: Study of pharmacokinetics and early clinical outcomes. Biology of Blood and Marrow Transplantation 2002;8:468-76.
11. Russell JA, Duan Q, Chaudhry MA, et al. Transplantation from matched siblings using once-daily intravenous busulfan/fludarabine with thymoglobulin: a myeloablative regimen with low nonrelapse mortality in all but older patients with high-risk disease. Biol Blood Marrow Transplant 2008;14:888-95.
12. Geddes M, Kangarloo SB, Naveed F, et al. High busulfan exposure is associated with worse outcomes in a daily i.v. busulfan and fludarabine allogeneic transplant regimen. Biol Blood Marrow Transplant 2008;14:220-8.
13. Russell JA, Kangarloo SB, Williamson T, et al. Establishing a Target Exposure for Once-Daily Intravenous Busulfan Given with Fludarabine and Thymoglobulin before Allogeneic Transplantation. Biology of Blood and Marrow Transplantation 2013;19:1381-6.
14. Milano F, Gutman JA, Deeg HJ, et al. Treosulfan-based conditioning is feasible and effective for cord blood recipients: a phase 2 multicenter study. Blood Adv 2020;4:3302-10.
15. Deeg HJ, Stevens EA, Salit RB, et al. Transplant Conditioning with Treosulfan/Fludarabine with or without Total Body Irradiation: A Randomized Phase II Trial in Patients with Myelodysplastic Syndrome and Acute Myeloid Leukemia. Biol Blood Marrow Transplant 2018;24:956-63.
16. Griffiths CD, Ng ESM, Kangarloo SB, et al. Fludarabine metabolite level on day zero does not affect outcomes of hematopoietic cell transplantation in patients with normal renal function. Bone Marrow Transplant 2014;49:589-91.
17. Seydoux C, Medinger M, Gerull S, et al. Busulfan-cyclophosphamide versus cyclophosphamide-busulfan as conditioning regimen before allogeneic hematopoietic cell transplantation: a prospective randomized trial. Ann Hematol 2021;100:209-16.

Table 1. Conditioning regimen, GVHD prophylaxis, and graft preferences by diagnosis. Only commonly used conditioning regimens for common HCT indications are covered here. See disease-specific chapters for other regimens.

Disease	Conditioning	GVHD Prophylaxis	Graft
Allogeneic HCT			
Hematologic Malignancies			
Standard	**Flu**(250mg/m^2) + **Bu**(15000uM.min) + **TBI**(2Gy x2)	ATG+CSA+MTX, except PTCy+Tacro+MMF if haplo*	PBSC
Previous TBI	**Flu**(250mg/m^2) + **Bu**(18000uM.min)	ATG+CSA+MTX, except PTCy+Tacro+MMF if haplo*	PBSC
Reduced intensity**	**Flu**(150mg/m^2) + **Treo**(30g/m^2)	ATG+CSA+MTX	PBSC
Second allogeneic transplant for relapse (same donor)	**Etoposide**(60mg/kg) + **TBI**(5Gy x1)	CSA	PBSC
Second allogeneic transplant for relapse (new donor)	**Etoposide**(60mg/kg) + **TBI**(5Gy x1)	CSA+MTX	PBSC
Second allogeneic transplant for graft failure	**Flu**(250mg/m^2) + **TBI**(5Gy x1)	ATG+CSA	PBSC
Aplastic Anemia			
Matched sib	**Flu**(120mg/m^2) + **Cy**(120mg/kg)	ATG+CSA+MTX	Marrow
Haploidentical or Unrelated	**Flu**(150mg/m^2) + **Cy**(29mg/kg) + **TBI**(2 or 4Gy x1)***	ATG+PTCy+MMF+Tacro	Marrow
Hemoglobinopathy			
Matched sib	**TBI**(3Gy x1)	Alemtuzumab+Sirolimus	PBSC
Haploidentical or Unrelated	**Flu**(150mg/m^2) + **Cy**(29mg/kg) + **TBI**(4Gy x1)	ATG+PTCy+MMF+Sirolimus	Marrow
Autologous HCT			
Multiple myeloma	**Melphalan** 200 mg/m^2****	NA	PBSC
Aggressive NHL (DLBCL, PTCL)	**(R)** + **Bu**(13500uM.min) + **Mel**(140mg/m^2)	NA	PBSC
Indolent NHL (FL, MZL, LPL, CLL/SLL)	**(R)** + **Mel**(180mg/m^2) + **TBI**(5Gy x1)	NA	PBSC
Mantle cell lymphoma	**(R)** + **Mel**(180mg/m^2) + **TBI**(5Gy x1)	NA	PBSC
Hodgkin lymphoma	**Gemcitabine** 1500 mg/m2 + **Melphalan** 200 mg/m^2	NA	PBSC
Primary CNS lymphoma	**(R)** + **Thiotepa**(600mg/m^2) + **Bu**(13500 uM.min)	NA	PBSC
Secondary CNS lymphoma	**(R)** + **Thiotepa**(500mg/m^2) + **Bu**(13500uM.min) + **Mel**(100mg/m^2)	NA	PBSC

* CSA+MMF if cord blood.
** For patients with CLL or rare patients with significant comorbidities (eg, liver, lung) or prior high-dose busulfan, who in spite of the comorbidities are thought to benefit from alloHCT.
*** 2 Gy if previous immunosuppressive therapy, 4 Gy (in a single fraction) if no previous immunosuppressive therapy.
**** 140-180 mg/m^2 if impaired renal function.
Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid leukemia; FL = follicular lymphoma; HL = Hodgkin lymphoma; LBCL = large B-cell lymphoma; LPL = lymphoplasmacytic lymphoma; MDS = myelodysplasia; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; PBSC = peripheral blood stem cells; PTCL = peripheral T-cell lymphoma; SLL = small lymphocytic leukemia; PBSC = peripheral blood stem cells; Flu = fludarabine, Bu = busulfan, TBI = total body irradiation, Mel = melphalan, R = rituximab, ATG = antithymocyte globulin, PTCy = posttransplant cyclophosphamide; MTX = methotrexate; MMF = mycophenolate mofetil, Tacro = tacrolimus, CSA = cyclosporine A.

Appendix A. Conditioning Protocol Details

Flu**(250mg/m^2)* **+ *Bu**(15000uM.min)* **+ *TBI**(2Gy x2)
Fludarabine 50 mg/m2/day on days -6 to -2
Busulfan 3.2 mg/kg/day on days -5 to -2, adjusted based on pharmacokinetics in order to achieve total busulfan exposure of 15000 uM.min
TBI 4 Gy delivered to midplane in two divided doses on day -1 or 0 (before graft infusion), at least 6 hours apart.

Flu**(250mg/m2)* **+ *Bu**(18000uM.min)
Fludarabine 50 mg/m2/day on days -6 to -2
Busulfan 3.2 mg/kg/day on days -5 to -2, adjusted based on pharmacokinetics in order to achieve total busulfan exposure of 18000 µmol·min/L

Cy**(120mg/kg)* + ***Bu**(<24000uM.min)
Cyclophosphamide 60 mg/kg IV on days -8 and -7
Busulfan 3.2 mg/kg IV on days -5, -4, -3, -2. Avoid daily AUC >24,000 umol.min/L (avoid overall AUC >24,000 umol.min/L).
The reason for using Cy+Bu instead of "conventional" Bu+Cy is a randomized study that showed borderline superiority of Cy+Bu due to lower hepatotoxicity and lower NRM.[17]
This conditioning should be used only in case of fludarabine shortage. Bu+Cy has been found in two randomized studies to result in similar overall survival as Flu+Bu,[2,3] *however, whether it is equivalent to Flu+Bu+4GyTBI is not known. Moreover, the busulfan toxic AUC of >24,000 uM.min has been determined in combination with fludarabine; it is not known whether it applies also to combination with cyclophosphamide. Moreover, in the randomized studies, daily busulfan dose was divided into two or four doses. We will use only one daily dose as an extrapolation from our Flu-Bu experience.*

Flu**(120mg/m^2)* **+ *Mel**(140mg/m^2)* ***(RIC)
Fludarabine 30 mg/m2 days -5 to -2
Melphalan 140 mg/m2 day -1

Flu**(150mg/m2)* **+ *Treo**(30g/m2)* ***(RIC)
Fludarabine 30 mg/m2 on days -6 to -2
Treosulfan 10 mg/m2 on days -4 to -2

Etoposide**(60mg/kg)* **+ *TBI**(5Gy x1)
Etoposide 60 mg/kg on day -4
TBI 500 cGy delivered to midplane in a single fraction on day 0 (before graft infusion)

***Flu**(250mg/m^2)* ***+ TBI**(5Gy x1)*
Fludarabine 50 mg/m2 on days -6 to -2
TBI 500 cGy to midplane on day -1 or 0

***Flu**(120mg/m^2)* ***+ Cy**(120mg/kg)*
Fludarabine 30 mg/m2/day on days -6 to -3
Cyclophosphamide 60 mg/kg on days -4 and -3

Flu**(150mg/m^2)* ***+ Cy**(29mg/kg)* ***+ TBI**(2 or 4Gy x1)* ***(Baltimore)
Fludarabine 30 mg/m2/day on days -6 to -2
Cyclophosphamide 14.5 mg/kg on days -6 and -5
TBI 2 or 4 Gy delivered to midplane in a single fraction on day -1 (2 Gy if previous immunosuppressive therapy, 4 Gy if no previous immunosuppressive therapy).
Note: ATG is given as 0.5 mg/kg on day -9, 2 mg/kg on day -8, and 2 mg/kg on day -7

Gem-Mel
Gemcitabine 75mg/m2 bolus then 1425mg/m2 infusion on day -1
Melphalan 200 mg/m2 on day -1

TBI**(3Gy x1)* ***(NIH)
TBI 300 cGy delivered to midplane in a single fraction on day -2
Note: Alemtuzumab is given as 0.03 mg/kg on day -7, 0.1 mg/kg on day -6, and 0.3 mg/kg on days -5, -4, and -3..

Mel 200
Melphalan 200 mg/m2 on day -1
Note: 140-180 mg/m2 if impaired renal function

***(R) + Etoposide**(60 mg/kg)* ***+ Mel**(180mg/m^2)*
(Rituximab 375 mg/m2 IV day -4)
Etoposide 60mg/kg day -4
Melphalan 180mg/m2 day -2

(R)BEAM (not used since 2018 due to carmustine becoming too expensive)
(Rituximab 375 mg/m2 IV on day -6)
Carmustine (BCNU) 300 mg/m2 on day -6
Etoposide 100 mg/m2 q12h x 8 doses on days -5 to -2
Cytarabine 200 mg/m2 q12h x 8 doses on days -5 to -2
Melphalan 140-160 mg/m2 on day -1

***Thiotepa**(600mg/m^2)* ***+ Bu**(13500uM.min) for Primary CNS Lymphoma*

Thiotepa 300 mg/m2 (Ideal BSA) on days -6 and -5 if age 18-60years
270mg/m2 (Ideal BSA) on days -6 and -5 if age 61-65years
240mg/m2 (Ideal BSA) on days -6 and -5 if age 66-70years
210mg/m2 (Ideal BSA) on days -6 and -5 if age >70years

Busulfan (only 3.2 mg/kg/day days -4 to -2 targeted to achieve busulfan AUC <13500 uM.min)
3.2 mg/kg (Ideal weight) IV daily on days -4 to -2 if age 18-60years
2.9mg/kg (Ideal weight) IV daily on days -4 to -2 if age 61-65years
2.55mg/kg (Ideal weight) IV daily on days -4 to -2 if age 66-70years
2.25mg/kg (Ideal weight) IV daily on days -4 to -2 if age >70years

PK testing is run on the first dose and the third dose is adjusted (if needed) to avoid a total AUC of over 13500 uM.min

***(R) + Thiotepa**(500mg/m^2)* ***+ Bu**(<13500uM.min)* ***+ Mel**(100 mg/m^2) for Secondary CNS Lymphoma*

(Rituximab 375 mg/m2 IV on day -7)

Thiotepa 250 mg/m2 (Ideal BSA) on days -6 and -5 if age 18-64years
225mg/m2 (Ideal BSA) on days -6 and -5 if age 65-69years
200mg/m2 (Ideal BSA) on days -6 and -5 if over age 70years

Busulfan (only 3.2 mg/kg/day days -4 to -2 targeted to achieve busulfan AUC <13500 uM.min)
3.2 mg/kg (Ideal weight) IV daily on days -4 to -2 if age 18-64years
2.9mg/kg (Ideal weight) IV daily on days -4 to -2 if age 65-69years
2.55mg/kg (Ideal weight) IV daily on days -4 to -2 if over age 70years

Melphalan 100 mg/m2 on day -1 if age 18-64years
90mg/m2 IV on day -1 if age 65-69years
80mg/m2 IV on day -1 if over age 70years

PK testing is run on the first dose and the third dose is adjusted to target total AUC of 13500 uM.min +/- 20%

***(R) + Bu**(1350uM.min)* ***+ Mel**(140mg/m^2)*

Rituximab 375 mg/m2 IV on day -5
Busulfan 3.2 mg/kg/day on days -4 to -2 targeted to achieve busulfan AUC of 13500 uM.min
Melphalan 140 mg/m2 on day -1

Appendix B. Pharmacokinetic Adjustment of Busulfan

The routine use of pharmacokinetic (PK) monitoring for busulfan exposure has led to reduction in treatment-related mortality and is considered standard of care in this program. Drug exposure is estimated from the area under the plasma concentration-time curve (AUC), expressed in μmol·min.[1] The expected exposure is first determined from a test dose given prior to the start of the preparative regimen, and the first and second of 4 busulfan doses are adjusted accordingly. The exposure is also determined from the first dose (of the 4 doses), and the third and fourth doses are adjusted accordingly only if the estimated total AUC is >20% or <20% from the target total AUC. Dosage adjustments are made by comparing the AUC obtained from the test or first dose with the desired AUC according to the formula:

Adjusted Dose (mg) = Actual Dose (mg) x (Target AUC (uM.min) / Observed AUC (uM.min))

Busulfan is infused at a constant dose of 80 mg/h. In the full intensity Flu+Bu preparative regimen pharmacokinetic testing is normally carried out on days -8 (test dose) and -5 (adjusted first full dose). The first dose (on day -5) and the second dose (on day -4) are adjusted based on the test dose PK. The third (day -3) and the fourth (day -2) doses are adjusted based on the first dose PK, but only if the estimated total AUC is >20% or <20% from target. Busulfan target AUC is 15000 μM.min for patients receiving TBI as part of the preparative regimen. For patients not receiving TBI, the target is 18000 μM.min. No PK determination / dose adjustment is done in the setting of reduced intensity conditioning.
In case of Bu-Cy preparative regimen, the busulfan test dose is given on day -10, and busulfan treatment doses on days -8 to -5 are adjusted analogous to Flu-Bu, however, there is no target AUC. The goal is to not to exceed total AUC of 24000 uM.min.

Appendix C. Results using our standard conditioning (Flu250 + Bu15000 + TBI4Gy) in combination with PBSC graft and ATG+CSA+MTX GVHD prophylaxis, using matched sib or 7-8/8 HLA matched unrelated donor

Based on Ousia et al,[5] and additional unpublished analyses.

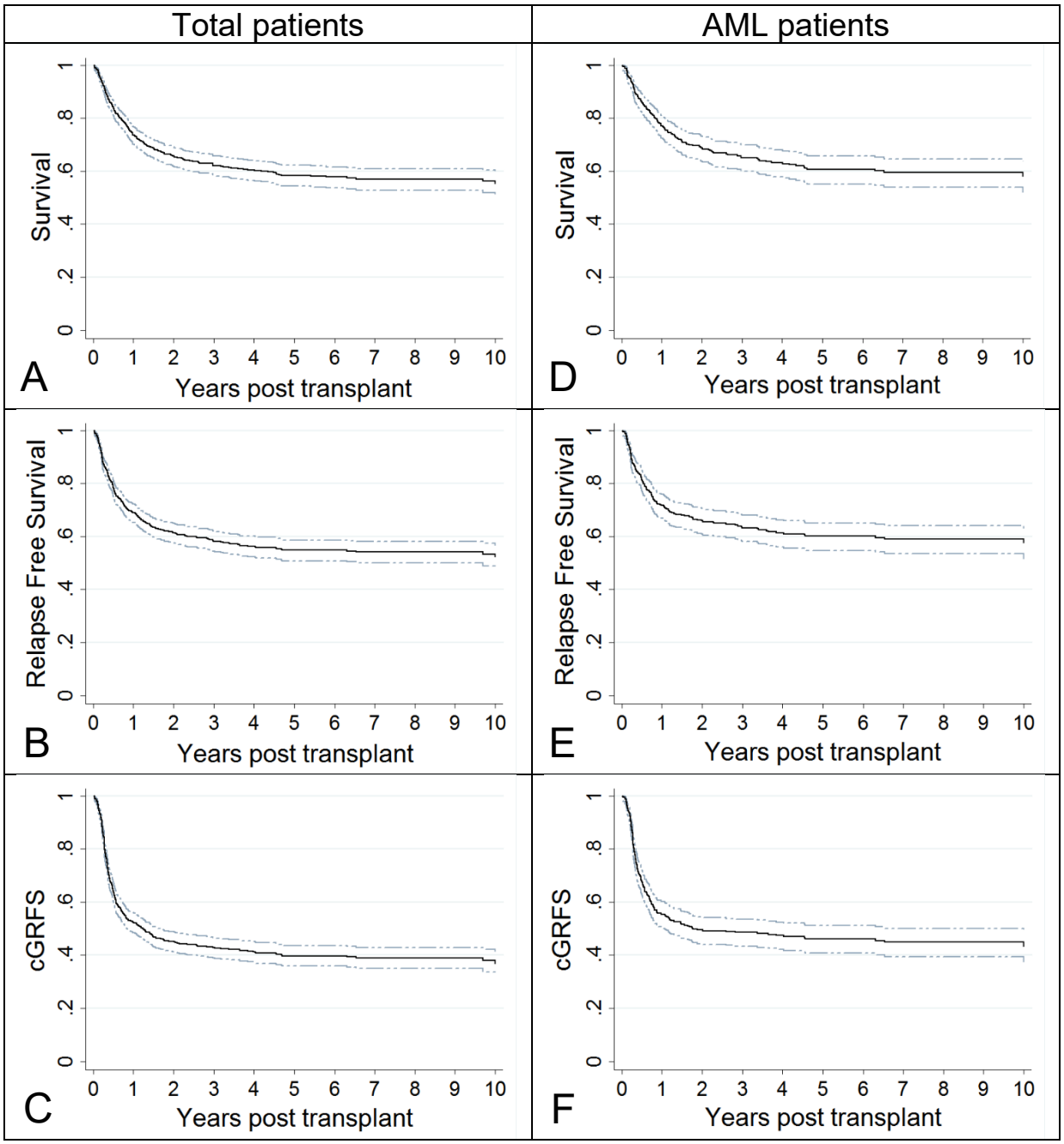


Figure 1. Overall survival (A), relapse-free survival (B), and chronic graft versus host disease- and relapse-free survival (cGRFS) (C) in the total cohort of 700 patients (any hematologic malignancy). Overall survival (D), relapse-free survival (E), and cGRFS (F) in patients with acute myeloid leukemia (AML). The dot-dash lines show 95% confidence intervals.

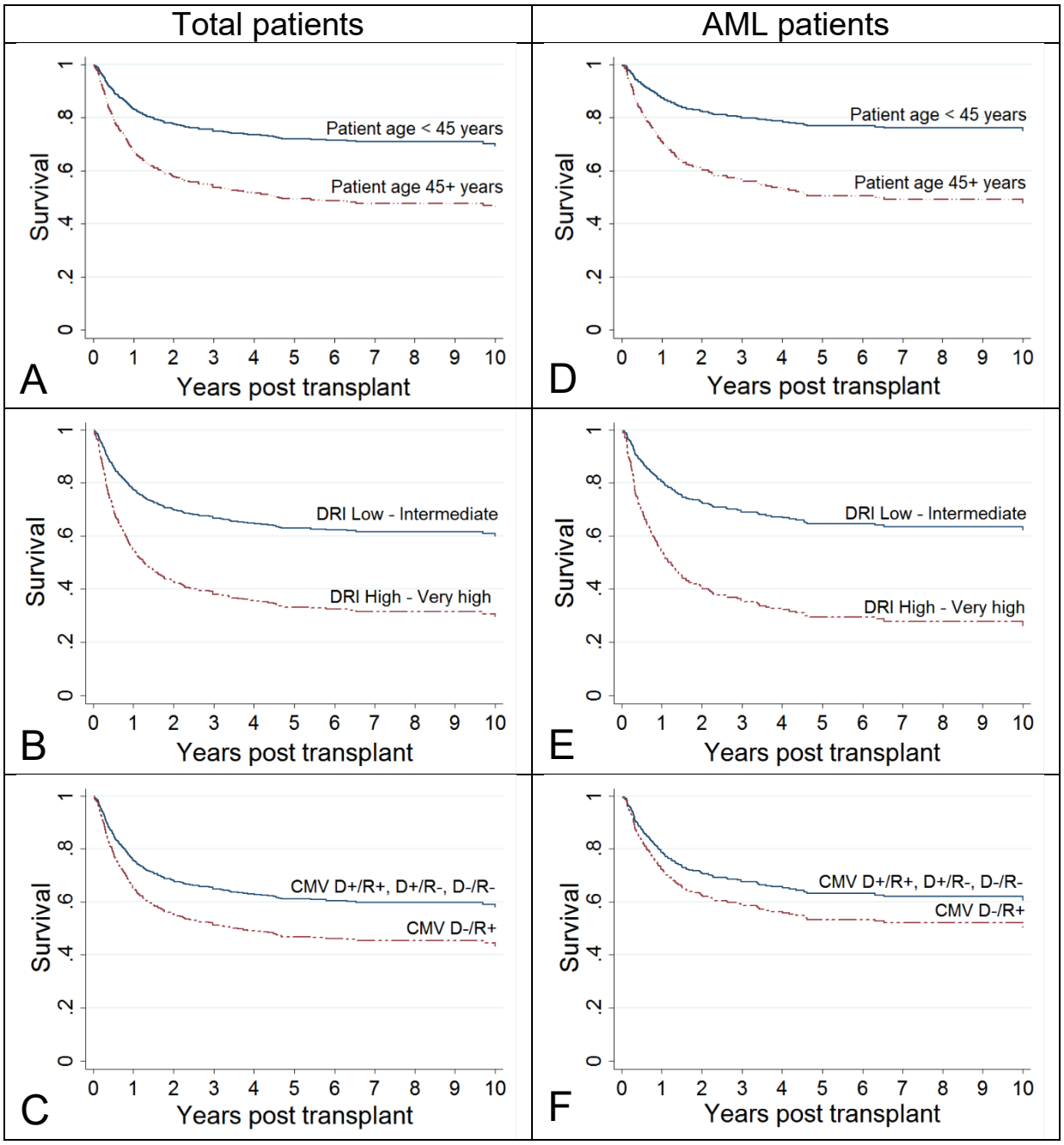


Figure 2. Impact of patient age, disease risk index (DRI), and CMV serostatus on overall survival in total patients (A, B, C) and patients with acute myeloid leukemia (D, E, F). All the differences were significant in multivariate analysis, except for the CMV serostatus in AML patients.

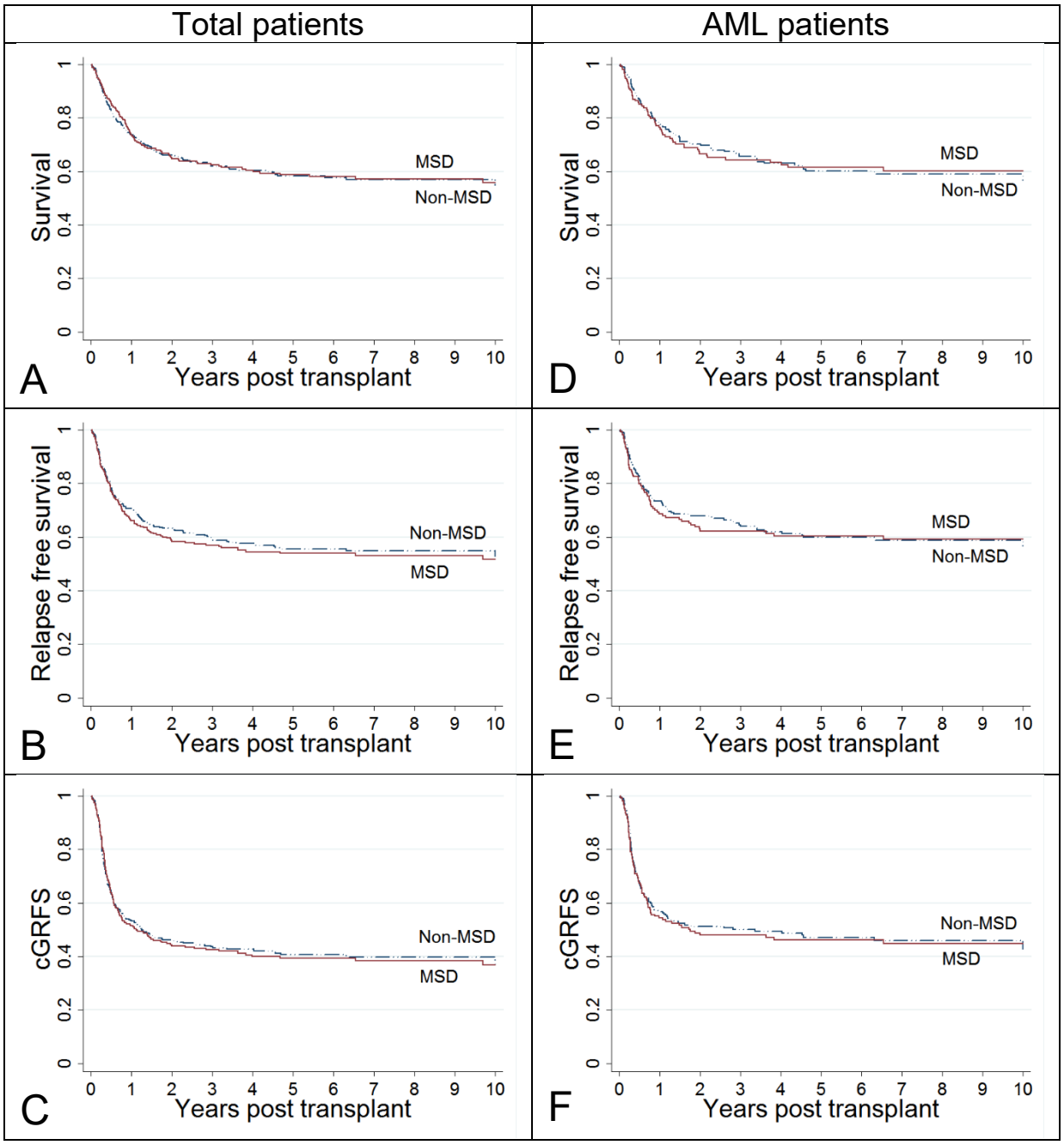


Figure 3. Virtually no impact of HLA matched sibling donor (MSD, solid red curve) vs non-MSD (mostly 7-8/8 HLA allele-matched unrelated donor, dashed blue curve) on OS, RFS, or cGRFS. None of the differences was significant in multivariate analysis.

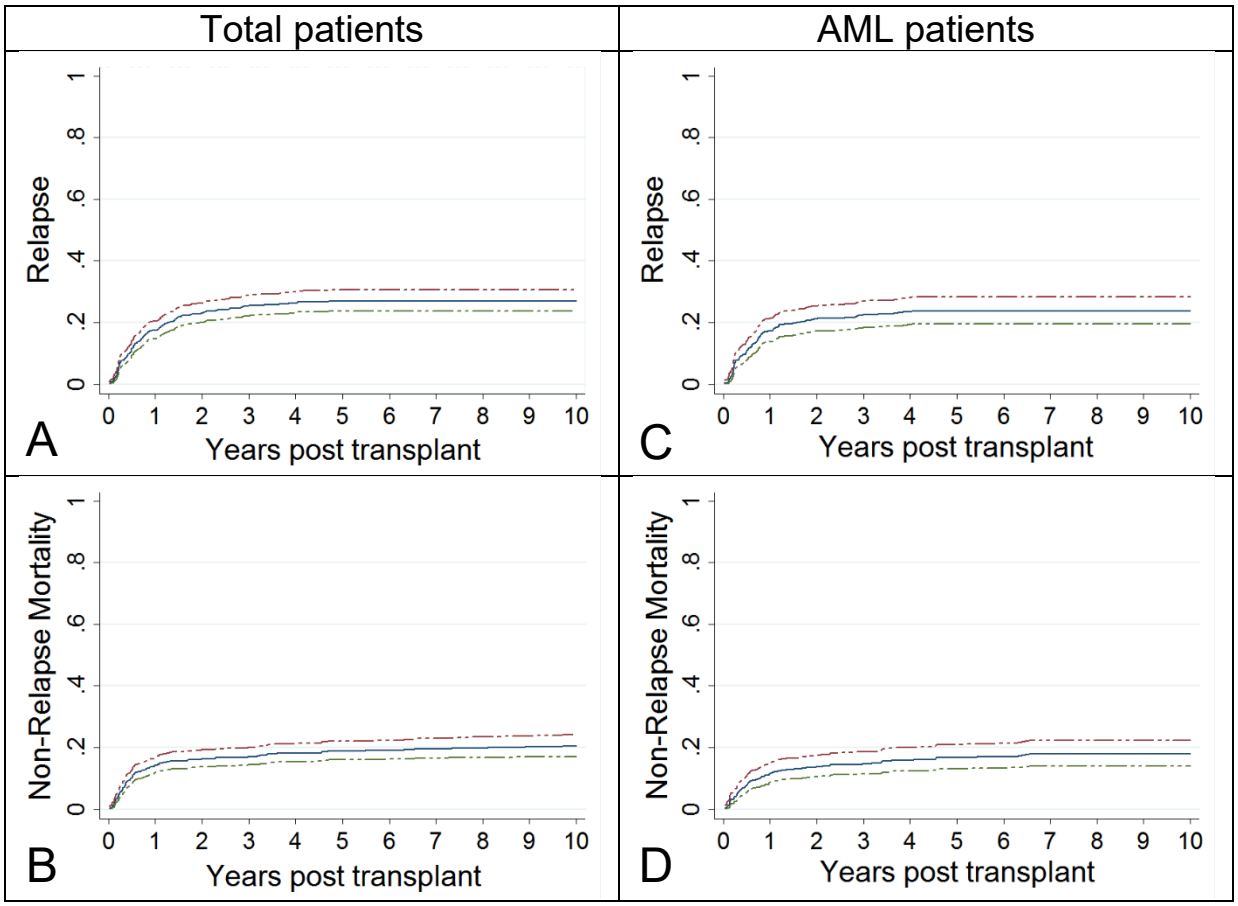


Figure 4. Relapse and non-relapse mortality in total patients (the whole cohort of 700 patients) (A, B) and patients with acute myeloid leukemia (C, D). The dot-dash lines show 95% confidence intervals.

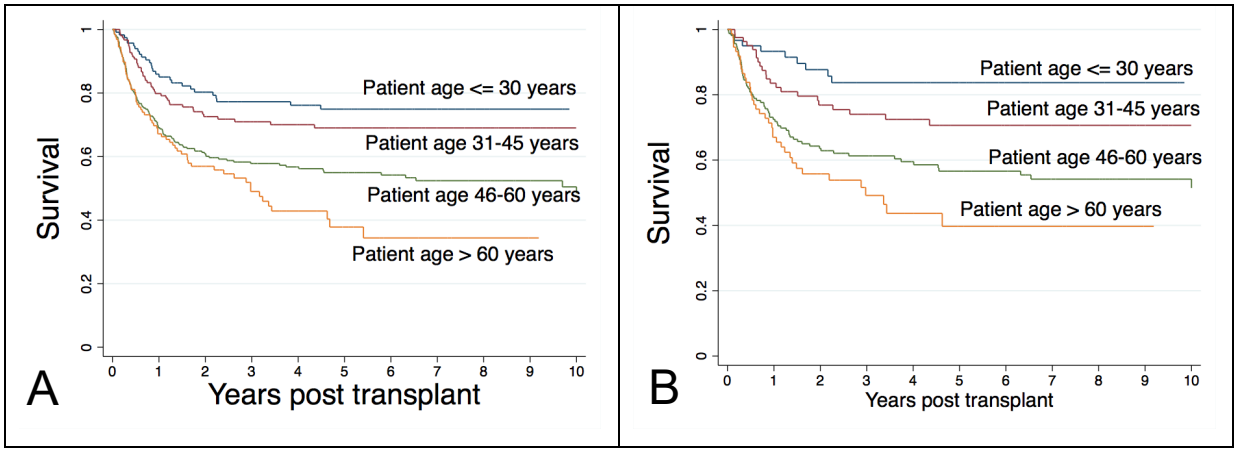


Figure 5. Overall survival by patient age among total patients (any hematologic malignancy) (A) and AML patients (B).

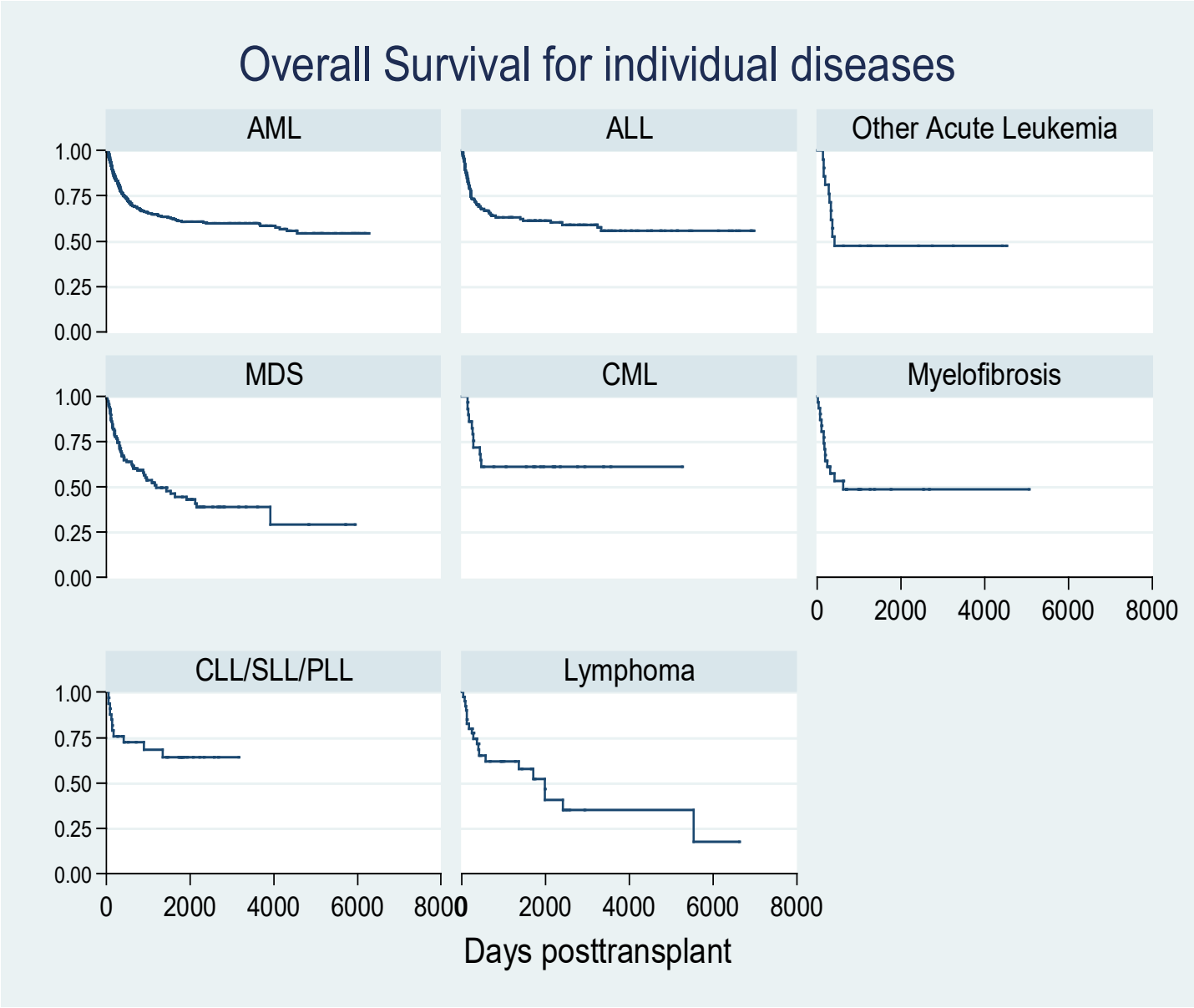


Figure 6. Overall survival for alloHCT recipients according to their disease. Patients received our standard conditioning (Flu+Bu+4GyTBI), PBSC graft, and GVHD prophylaxis with ATG, MTX, and CSA. All disease stages are included.

Transplantation Eligibility Assessment: Patient Factors

Presented by: Jason Tay

Summary

1. We recommend the routine documentation and use of the Hematopoietic cell transplantation (HCT) specific comorbidity index (HCT-CI) and its components as part of the pre-transplant evaluative process.
2. A Frailty & Functionality Assessment should be performed for all patients undergoing allogeneic HCT, regardless of age, and the HCT frailty score should be calculated. A more in-depth Geriatric Assessment can be considered in select patients, particularly those over age 65, to better aid decision making. It would also be good practice in the autologous HCT setting but should be individualized.
3. The following are RELATIVE contraindications for HCT. A referral to appropriate subspecialty services is indicated if HCT is being considered for a patient who does not meet any of these minimal thresholds:
    a. Age >65
    b. Karnofsky performance score (KPS) <60
    c. FEV1 or DLCO <60% predicted
    d. LVEF <45% or arrhythmia
    e. Bilirubin/ALT/ALP >2x upper normal limit (UNL)
    f. Creatinine >2x ULN
    g. Uncontrolled infection, including dental
    h. HCT frailty scale Score ≥ 5.5
4. The following are ABSOLUTE contraindications for HCT.
    a. Active second malignancy
    b. Cirrhosis of the liver
    c. Pregnancy
    d. HCT-CI ≥3 plus one abnormal IADL (ability to use phone, laundry, shopping, mode of transportation, food preparation, responsibility for own medications, housekeeping, ability to handle finances) in patient's >65 years.
5. Early (ideally at diagnosis of malignancy) referral of the patient with mental illness or other psychosocial concerns to psychology, social work, psychiatry as appropriate is important. When psychosocial factors severely impair functioning and/or adherence to treatment plan, or place the patient at immediate safety risk (e.g., actively psychotic, suicidal, substance dependent, extreme poverty, high degree of family conflict), HCT may be deferred in order to prioritize stabilization of psychosocial concerns.
6. The ultimate decision to proceed to HCT is an interdisciplinary team-based decision paying attention to recipient characteristics and their perceived "trade-offs" with disease and donor characteristics.

7. Eligibility for chimeric antigen receptor T-cell therapy (CAR-T) will follow the same principals for assessment as in standard HCT.

Background

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for a variety of malignant and nonmalignant hematological disorders. The decision to recommend and proceed with HCT is complex and multi-faceted. Prior to recommendation a throughout assessment of 1) Disease characteristics, 2) Patient characteristics – Physical and Psychosocial, and 3) Donor characteristics (allogeneic setting) is required.

The relative contributions of these characteristics (potentially overlapping) to HCT success is not and unlikely to be clearly defined. In part, evaluations of individual characteristics within observational studies variably consider other pertinent characteristics. Moreover, secular trends in HCT technology and supportive care would suggest the relative contributions would be "fluid". *The ultimate decision to proceed to HCT is an interdisciplinary team-based decision paying attention to these characteristics and their perceived "trade-offs".*

While it is important to acknowledge that patient characteristics are associated with post-HCT outcomes, there is no clear and/or consistent evidence that modification of these characteristics clearly attenuates post-HCT outcomes –modifiable risk factor(s). This review focuses on **Patient** characteristics and draws attention to assessments and variables that might influence the decision to proceed with HCT.

Physical Assessment(s)

A detailed history, physical examination complemented with investigative diagnostics is a crucial 1st step in documenting and assessing comorbidities[1-3]. The rationale is presented in the following sections:

Age

An ideal HCT candidate should be in excellent physical and physiologic health at the time of HCT. There is a movement to consider physiologic age over chronologic age in the determination of HCT eligibility. However, the chronologic age could be considered a simple variable that embraces a multitude of patient characteristics.

In the autologous setting, data on the impact of age on outcomes post HCT is predominantly in myeloma setting. Data from randomized controlled trials would support autologous HCT up to a biologic age of 65 years. In contrast, there is no randomized controlled trial data supporting autologous HCT in patients aged >65 years with multiple myeloma. However, there are indeed observational studies that suggest that autologous HCT can be safely performed in older patients in myeloma[4-8]. There are fewer studies examining its impact in the lymphoma setting[9-11]. The paucity of

data would suggest that biologic age should not be sole criteria used to determine eligibility for autologous HCT. Rather, one may need to consider attenuating the dosing of the conditioning regimen to compensate for age among other factors as discussed.

In the allogeneic setting, CIBMTR registry data suggests that the median age of HCT has increased to up to 75 years over the last few decades[12]. Indeed, a retrospective study from EBMT suggests that there is no significant association between age and relapse or non-relapse mortality in a cohort of 1333 patients (age 50-74 years)[13]. Further, a similar analysis from CIBMTR in 1080 patients (>40 years) receiving a reduced intensity conditioning found that chronologic age did not impact rates of non-relapse mortality, relapse or GVHD[14]. Finally, a review of 372 patients aged 60-75 enrolled in prospective clinical trials of a reduced intensity conditioning determined that age did not appear to influence GVHD, PFS or OS but older individuals had increased bacterial infections and hospitalization[15].

Given potential and inherent biases in the assessment of physiologic age, there is increasing interest in utilizing biomarkers of physiologic age[16]. Indeed, there are numerous candidate markers including: $p16^{INK4A}$, Leukocyte telomere length, DNA methylation, miRNA, Immunosenescence, SASP, Anemia, IL-6, CRP, NT-proBNP, Albumin, D-dimer, TNF and sICAM-1. Further, various geriatric assessment scales have also been used[17,18]. Among these, it appears that $p16^{INK4A}$ may be a leading biomarker candidate – a molecular maker of cellular senescence[19-21].

Observational health outcomes research evaluating age is inherently confounded by indication that might suggest a more conservative approach in utilizing age in determining HCT eligibility. Taken together, it is reasonable to consider using a cautious and extensive evaluation for older (e.g. >65years) or frailer patients.

Performance Status

With respect to performance status assessment, we prefer the Karnofsky Performance Score (KPS) score over Eastern Cooperative Oncology Group (ECOG) score as it allows a more “granular” range to base one’s assessment. Moreover, the assessment of performance status is subjective, and a wider scoring range may improve the quality of the assessment. Given concerns that performance status is clinician assigned with overestimation[22], a geriatric assessment (GA) has its proponents in older patients[23,24]. See section on Geriatric assessments.

We suggest that it is reasonable to proceed with HCT if the KPS score >60 and consider utilizing CGA in individuals who are >65 years of age to better guide decision making. In those with a KPS of <60, a more extensive evaluation would be warranted. Further, we suggest that HCT be not offered in the presence of a HCT-CI score of ≥3 and one abnormal ADL.

Pulmonary Evaluation

Post-HCT pulmonary complications such as therapy related lung toxicity, pulmonary GVHD and its variants, TRALI and infectious complications can occur. Pre-existing lung disease as measured by pulmonary function tests (PFTs) can increase the risk and morbidity of post-HCT pulmonary complications with up to 3% and 24% of autologous and allogeneic HCT patients developing severe pulmonary complications requiring mechanical ventilation[25]. Indeed, an abnormal PFT pre-HCT is associated with poorer post-transplant outcomes[26-29]. Further, smoking pre-HCT is independently associated with poor outcomes[30].

The proposed cutoff for eligibility in HCT in clinical trials is typically a corrected DLCO >50% although a true cutoff is unknown. This cutoff which may be dependent on the planned conditioning chemotherapy[31]. In the allogeneic setting, a higher threshold of DLCO>60% has been used. Moreover, the PAM score (described later) uses a DLCO cutoff of 60%[32]. The correlation between FEV_1 and DLCO pre-HCT is poor, with pre-HCT FEV_1 independently predictive of early respiratory failure[33,34].

Taken together, it is optimal to consider HCT in an individual with a DLCO >60% and a FEV_1>60%. In all other scenarios, the case should be discussed at an individual basis.

Cardiac evaluation

In general, individuals with poor cardiac reserve with a LVEF <40%, uncontrolled arrhythmia or coronary artery should not proceed with HCT[35]. Overall, the rate of major or life-threatening cardiac events post-HCT has been estimated to be <1%[36].

Cardiac injury can occur post-HCT, and it is assumed to be more serious in individuals with less cardiac reserve. A higher LVEF threshold maybe warranted when cardiotoxic conditioning (e.g., cyclophosphamide or TBI) is contemplated. However, it may be reasonable to accept a LVEF of >45% in most circumstances[37,38]. Separately, there is also an association between prolonged QT and QT dispersion noted on routine EKG with post-HCT morbidity from heart failure[39,40]. Further, it would be important to optimize cardiac risk factors prior to HCT[41].

Taken together, it is optimal to consider HCT in an individual with a LVEF>45% with a normal EKG. In all other scenarios, the case should be discussed at an individual basis.

Hepatic Evaluation

Baseline elevations of serum transaminases and alkaline phosphatase are associated with an increased risk of sinusoidal obstruction syndrome (SOS) post-HCT in the allogeneic setting[42].

Serum hyperferritinemia is also associated with increased risk of SOS, disease free and overall survival[43-47]. Given these associations, it may be reasonable to consider chelation therapy for iron

overload prior to HCT, in particular patients with multiple red cell transfusion supports; however, whether the chelation improves outcomes has not been reported.

Taken together, it is reasonable to proceed with HCT if the liver function tests as measured by (Bilirubin, AST, ALT or ALP) are < 2 times upper limit of the normal reference range.

Seropositivity for Hepatitis B, C or HIV should not preclude HCT, recognizing that it affects peri-transplant care, where viral prophylaxis or optimization of anti-viral therapy would be required. Unsurprisingly, viral hepatitis is associated with increased risk of reactivation, SOS, liver disease post-HCT and non-relapse mortality[48-50]. The use of Transient Elastography (Fibroscan) is suggested if there is clinical concern of cirrhosis[51].

In general, it is reasonable to exclude patients with frank cirrhosis from HCT.

Nutritional Evaluation

There is a paucity of evidence to suggest a specific nutritional state that would preclude HCT. However, is notable that patients that medically obese have similar post- autologous HCT outcomes as patients with a normal BMI[52-55]. Interestingly, obesity is associated with higher non-relapse mortality[56] but a lower relapse rate, resulting in similar overall survival in the allogeneic setting[57] and low BMI is associated with poor HCT outcome[56,58]. In contrast, a Chinese study would suggest that overweight and obese patients had a superior overall survival when compared with underweight and normal-weight patients (HR=0.60; 95% CI: 0.38-0.95)[59].

Consequently, it may be reasonable to attempt to increase BMI before HCT, but it has not been reported whether this intervention improves outcome.

Renal Function Evaluation

Renal dysfunction is associated with a higher morbidity and mortality in patients undergoing autologous HCT for myeloma[60-62]. Importantly, the value of autologous transplants studied in a randomized fashion only included patients with good renal function. In contrast, there is a paucity of data in the autologous setting in lymphoma given that traditional conditioning chemotherapy was not administered in patients with a serum creatinine >177micromol/L.

A similar argument applies in the allogeneic setting and maybe more pertinent given that acute renal injury can occur 15-18% of patients receiving allogeneic HCT[63]. Further, there is some evidence to support an increased risk of non-relapsed mortality in patients with renal impairment pre-HCT[64]. Indeed, long-term follow-up data suggests that the more severe the acute renal injury peri-HCT, the higher the likelihood of chronic kidney disease[65]. Interestingly, the risk of acute renal injury could be anticipated using the HCT-CI (see discussion later)[66].

Overall, it is reasonable to proceed with HCT where the Creatinine is < 177micromol/L and are < 2 times upper limit of the normal reference range. All other scenarios should be individualized.

Dental Evaluation
The goal of pre-HCT dental assessments is to identify potential sources of infection during the peri-HCT period[67,68]. This appears to be good practice but there has been no clear evidence to support an association between radiographic periodontal disease and infections/mortality post-HCT[69,70].

Active Infections
It appears to be good practice that HSCT should be deferred if there is active infection or infection(s) that are not responding to therapy to decrease the odds of morbidity and mortality peri-HSCT.

Comorbidity Indices

There are multiple standardized co-morbidity indices in clinical use that aims to aid pre-HCT assessments[71]. The purpose would be to incorporate and assign differing weights to characteristics considered in the above sections. However, it is important to note that not all characteristics are considered or considered in the same fashion in the derivation studies.

Kaplan-Feinstein Scale
The Kaplan-Feinstein Scale (KFS) was originally developed to evaluate the impact of survival in patients with diabetes based on comorbid conditions and involves assigning Grades (range 1-3) to 12 comorbid conditions[72]. Artz et al. evaluated 105 consecutively enrolled patients who underwent HCT, receiving reduced intensity conditioning with fludarabine, melphalan, and alemtuzumab. A simple scale combining the Kaplan-Feinstein Scale (KFS) and Eastern Cooperative Oncology Group Performance Status (PS) scale PS enabled separation of high- from low-risk patients, with 6-month cumulative incidences 50% and 15%, respectively for transplant-related mortality (P = .001)[73].

Pre-transplant Assessment of Mortality Score- PAM Score
This risk score was developed at the Fred Hutchinson center and incorporates 8 pre-transplantation clinical variables: patient age, donor type, disease risk, conditioning regimen, FEV1, carbon monoxide diffusion capacity, serum creatinine level, and serum alanine aminotransferase concentration[32]. This score is useful for predicting the risk for death within the first 2 years after HCT.

The authors re-evaluated the PAM score using a contemporary cohort (2003-2009) to update and recalibrate its predictive capability[74] and the score was also validated in non-Caucasians[75]. Importantly, the score was modified where carbon monoxide diffusing capacity, serum alanine aminotransferase, and serum creatinine concentrations were no longer significantly associated with 2-year mortality, whereas patient and donor cytomegalovirus serology was associated with mortality. However, there is also literature to support an assertion that the PAM score may not be useful in all

allogeneic[76,77] or autologous[78] settings. The following is a link to an online calculator: http://pamscore.org/

EBMT Score

The EBMT risk score incorporates both recipient and disease variables. It evaluates five factors: age of patient, disease stage, time interval from diagnosis to transplant, donor type and donor recipient sex combinations. The current EBMT risk score is an extension of the "old" CML risk score. This scoring system explains 63% of the post-transplant outcomes in the EBMT registry[79]. More recently, the EBMT was re-evaluated in patients with primary or secondary myelodysplasia undergoing an allogeneic transplant where the EBMT score predicts overall survival and transplant related mortality but did not correlate with relapse risk[80]. Similarly, the EBMT score has utility in the autologous setting[81].

Hematopoietic cell transplantation specific comorbidity index (HCT-CI)

Using the Charlson Comorbidity Index[82] as a template, Sorror et al. re-developed this tool as a prognostic tool to better gauge post-allogeneic transplant survival outcomes – HCT-CI[83]. This index embraces the variables discussed in Section 2. This index has been validated and is independent of disease characteristics. Importantly, the variables that were considered in this model are predominantly physical with little to no evaluation of mental or psychosocial variables. The use of the HCT-CI allows an estimation of the transplant-related mortality (see appendix 1). The following is web link to facilitate score calculations: http://www.hctci.org/Home/Calculator

HCT-CI in clinical settings and comparisons with other scoring systems

The HCT-CI has been evaluated and deemed prognostically useful in a variety of allogeneic transplant settings with modifications to incorporate combinations of age, remission status and performance status[84-89]. Further, modifications of the HCT-CI have been used in the autologous setting[90-93]. On reviewing our local data on 700 patients who received allogeneic HCT, HCT-CI did not appear to be associated with post-HCT outcomes[94].

Others have attempted to compare the accuracy of EBMT Score and the HCT-CI. For instance, Michaelis et al., in a single centre retrospective analysis using regression modeling suggest that a modified Pre-Transplant EBMT Risk Score is superior to the HCT-CI Score in predicting overall survival and non-relapse mortality after allogeneic HCT in patients with acute myeloid leukemia[95]. Separately and similarly, Terwey el al. evaluated HCT-CI and modified EBMT Risk score in the adult patients with ALL within a single European center and suggests that the EBMT risk score may be preferable over the HCT-CI[96].

The PAM score was compared with the HCT CI at a single institution and suggests the HCT-CI was more predictive of overall survival[93] but the conclusions are inconsistent[97].

Taken together, there is no clear co-morbidity index that clearly embraces all aspects of recipient and/or disease variables. Moreover, the accuracy of prediction tools is likely dependent on local variables that are either known or unknown. However*, it is reasonable to adopt the HCT-CI as the default index as it is the most widely used tool for pre-HCT comorbidity assessment. The routine use of this tool would allow within-center and cross-center outcome comparisons.* Moreover, it has been adopted by the CIBMTR.

Geriatric Assessments

In patients ≥ 65 years receiving chemotherapy, geriatric assessment (GA) should be used to identify vulnerabilities that are not routinely captured in oncology assessments. There are many variants of GAs with different domains. In principle, it would include domains of functional status, physical performance and falls, comorbid medical conditions, depression, social activity/support, nutritional status, and cognition.

The comprehensive geriatric assessment (CGA) include domains of functional status, cognitive function, comorbidities & geriatric syndromes, polypharmacy, psychological status, social support and nutritional status and is suggested in the practice guidelines developed by the National Comprehensive Cancer Network[98] as well as ASCO[99]. The use of such tools are able to predict adverse outcomes (including chemotherapy toxicity and mortality), which can help inform shared discussion making with the patient. The ASCO guidelines[99] suggest a Minimum Data Set for Practical Assessment of Vulnerabilities in Older Patients (>65 years) With Cancer. Specifically, they recommend:

1. Predict chemotherapy toxicity (if clinically applicable): Cancer and Aging Research Group (CARG) or Chemotherapy Risk Assessment Scale for High-Age Patients tools
    a. *The CARG tool takes < 5 minutes to complete and is freely available online for use on the CARG website*
    b. *https://www.mycarg.org/?page_id=934*
2. Estimate (noncancer) life expectancy (if clinically applicable): ePrognosis[100], Project Big Life[101]
    a. *https://eprognosis.ucsf.edu/leeschonberg.php*
    b. *https://www.projectbiglife.ca/life-expectancy-home*
3. Functional assessment: instrumental activities of daily living
    a. *The Lawton Instrumental Activities of Daily Living. (IADL) Scale is commonly used where any dependence on any task signifies impairment[102].*
    b. *https://neurotoolkit.com/lawton-iadl-scale/*
4. Comorbidity assessment: medical record review or validated tool
    a. *See Section on HCT-CI*
5. Screening for falls, one question: how many falls or falls with an injury have you had in the previous 6 months (or since your last visit)?

    a. *A simple one-item can be useful: "How many falls have you had in the previous 6 months (or since your last visit)?"*
6. Screening for depression: Geriatric Depression Scale[103] or other validated tool
    a. *GDS 15 item: a score of 5 suggests depression and requires follow-up*
    b. *https://neurotoolkit.com/geriatric-depression-scale/*
7. Screening for cognitive impairment: Mini-Cog[104] or Blessed Orientation-Memory-Concentration test[105]
    a. *The Mini-Cog consists of two components, a 3-item recall test for memory and a simply scored clock drawing test*
    b. *https://mini-cog.com/mini-cog-instrument/standardized-mini-cog-instrument/*
8. Screening for malnutrition: weight loss/body mass index
    a. *Assess for Unintentional weight loss; 10% weight loss from baseline weight); BMI <21 kg/m^2.*

This link from the Cancer and Aging Research Group *provides online calculators for patient and healthcare providers for Geriatric Assessments: https://www.mycarg.org/?page_id=898*

The use of GA was able to identify older patients with inferior survival undergoing allogeneic HCT[106]. Specifically, limitations in instrumental activities of daily living (HR 2.38, 95%CI: 1.59–3.56; P<0.001), slow walk speed (HR 1.80, 95%CI: 1.14–2.83; P=0.01), high comorbidity by hematopoietic cell transplantation-specific comorbidity index (HR 1.56, 95%CI: 1.07–2.28; P=0.02), low mental health by short-form-36 mental component summary (HR 1.67, 95%CI: 1.13–2.48; P=0.01), and elevated serum C-reactive protein (HR 2.51, 95%CI: 1.54–4.09; P<0.001) were significantly associated with inferior overall survival. Further, it is notable that the 2-year overall survival was zero in patients >60 years in the presence of one abnormal Instrumental Activity of Daily Living (IADL) by Lawton, and a HCT-CI score of ≥3.

More recently, Deschler et al.[107] performed a concurrent GA by Up-and- Go and quality of life by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C-30 assessments in addition to disease-specific data in 106 older (median age 66 years) patients undergoing allogeneic HCT. Collecting data at 4 time-points (before HCT and days +30, +100 and +180), they demonstrate that negative prognostic factors for PFS were age (HR 1.084) and Comorbidity index by HCT-CI (HR 1.13), while the negative prognostic factors for OS were age (HR 1.08), performance status by Karnofsky Index (HR 0.97), quality of life by EORTC QLQ C- 30 fatigue (HR 1.09) and GA by Up-and-Go (HR 3.26). Geriatric assessments have also been utilized the autologous HCT setting for myeloma, where impairments in geriatric domains are common even among those considered to have a good performance states[108] and can identify patients who are at a greater risk for morbidity[109]. Such studies suggest and emphasize that CGA is strongly associated with post-HCT outcomes and has a higher HR, even when other traditional patient and disease variables are factored in.

Frailty & Functionality Assessment

The concepts that encompass frailty has been recently summarized by an excellent review article[110]. The authors suggest that the historic use of chronologic age, comorbidities and performance may be too simplistic to capture a full sense of vitality. They and others have suggested that the regular incorporation of frailty measurements such as CGA may be useful in evaluating fitness for HCT[111].

Implementation of routine GAs is impractical, however, as it requires qualified specialists to perform these evaluations (not readily available), and the time needed to perform them is often unavailable or too-taxing for patients. A pilot prospective study of a "clinic-friendly" Frailty & Functionality assessment in routine clinical assessment in allogeneic SCT has been published and involved performing the assessment successfully in approximately 5 minutes[111]. It can be used to calculate an HCT "frailty" score that identify patients as fit, "pre-frail", and frail, which has correlated with overall survival[112].

HCT Frailty Scale

Evaluated Parameter	Score – Normal 0, Abnormal – as indicated
Clinical Frailty Score ≥3	1.5
IADL Score ≥1 limitation	1
Timed Up & Go Test	1.5
Grip Strength	1 (Abnormal is <16kg (female) and <26kg (male))
Self-rated Health Questionnaire	1
Fall in last 6 months	1
Albumin level	1.5
C-reactive protein	2

A video on how to perform this assessment is available at the following link:
https://youtu.be/RPrCnWothlY

A total score is calculated, with fit ≤1, pre-frail >1 and <5.5, and frail ≥5.5. The estimated probabilities of 1-year OS in each group of frailty, were, respectively: 83.7%, 75.6%, and 52.8% ($p < 0.001$) in the training cohort and 90.3%, 69.5%, and 46.2% ($p < 0.001$) in the validation cohort[113]. Additionally, the estimated 1-year NRM of fit, pre-frail, and frail patients were 6.4%, 14.8%, and 31.2%, respectively. Frailty also did not necessarily correlate with performance status and HCT-CI score. Although, a clear cut-off score has not been established as to which patients should not be offered HCT, this should be considered an independent factor in the decision-making process for proceeding with allogeneic HCT.

Salas *et al.* externally validated their score via sixteen Spanish Institutions[113]. Between 2021 and 2023, 341 candidates for allogeneic HCT participated. They state: "Ninety-four (27.6%) adults were classified as fit, 203 (59.5%) as pre-frail, and 44 (12.9%) as frail. Frail patients were more likely to have a KPS<90% (OR 2.80, p<0.01) and an abnormal result of the Mini-Cog test (<3) (OR 8.21,

P<0.001). The probability of being frail was independent of age (continuous) (p=0.654), sex (p=0.323), and comorbidities (HCT-CI>3) (p=0.196) (multivariate binary regression analysis)". They demonstrate that 1-year OS was higher with frailty measured at the time of HCT admission; respectively, 20%, 66.8% and 78.9%. (p<0.001). Interestingly, they suggest that a pre-transplant rehabilitation (pre-hab) program may be able to modify this risk factor. In contrast, the value of frailty assessments in the autologous setting is less clear[114] where pre-HCT frailty did not correlate with prolonged hospitalization or overall survival. Others have reported that persistence of frailty determines poor outcomes[115].

Taken together, there appears to a complex interplay between frailty, disease status and type of HCT that determines post-HCT outcomes. Additionally, it is possible that frailty is a modifiable risk factor for post-HCT outcomes with pre-habilitative interventions.

Patient Eligibility for chimeric antigen receptor T-cell therapy (CAR-T)

The eligibility for CAR-T cells will be predominantly assessed on disease-based factors (see appropriate chapters for discussion). The principals as described in the preceding paragraphs for standard allogeneic and autologous HCT would apply. Recognizing there is a paucity of evidence, there is a sense that lower thresholds for eligibility from the perspective of patient factors may apply given that there is no high-dose therapy.

There are areas of uncertainty on whether a history of malignancy, allogeneic HCT, prior treatment with BiTE antibodies or CNS involvement represented an exclusion criteria[116]. The following table summarizes the eligibility criteria from large RCTs and the recommendations from EBMT/JACIE[117]. Our center would support these pragmatic guidelines.

Characteristics	ELIANA (ALL Kymriah™)	JULIET (CLMCL Kymriah™)	ZUMA-1 (High-grade B-cell NHL Yescarta™)	EBMT recommendations	Comment
Age limit (NHL)	N/A	≥ 18 years SPC-No data are available on children < 18 years of age	≥ 18 years SPC-No data are available on children < 18 years of age	No upper age limit	Decision should be based on physical condition rather than age
Age limit (ALL)	'Age 3 years at the time of screening to age 21 years at the time of initial diagnosis' SPC-up to 25 years of age	N/A	N/A	**Follow SPC	Ability to collect sufficient cells by apheresis can be a limiting factor in infants and small children

ECOG PS Performance Status	Karnofsky (age≥16 years) or Lansky (age < 16 years) PS ≥50 at screening	ECOG PS of either 0 or 1 at screening	ECOG PS of 0 or 1	>2 not recommended Note, however, that real-world data with Yescarta™ included patients with ECOG PS>2	Prognosis may be less poor in the decline in PS is due to active disease
History of malignancy	No prior malignancy, except carcinoma *in situ* of the skin or cervix treated with curative intent and with no evidence of active disease	No previous or concurrent malignancy except adequately treated BCC or SCC, *in situ* cancer of the breast or cervix treated and without recurrence for 3 years, primary malignancy resected and in remission for more than 5 years	No history of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years	Absence of history of malignancy other than carcinoma *in situ* (e.g. cervix, bladder, breast) unless disease-free and off therapy for at least 3 years	
Prior allo-HCT	Not excluded; however, excluded if grade II-IV acute or extensive chronic GvHD	Excluded	Excluded	Not a contraindication	Active GvHD is listed as a reason to delay treatment in the Kymriah ™ and Yescarta™ SPC
Prior anti-CD19/ anti-CD3 BiTE antibodies or any other CD19 therapy	Excluded Not a contraindication as per SPC	Excluded	Excluded if prior CD19 targeted therapy	Not a contraindication	
Previous CAR-T-cell therapy	Not applicable in trials Not in SPC	Not applicable in trials Not in SPC	Excluded	Not a contraindication	Further Car T-cell therapy outside of clinical trials is to be avoided
History of autoimmune disease	Not an exclusion criterion	Not an exclusion criterion	Not an exclusion criterion	Not recommended in active autoimmune disease resulting in end-organ injury or requiring systemic immune-suppression or systemic disease-modifying agents within the last 2 years	Individualized risk-benefit assessment required
Current systemic immune-suppressive treatment	Any GvHD therapy must be stopped more than 4 weeks prior to enrollment to confirm that	Any immunosuppressive medication must be stopped more than 4 weeks prior to enrollment	Any immunosuppressive medication must be stopped more than 4 weeks to enrollment	Contraindication	Intermittent topical, inhaled or intranasal corticosteroids are allowed

	GvHD recurrence in not observed				
Existing or suspected fungal, bacterial, viral, or other infection	Active of latent HBV or HCV (test within 8 weeks of screening) or any uncontrolled infection at screening	Uncontrolled active or latent HBV or active HCV; Uncontrolled acute life-threatening bacterial, viral or fungal infection (e.g. blood cultures positive < 72 h prior to screening)	Known history of HIV, HBV (HepBs Ag positive) or HCV (anti-HCV); Clinically significant active infection, or currently receiving IV antibodies or within 7 days of enrollment	Relative contra-indication; individualized risk-benefit assessment required	Active infection should be controlled and on treatment prior to leukapheresis
History of CNS disease	CNS involvement by malignancy defined as CNS-3 as per NCCN guidelines excluded; however, those with history of effectively treated CNS disease were eligible	Active CNS involvement by malignancy excluded	Subjects with detectable CSF malignant cells, or brain metastases, or with history of CSF malignant cells or brain metastases excluded	Relative contra indication; individualized risk-benefit assessment required	Caution required as higher risk of neurological toxicity

ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; EBMT: European Society for Blood and Marrow Transplantation; N/A: not available; SPC: summary of product characteristics; ECOG: Eastern Cooperative Oncology Group; PS: performance status; BCC: basal cell carcinoma: SCC: squamous cell carcinoma; allo-HCT: allogenic hematopoietic cell transplantation; GvHD: graft-versus-host disease; BiTE: bispecific monoclonal antibodies; CAR: chimeric antigen receptor; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; CNS: central nervous system; NCCN: National Comprehensive Cancer Network.

Psychosocial Assessment

Psychosocial assessment(s) forms an important piece in pre-HCT evaluation, performed by different clinicians –physicians, psychologists, social workers and nurses. A dedicated program and staff is preferred to ensure consistency and expertise.

The following observations could suggest that measures (complex interventions) that broadly support and improve psychosocial health may lead to improve post-HCT psychosocial, patient reported outcomes as well as traditional medical post-HCT outcomes (e.g. survival). A recent cross-sectional sample of 351 HCT recipients at NCI-designated centers suggest that only 14% of patients presenting with pre-HCT psychosocial evaluation utilized psychotherapy services – patients who utilized services reported lower levels of distress, depression and anxiety[118].

Psychosocial Uncertainties

Foster et al. performed a survey of HCT professionals in 2006 using 17 case vignettes each representing a different psychosocial issue to which respondents indicated whether or not they would recommend proceeding with allogeneic HCT. In six vignettes, at least 64% indicated do not proceed: suicidal ideation (86.8%) uses addictive illicit drugs (81.7%), history of noncompliance (80.5%), no lay caregiver (69.3%), alcoholic (64.8%), and mild dementia/Alzheimer's (64.4%). In 10 vignettes, at least 73% indicated proceed. On four vignettes, professional subgroups differed in their recommendation on whether or not to proceed with allogeneic BMT[119].

Interestingly, a follow-up survey of 62 chairpersons of the hospital ethics committees (HEC) with an accredited HCT program elicited whether they would recommend HCT in the 6 scenarios (as above) where the majority HCT clinicians would not. Opinions regarding transplant differed in one case only, in a patient with mild dementia; 27% of HEC chairpersons recommended not proceeding with BMT, which was significantly lower than that of nurses (68%, P<0.001), physicians (63.5%, P<0.001) and social workers (51.9%, P=0.05)[120].

Psychosocial pre-HSCT Assessment Tools

Although a Gestalt approach to assessment is feasible, a formal validated tool is preferred. Indeed, there are numerous general screening tools including distress screening tools[121-123], but may not be specific to the HCT population.

Garcia et al. developed a psychosocial structured interview to assess candidates for HCT with the interview averaging 50 minutes to complete[124]. In the absence of a comprehensive and validated tool, we suggest using this structured interview tool to ensure consistent history taking. The elements garnered from this structured inter- view could potentially be utilized to subsequently populate other scales and questionnaires.

Psychosocial assessment of candidates for transplantation (PACT)

This scale captures information in four domains (social support, psychological health, lifestyle factors, and patients understanding of the transplant process) with eight subscales, each rated on a 5-point scale[125]. This scale was originally developed for clinical decision-making in psychosocial screening of organ transplant (heart and liver) candidates[126]. The use of PACT rating at a single institution study was associated with non-relapse mortality (HR 0.82 per point increase [95% CI, 0.69-0.98], P=0.03), but not with overall survival (HR 0.91 [95% CI, 0.79-1.05], P=0.18). There was no association between final PACT rating and neutrophil or platelet engraftment, acute or chronic GVHD, or relapse[127]. In contrast, data from Japan suggests that lower PACT scores in the domain of compliance with medications and medical advice were significantly associated with poorer OS (HR = 1.75, P = 0.03)[128].

Patient Health Questionnaire (PHQ)

In a small randomized study[129], the Patient Health Questionnaire (PHQ) was used to assess for depressive disorders, anxiety, substance abuse, and problems in occupational or interpersonal functioning (functional disruption) and was provided to patients before meeting with their medical provider (n = 50; experimental group) or afterwards (n = 51; control group). The prevalence of clinically significant depression (21%), anxiety (14%), or suicidal ideation (8%) did not differ between the 2 groups. Patients in the experimental group were likely to have discussion of psychological symptoms than the control group (68% versus 49%, P = .05). Medical providers were significantly more satisfied with the management of psychological issues for the experimental group (P < .001). Patients with depression or anxiety were significantly more likely to prefer the PHQ be used at future visits (P = .02 and P = .001, respectively).

The Transplant Evaluation Rating Scale (TERS)

The TERS score is a compilation of scores on 10 weighted factors: psychiatric history of Axis I disorder, psychiatric history of Axis II disorder, substance abuse, health behaviors, compliance, quality of family/social support, history of coping, coping with disease and treatment, quality of affect, and mental status. The TERS was prospectively used at a single institution[130]; where patients in the high-risk TERS group had significantly longer hospital stays during the first 180 days and 1 year post–allogeneic HSCT compared with the low-risk group (16 vs 13 and 21 vs 16 days; P = .05 and .02, respectively). In their multivariable analysis, intermediate- and high-risk TERS scores predicted for inferior OS, similar DFS, and higher NRM compared with low-risk TERS score. In a subset analysis of patients with low/intermediate risk per Disease Risk Index, multivariable analysis showed that high- and intermediate-risk TERS scores predicted for significantly worse OS, worse DFS, higher NRM, and similar relapse rates compared with low-risk TERS score. Additionally, poor TERS scores have also been associated with higher readmission rates[109].

Distress

Distress is a complex term that is utilized to embrace multiple aspects mental health states. This broad concept has been evaluated in the context of HCT using different scales (validated and unvalidated). Consequently, it is challenging to given firm conclusions on its association with post-HCT outcomes.

Cancer and treatment specific distress pre-allogeneic HCT is associated with post-traumatic stress disorder (PTSD). Specifically, uncertainty, appearance and sexuality as well as health burden were concepts associated with PTSD[131]. It has been estimated that PTSD occurs in 3.3% of HCT recipients; interestingly PTSD in HCT recipient caregivers is estimated at 6.6% (p=0.02)[132]. Pre-HCT psychological distress as measured with an unvalidated Likert-like scale was unrelated to survival in a single centered study[133].

Taken together, the presence of pre-transplant patient distress may have psychologic consequences post-transplant but does not clearly influence survival. Moreover, the management of distress of peri-

HCT is not well-defined with a recent systematic review suggesting psychological interventions (cognitive behavioral or emotional processing methods) may provide some benefit in alleviating distress in HCT but conclusions remain tentative in light of methodological limitations and risk of bias in their included studies[134].

Interestingly, a recent RCT randomly assigning 160 patients undergoing HCT to receive inpatient palliative care integrated with transplant care (n = 81) or transplant care alone (n=79) suggest that intervention participants reported lower depression symptoms, lower PTSD symptoms but no difference in HRQOL or anxiety[135]. The intervention was composed of a palliative care clinician reviewing care at least twice a week broadly addressing topics of nausea, pain and mucositis, fatigue, insomnia, bowel problems, and psychological distress.

Anxiety and Depression

A recent prospective observational study in six German allogeneic HCT centers evaluated the prevalence of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS), comparing it to gender- matched controls (reference). They demonstrate that the rates of HADS-defined depression increased from 12% before HCT to up to 30% at 5 years after HCT, while anxiety was highest before HCT and settles to control baseline after HCT.

Pre-HCT clinical depression is associated with lower overall survival and higher acute GVHD among allogeneic transplant recipients[136]. Further, it is associated with fewer days alive and out of hospital within the 1st 100 days after autologous and allogeneic setting. This could suggest routine screening for depression and providing pre-emptive pharmacologic and/or psychologic therapies to mitigate this risk factor.

Non-Compliance

Compliance has been defined as the extent to which a person's behavior (in terms of medication, following diets, or executing lifestyle changes) coincides with medical or health advice[137]. The prevalence on non-compliance is unknown in the HCT population[138]. Rate of adherence to oral medications ranged from 33% to 94.7%[139,140] where it has been associated with increased risk of infections in the pediatric HCT setting[141]. Overall, there is a paucity of research that evaluates the consequences of noncompliance in adult HCT patients, nor the predictive value of pre-transplant compliance in determining post-transplant behavior. Further, the impact of compliance on therapeutic outcomes and the interventions that effectively increase compliance are all unknown.

Mumby et al. in a study of 151 autologous HCT patients suggests 80% of patients were deemed non-compliant with an aspect of the transplant on ≥1 day[142]. Non-compliance was defined as refusal of oral hygiene, prescribed exercise programs, oral nutrition and/or prescribed medications. In a multivariate analysis, the predictors of non-compliance in their cohort of patients were 1) gender - men, 2) presence of depression, 3) global distress and 4) nausea and vomiting severity. Interestingly,

a small and older study of 92 HCT patients did not identify compliance as predictive of post-HCT outcomes[143].

More recently, a single centre study from Japan retrospectively assigning the PACT scale to 119 HCT recipients demonstrate that lower PACT scores in the domain of compliance with medications and medical advice were significantly associated with poorer OS (HR = 1.75, P = 0.03)[128].Similarly, the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) scale was able to predict nonadherence defined as at least 1 life-threatening nonadherence event in the first 6 months post-transplant[144].

It has been suggested that the following considerations may improve compliance[138]: 1) Provision of clear and consistent information with specific information on why consistent compliance is beneficial, 2) simplify treatment, 3) prioritize environmental precautions and health behaviors, 4) suggest ways to assist with forgetfulness, and 5) tailor the regimen as much as possible to the lifestyle of the patient.

Due to the paucity of data, non-compliance should not be an absolute contraindication to HCT.

Substance Abuse

Lifetime substance abuse appears to be associated with adverse outcomes post-HCT[145]. In a single center case –control study, Chang et al. identified 17 individuals with lifetime substance abuse where with alcohol (71%), marijuana (30%), and opiates (30%) were identified as the principal substances of abuse. They identified controls, matching for disease and stage, type of transplant, pre-HCT conditioning regimen, and age. Survival analysis demonstrated reduced survival times for patients with substance abuse (p = .0022)[146] with 15 of 17 patients dying within the first year. Interestingly, a follow-up study did show this association[147]. Graf et al. suggest that a history of alcohol use disorder was associated with non-relapse mortality (HR 2.17; p=0.004) in an analysis of 754 patients undergoing autologous HCT for lymphoma at a single centre[148].

Due to the paucity of data, substance abuse should not be an absolute contraindication to HCT.

Other Psychological Functioning and Coping Styles

Data on aspects of psychological functioning/coping style is sparse. However, a recent study evaluating 332 recipients of HCT using measures of illness perceptions (beliefs about cancer consequences and course, personal and treatment control over cancer, and understanding of one's cancer) suggest that greater personal and treatment control was associated with a healthier diet and reported greater well-being. Further, a better understanding of their cancer also was associated with a healthier diet, less depression, less anxiety, and greater well-being[149]. In addition, greater personal resilience (composite variable of self-esteem, mastery, and optimism) may promote better psychologic adjustment via improvements in depressive symptoms with decreased use of

maladaptive meaning-making (searching for a reason for one's illness) was associated with less PTSD symptoms[150]. Similar findings were noted by Barata *et al.*[151].

Financial/Socioeconomic Status

The socioeconomic status (SES) of the recipient is associated with poor HCT outcomes due to multiple interrelated factors[152,153]. Specifically, lower attained education was associated with increased distress (P = .002), lower income was related to worse physical functioning (P = .005) and increased distress (P = .008), lower attained education was associated with worse physical functioning (P < .01)[154].

Further, low SES is also associated with higher risks of all-cause mortality (hazard ratio (HR) 1.98, P=0.012) and non-relapse mortality (NRM) (HR 2.22, P=0.028), but similar risks of relapse mortality (HR 1.01, P=0.97) compared with high SES patients. A trend toward better survival and lower NRM for high SES patients with no chronic GVHD was observed; low SES patients without GVHD had similar survival as patients with chronic GVHD[155]. Similar results were noted by Silla et al[156]. In contrast, Hamilton et al. suggest that SES was not associated with chronic GVHD outcomes[157].

Interestingly, Knight et al. suggests that low SES effects are modulated through upregulation of conserved transcriptional response to adversity (CTRA)[158]. From a psychologic perspective, it has been suggested that the effects of "objective" SES is modulated through the individual's "subjective" SES[159] .

The influence of SES is less clear in the autologous setting[160,161] and it is likely that other patient and/or disease factors are more important in this setting.

Caregiver Considerations

There is an increasing reliance on caregivers as HCT programs shift towards an outpatient setting. In general, outpatient HCT are performed when there is a consistent caregiver. This invariably shifts the burden of care on to the caregiver. Indeed, caregivers are emotionally vulnerable than patients before HCT where cancer-related distress was the strongest correlate of anxiety and depression in both patients and caregivers[162]. Acknowledging, understanding and supporting the caregiving role would be prudent from the perspective of the HCT program.

The consistent presence of a caregiver is independently associated with superior post-allogeneic HCT overall survival[125,143,163], but the results are mixed[164,165].The optimal caregiver(s) and the quality of the caregiver remains unclear, however there is evidence to suggest the quality of the caregiver may matter more than caregiver consistent presence[166]. Caregivers commonly report elevated distress pre-HCT and both patient and caregiver distress were associated with patient HRQOL, with patients' physical well-being a significant contributor to caregiver well-being[167]. Interestingly, patient's perception of over-benefiting within a dyadic relationship was associated with patient distress, but not

the patient's self-perceived burden[168]. Separately, there is evidence to suggest that unmarried status is associated with worse sleep in the allogeneic setting[154].Overall, there is a paucity of evidence to guide practice as summarized by a systematic review[169].

Integrating Psychosocial Factors

Due to lack of definitive evidence, none of the psychosocial factors discussed above represent absolute contraindications to HCT. However, it needs to be recognized that there is also a lack of safety data for patients who exhibit severe psychiatric illness (e.g. major depression, suicidal ideation/planning, psychotic illness with delusions/hallucinations, etc.), active abuse of alcohol or street drugs, or those who demonstrate profound degrees of non-compliance. Prior to accepting that such patients are eligible to proceed with HCT, they require early referral (ideally at diagnosis of malignancy) to psychology, social work, or psychiatry as appropriate. If the patient does not demonstrate engagement and compliance with psychosocial services, or if psychosocial concerns are not stabilized, transplant may be deferred in order to prioritize patient safety. This would be considered especially when psychosocial factors severely impair functioning and/or adherence to treatment plans or place the patient at immediate safety risk (e.g., actively psychotic, suicidal, substance dependent, extreme poverty, high degree of family conflict).

Table 1: Optimal physiologic parameters for transplant eligibility[1]

Physiologic Parameters	Optimal "Cut-Offs"
Age and Performance Status	
Age (years)	≤65
KPS	>60
Pulmonary	
FEV_1 (% of predicted value)	>60
DLCO (% of predicted value)	>60
Cardiac	
LVEF (%)	>45
Heart rhythm	Normal
Hepatic	
Serum Bilirubin	<2 x normal
ALT/AST/ALP	<2 x normal
Renal	
Serum Creatinine	<2 x normal
Second active malignancy	Absent
Pregnancy test	Negative
Uncontrolled Infections including dental	Absent

KPS=Karnofsky performance Status; FEV1=force expiratory volume in 1 second; DLCO=diffusion capacity; ALT/AST/ALP=alanine aminotransferase/aspartate aminotransferase/alkaline phosphatase; LVEF= Left ventricular ejection fraction

Table 2: Hematopoietic cell transplantation specific comorbidity index (HCT-CI)[83]

Co-morbidity	Definition/compartments	Yes	Score
1. Arrhythmia	-Atrial fibrillation* -Atrial flutter* -Sick sinus syndrome* -Ventricular arrhythmia*	☐ ☐ ☐ ☐	1
2. Cardiovascular	-Coronary artery disease* -Congestive heart failure* -Myocardial infarction* -Ejection fraction ≤50%§	☐ ☐ ☐ ☐	1
3. Inflammatory bowel disease	-Crohn's disease* -Ulcerative colitis*	☐ ☐	1
4. Diabetes	-Treated with insulin or oral hypoglycemic drugs§	→	1
5. Cerebro-vascular	-Transient ischemic attacks* -Cerebro-vascular ischemic or hemorrhagic stroke*	☐ ☐	1
6. Depression/anxiety	-Requiring psychological consultation and/or specific treatments§	→	1
7. Hepatic - mild	-Chronic hepatitis§ -Bilirubin >ULN- 1.5 X ULN§ -AST/ALT >ULN- 2.5 X ULN§	☐ ☐ ☐	1
8. Obesity	-Body mass index >35 (adults)§ -Body mass index-for-age ≥95% percentile (children)§	☐ ☐	1
9. Infection	-Requiring anti-microbial treatment before, during, and after the start of conditioning§	→	1
10. Rheumatologic	-Requiring Treatment*	→	2
11. Peptic ulcer	-Confirmed by endoscopy and requiring treatment*	→	2
12. Renal	-Serum creatinine >2mg/dl (or >177µmol/L)§ -On dialysis§ -Prior renal transplantation*	☐ ☐ ☐	2
13. Pulmonary - Moderate	-DLco corrected for hemoglobin 66-80% of predicted§ -FEV1 66-80% of predicted§ -Dyspnea on slight activity§	☐ ☐ ☐	2
14. Pulmonary - Severe	-DLco corrected for hemoglobin ≤ 65% of predicted§ -FEV1 ≤ 65% of predicted§ -Dyspnea at rest or requiring oxygen therapy§	☐ ☐ ☐	3
15. Heart valve disease	-Except asymptomatic mitral valve prolapse§	→	3
16. Prior solid malignancy	-Treated with surgery, chemotherapy, and/or radiotherapy, excluding non-melanoma skin cancer*	→	3
17.Hepatic - moderate/severe	-Liver cirrhosis§ -Bilirubin > 1.5 X ULN§ -AST/ALT > 2.5 X ULN§	☐ ☐ ☐	3
		Total Score	

*Diagnosed at any time in the patient's past history
§Detected at the time of pretransplant assessment - ULN indicates upper limit of normal; DLco, diffusion capacity of carbon monoxide; FEV1, forced expiratory volume in one second; AST, aspirate aminotransferase; and ALT, alanine aminotransferase

The HCT-CI is able to classify patients into three risk groups:

	Non-Relapse Mortality		Overall Survival	
	HR (95% CI)	2-year %	HR (95% CI)	2-year %
Score				
0	1.0	14	1.0	71
1 - 2	1.42 (0.8-2.7)	21	1.31 (0.8-2.0)	60
>3	3.54 (2.0-6.3)	41	2.69 (1.8-4.1)	34

Table 4: Psychosocial Assessment Interview of Candidates for Hematopoietic Stem cell Transplantation (PAIC-HSCT)[124].

1. IDENTIFICATION, SOCIAL AND DEMOGRAPHIC INFORMATION

1.1. Name: _____

1.2. Gender: _____ (1-Male / 2-Female)

1.3. Date of birth: _____/_____/_____

1.4. Marital status: _____ (1-Single / 2-Married / 3-Widowed / 4-Divorced)

1.5. Instruction level: _____ years

1.6. Do you have any difficulties to read? _____ (1-Yes / 2-No)

1.7. Occupation: _____ _____ _____

1.8. Current job status: _____ (1-Employed / 2-Unemployed / 3-Retired / 4-Sick leave)

1.9. Job contract: _____ (1-Formal / 2-Unofficial)

1.10. What is the longest period you remained in a job? _____ years

1.11. Monthly income: _____

1.12. Ethnicity: _____ (1-Caucasian, 2-Black, 3-Asian, 4-Brown)

1.13. Religion: 1._____ 2. None

1.14. How often do you visit temples or participate at church meetings? _____ times/month

1.15. Children: _____

1.16. Home address: _____

1.17. Telephone number: _____

1.18. Person who takes care of you: _____

1.19. Your family relationship with this person: _____

1.20. His/her telephone number: _____

1.21. Donor: _____

1.22. Family relationship with your donor: 1. _____ 2. None

2. COMPREHENSION OF THE ILLNESS

2.1. How have you discovered you are sick?

2.2. Do you know what your illness is? ☐Y ☐N ☐Partially

2.3. Do you know any possible causes of this illness? ☐Y ☐N ☐Partially

2.4. Do you know consequences and treatments of your illness? ☐Y ☐N ☐Partially

2.5. Have you got any previous medical treatment?

2.6. What medicines do you currently take? ☐Y ☐N ☐Partially

3. COMPREHENSION OF THE TRANSPLANTATION

3.1. What is bone marrow ☐Y ☐N ☐Partially

3.2. What is a hematopoietic stem cell transplant and how can it help your health? ☐Y ☐N ☐Partially

3.3. Considering your clinical condition, what are the advantages and disadvantages of the HSCT? ☐Y ☐N ☐Partially

3.4. Do you know why you have been chosen to undergo a HSCT? ☐Y ☐N ☐Partially

3.5. Can you tell me what you know about what will happen during the transplant once you are in hospital? ☐Y ☐N ☐Partially

3.6. Can you tell me what you know about the period following your discharge from hospital? ☐Y ☐N ☐Partially

3.7. What are the possible side effects of the medicines used during the transplantation? ☐Y ☐N ☐Partially

3.8. Do you think you understand all the risks of the treatment you are going to go through? ☐Y ☐N ☐Partially

3.9. What are the possible complications and late effects of a HSCT? ☐Y ☐N ☐Partially

3.10. Did you have the chance to meet somebody who has already undergone a HSCT? ☐Y ☐N ☐Partially

3.11. How was this meeting?

3.12. Do you believe you have received enough information to make a decision about HSCT? ☐Y ☐N ☐Partially

4. MEDICAL COMPLIANCE

4.1. In previous medical treatments did you miss consultations? Did you refuse to take prescribed drugs or did you stop taking them without medical consent? Did you refuse to follow medical advices or restrictions? Did you refuse to do any exams prescribed by your doctor? ☐Y ☐N ☐Partially

4.2. Have you ever interrupted a medical treatment before the scheduled end? ☐Y ☐N ☐Partially

(Questions 4.3 - 4.5 are about the pre-transplant procedures)

4.3. Did you miss any consultations with your doctor? If yes, tell us why. ☐Y ☐N

4.4. Did you refuse to follow medical advices or restrictions or did you refuse to do any exams prescribed by your doctor? If yes, tell us why. ☐Y ☐N ☐Partially

4.5. Did you refuse to attend the psychosocial assessment? If yes, tell us why. ☐Y ☐N ☐Partially

(Question 4.6 should be answered by the interviewer)

4.6. Is the patient against the psychosocial evaluation? ☐Y ☐N ☐Partially

5. LIFE STYLE

5.1. Do you practice physical exercises regularly or did you use to do it before the illness? ☐Y ☐N ☐Partially

5.2. Do you have a healthy eating pattern? ☐Y ☐N ☐Partially

5.3. BMI[1]: _____ Weight: _____kg Height: _____m

5.4. Do you usually have spare moments or meetings with friends? ☐Y ☐N ☐Partially

5.5. Are you satisfied with your sexual performance? ☐Y ☐N ☐Partially

5.6. Has the illness affected your sexual performance? ☐Y ☐N ☐Partially

5.7. After the transplant you will need to change your way of living. Do you agree with this? ☐Y ☐N ☐Partially

5.8. Are you satisfied with the your quality of life ☐Y ☐N ☐Partially

Smoking:

5.1. Do you smoke? (if you have stopped, please answer the next items 5.2 and 5.4) ☐Y ☐N

5.2. How long did you smoke? _____ years

5.3. How long did you stop smoking? _____ years

5.4. The fact of being ill has affected your decision of stopping smoking? ☐Y ☐N ☐Partially

Alcoholism:

5.5. Have you ever felt you should cut down on your drinking? ☐Y ☐N

5.6. Have people annoyed you by criticizing your drinking? ☐Y ☐N

5.7. Ever felt bad or guilty about your drinking? ☐Y ☐N

5.8. Have you ever had a drink first thing in the morning to steady Your nerves or get rid of a hangover? ☐Y ☐N

6. COPING STRATEGIES

6.1. How do you usually behave in difficult situations?

6.2. How did you face the fact of being sick when your illness was diagnosed?

6.3. How have you changed your life due to the illness?

6.4. How do you face the fact that you need to undergo to transplantation?

As you respond to each of the statements below, please keep in mind the moment when your doctor told you would need to undergo to a Hematopoietic Stem Cell Transplantation. Read each statement carefully and indicate to what extent you used it in the situation, by putting on a circle in front of the response. (0 – Does not apply or not used; 1 – Used somewhat; 2 – Used quite a bit; 3 – Used a great deal)

6.5.	I took it out on other people	0	1	2	3
6.6.	I expressed anger to the person(s) who caused the problem	0	1	2	3
6.7.	I made light of the situation and refused to get too serious about it	0	1	2	3
6.8.	I refused to believe that it had happened	0	1	2	3
6.9.	I tried to keep my feelings to myself	0	1	2	3
6.10.	I looked for the silver lining, so to speak; I tried to look on the bright side of things	0	1	2	3
6.11.	I asked a relative or friend I respected for advice	0	1	2	3
6.12.	I talked to someone about how I was feeling	0	1	2	3
6.13.	I made a promise to myself that things would be different next time	0	1	2	3
6.14.	I criticized or lectured myself	0	1	2	3
6.15.	I wished that the situation would go away or somehow be over with	0	1	2	3
6.16.	I fantasized or wished about how things could turn out	0	1	2	3
6.17.	I knew what had to be done, so I doubled my efforts to make things work	0	1	2	3
6.18.	I am making a plan of action and following it	0	1	2	3
6.19.	I rediscovered what is important in life	0	1	2	3
6.20.	I changed or grew as a person in a good way	0	1	2	3

7. MENTAL STATUS EXAMINATION

7.1. Memory disorders ☐Y ☐N _____

7.2. Attention or concentration disorders ☐Y ☐N _____

7.3. Sleep disorders ☐Y ☐N _____

7.4. Appetite disorders ☐Y ☐N _____

7.5. Energy level change ☐Y ☐N _____

7.6. Loss of interest in activities ☐Y ☐N _____

7.7. Panic attack ☐Y ☐N _____

7.8. Speech disturbance ☐Y ☐N _____

7.9. Impulsiveness ☐Y ☐N _____

7.10. BPRS (Brief Psychiatric Rating Scale)[2]

This form consists of 18 symptom constructs, each to be rated in a 7-point scale of severity ranging from 'not present' to 'extremely severe' If a specific symptom is not rated, mark 'NA' (not assessed). Circle the number headed by the term that best describes the patient's present condition

Somatic concern	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Anxiety	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Emotional Withdrawal	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Conceptual disorganization	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Guilt	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Tension	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Mannerisms and posturing	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Grandiosity	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Depression	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Hostility	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Suspiciousness	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Hallucinations	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Motor retardation	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Uncooperativeness	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Unusual thought content	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Blunted affect	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Excitement	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7
Disorientation	0 --------- 1 --------- 2 --------- 3 --------- 4 --------- 5 --------- 6 --------- 7

8. PSYCHIATRIC HISTORY

8.1. Psychotic disorders ☐Y ☐N _____

8.2. Depressive disorders ☐Y ☐N _____

8.3. Anxiety disorders ☐Y ☐N _____

8.4. Eating disorders ☐Y ☐N _____

8.5. Suicide attempts ☐Y ☐N _____

8.6. Psychiatric hospitalizations ☐Y ☐N _____

8.7. Use of psychotropic drugs (What of them) ☐Y ☐N _____

8.8. Use of home-made teas or beverages with calming effects? ☐Y ☐N _____

8.9. Use of alcohol (Duration and intensity) ☐Y ☐N _____

8.10. Use of prohibited or illegal drugs (Kind, duration of use motivation to quit) ☐Y ☐N _____

8.11. Violent behavior ☐Y ☐N _____

8.12. Problems with the police ☐Y ☐N _____

9. FAMILY HISTORY

9.1. Are there in your family any relatives who have or had any psychiatric problems (treatments, hospitalizations, suicide, and use of calming drugs or antidepressants)? ☐Y ☐N

9.2. Has anyone in your family used illegal drugs? ☐Y ☐N

9.3. Did anyone in your family die in the past six months? ☐Y ☐N

9.4. Has any relative or friend of yours had cancer?
If yes, could you please tell me how this experience was? ☐Y ☐N

10. SOCIAL AND FAMILY SUPPORT

10.1. In some of the stressful situations you have been through, who has given you emotional support? _____

10.2. In financial difficulty, who has given you economic support? _____

10.3. Since the beginning of your disease, who has given you emotional support? _____

10.4. Since the beginning of your disease, who has given you financial support? _____

10.5. Who will take care of you (caregiver) during your hematopoietic stem cell transplant (HSCT)? _____

10.6. Did your caregiver attend consultations with you? Do you think he/she was well informed about the care you will need during your recovery?_____

10.7. Please, tell me about the relationship between you and the caregiver? _____

11. EXPECTATION OF THE TRANSPLANTATION

11.1. How do you think this treatment will be?

11.2. Do you worry about the failure of this treatment?

11.3. How do you think your hospitalization time will be? And the recovery time after HSCT?

11.4. Do you believe you will recover your previous health status after the transplant? If you believe it, how long you think it will take you to be recovered? ☐Y ☐N ☐ Partially

11.5. Considering your answers above tell us about your plans for the future?

(Make the following questions only at the end of the interview, after all other questions are answered)

While you answered these questions you had the opportunity to think about many aspects of this moment of your life: your understanding about the illness and about your transplant, your expectations, your emotional feelings, the way you face crisis situations, the way you follow medical prescriptions, your lifestyle, how your family is and how you can count or rely on it. Furthermore, you had the opportunity to think about how you enjoy your life:

Do you think this interview is too long or boring? ☐Y ☐ N ☐ Partially

Do you think this interview helped you get prepared for the transplant? ☐Y ☐ N ☐ Partially

Do you think this interview helped you think about aspects concerning your illness or your transplant which you had not considered before? ☐ Y ☐ N ☐ Partially

Would you like to make any comments? ☐ Y ☐ N ☐ _____

References

1. Hamadani M, Craig M, Awan FT, Devine SM. How we approach patient evaluation for hematopoietic stem cell transplantation. *Bone Marrow Transplant*. Aug 2010;45(8):1259-68. doi:10.1038/bmt.2010.94
2. Deeg JHS, B.M. Determining eligibility for allogeneic hematopoietic cell transplantation. In: Chao N, ed. *UpToDate*. Wolters Kluwer; 2023.
3. Holmberg LAD, J.H.; Sandmaier, B.M. . Determining eligibility for autologous hematopoietic cell transplantation. In: Chao N, ed. *UpToDate*. Wolters Kluwer; 2023.
4. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol*. May 20 2007;25(15):1993-9. doi:10.1200/JCO.2006.09.0100
5. Badros A, Barlogie B, Siegel E, et al. Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *Br J Haematol*. Sep 2001;114(3):600-7. doi:10.1046/j.1365-2141.2001.02976.x
6. Siegel DS, Desikan KR, Mehta J, et al. Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood*. Jan 1 1999;93(1):51-4.
7. Kumar SK, Dingli D, Lacy MQ, et al. Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: Results from a matched pair analysis. *Am J Hematol*. Aug 2008;83(8):614-7. doi:10.1002/ajh.21191
8. Sharma M, Zhang MJ, Zhong X, et al. Older patients with myeloma derive similar benefit from autologous transplantation. *Biol Blood Marrow Transplant*. Nov 2014;20(11):1796-803. doi:10.1016/j.bbmt.2014.07.013
9. Elstrom RL, Martin P, Hurtado Rua S, et al. Autologous stem cell transplant is feasible in very elderly patients with lymphoma and limited comorbidity. *Am J Hematol*. Apr 2012;87(4):433-5. doi:10.1002/ajh.23108
10. Martin N, Borchiellini D, Coso D, et al. High-dose chemotherapy with carmustine, etoposide, cytarabine and melphalan followed by autologous stem cell transplant is an effective treatment for elderly patients with poor-prognosis lymphoma. *Leuk Lymphoma*. 2015;56(8):2379-87. doi:10.3109/10428194.2014.1001987
11. Chihara D, Izutsu K, Kondo E, et al. High-dose chemotherapy with autologous stem cell transplantation for elderly patients with relapsed/refractory diffuse large B cell lymphoma: a nationwide retrospective study. *Biol Blood Marrow Transplant*. May 2014;20(5):684-9. doi:10.1016/j.bbmt.2014.01.025
12. Bolon YTA, R.;Allbee-Johnson, M;Estrada-Merly, N.;Lee, S.J. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2022. . Center for International Blood & Marrow Transplant Research.
13. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. *J Clin Oncol*. Jan 20 2010;28(3):405-11. doi:10.1200/JCO.2009.21.8073
14. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol*. Apr 10 2010;28(11):1878-87. doi:10.1200/JCO.2009.25.4821
15. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. Nov 2 2011;306(17):1874-83. doi:10.1001/jama.2011.1558
16. Rosko A, Artz A. Aging: Treating the Older Patient. *Biol Blood Marrow Transplant*. Feb 2017;23(2):193-200. doi:10.1016/j.bbmt.2016.11.007
17. Muffly LS, Boulukos M, Swanson K, et al. Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. *Biol Blood Marrow Transplant*. Mar 2013;19(3):429-34. doi:10.1016/j.bbmt.2012.11.006
18. Holmes HM, Des Bordes JK, Kebriaei P, et al. Optimal screening for geriatric assessment in older allogeneic hematopoietic cell transplantation candidates. *J Geriatr Oncol*. Oct 1 2014;5(4):422-30. doi:10.1016/j.jgo.2014.04.004
19. Liu Y, Johnson SM, Fedoriw Y, et al. Expression of p16(INK4a) prevents cancer and promotes aging in lymphocytes. *Blood*. Mar 24 2011;117(12):3257-67. doi:10.1182/blood-2010-09-304402
20. Liu Y, Sanoff HK, Cho H, et al. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell*. Aug 2009;8(4):439-48. doi:10.1111/j.1474-9726.2009.00489.x
21. Melzer D, Frayling TM, Murray A, et al. A common variant of the p16(INK4a) genetic region is associated with physical function in older people. *Mech Ageing Dev*. May-Jun 2007;128(5-6):370-7. doi:10.1016/j.mad.2007.03.005
22. Lagro J, Studenski SA, Olde Rikkert MG. Predicting chemotherapy toxicity in older adults and the importance of geriatric assessment. *J Clin Oncol*. Feb 10 2012;30(5):560; author reply 561-2. doi:10.1200/JCO.2011.39.4858

23. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. *Leuk Res*. Mar 2014;38(3):275-83. doi:10.1016/j.leukres.2013.12.018
24. Owusu C, Berger NA. Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care. *Clin Pract (Lond)*. 2014;11(6):749-762. doi:10.2217/cpr.14.72
25. Ho VT, Weller E, Lee SJ, Alyea EP, Antin JH, Soiffer RJ. Prognostic factors for early severe pulmonary complications after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2001;7(4):223-9. doi:10.1053/bbmt.2001.v7.pm11349809
26. Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. *Chest*. May 1992;101(5):1257-64. doi:10.1378/chest.101.5.1257
27. Savani BN, Montero A, Wu C, et al. Prediction and prevention of transplant-related mortality from pulmonary causes after total body irradiation and allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. Mar 2005;11(3):223-30. doi:10.1016/j.bbmt.2004.12.328
28. Savani BN, Montero A, Srinivasan R, et al. Chronic GVHD and pretransplantation abnormalities in pulmonary function are the main determinants predicting worsening pulmonary function in long-term survivors after stem cell transplantation. *Biol Blood Marrow Transplant*. Dec 2006;12(12):1261-9. doi:10.1016/j.bbmt.2006.07.016
29. Singh AK, Karimpour SE, Savani BN, et al. Pretransplant pulmonary function tests predict risk of mortality following fractionated total body irradiation and allogeneic peripheral blood stem cell transplant. *Int J Radiat Oncol Biol Phys*. Oct 1 2006;66(2):520-7. doi:10.1016/j.ijrobp.2006.05.023
30. Marks DI, Ballen K, Logan BR, et al. The effect of smoking on allogeneic transplant outcomes. *Biol Blood Marrow Transplant*. Oct 2009;15(10):1277-87. doi:10.1016/j.bbmt.2009.06.005
31. Chien JW, Sullivan KM. Carbon monoxide diffusion capacity: how low can you go for hematopoietic cell transplantation eligibility? *Biol Blood Marrow Transplant*. Apr 2009;15(4):447-53. doi:10.1016/j.bbmt.2008.12.509
32. Parimon T, Au DH, Martin PJ, Chien JW. A risk score for mortality after allogeneic hematopoietic cell transplantation. *Ann Intern Med*. Mar 21 2006;144(6):407-14. doi:10.7326/0003-4819-144-6-200603210-00007
33. Parimon T, Madtes DK, Au DH, Clark JG, Chien JW. Pretransplant lung function, respiratory failure, and mortality after stem cell transplantation. *Am J Respir Crit Care Med*. Aug 1 2005;172(3):384-90. doi:10.1164/rccm.200502-212OC
34. El-Khatib M, Bou-Khalil P, Abbas O, Salman A, Jamaleddine G. Value of pretransplant pulmonary function tests in predicting pulmonary complications after autologous peripheral stem cell transplantation. *Lung*. Dec 2007;185(6):321-4. doi:10.1007/s00408-007-9047-5
35. Coghlan JG, Handler CE, Kottaridis PD. Cardiac assessment of patients for haematopoietic stem cell transplantation. *Best Pract Res Clin Haematol*. Jun 2007;20(2):247-63. doi:10.1016/j.beha.2006.09.005
36. Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977-1997. *Bone Marrow Transplant*. Aug 2001;28(3):283-7. doi:10.1038/sj.bmt.1703133
37. Qazilbash MH, Amjad AI, Qureshi S, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients with low left ventricular ejection fraction. *Biol Blood Marrow Transplant*. Oct 2009;15(10):1265-70. doi:10.1016/j.bbmt.2009.06.001
38. Hurley P, Konety S, Cao Q, Weisdorf D, Blaes A. Hematopoietic stem cell transplantation in patients with systolic dysfunction: can it be done? *Biol Blood Marrow Transplant*. Feb 2015;21(2):300-4. doi:10.1016/j.bbmt.2014.10.011
39. Akahori M, Nakamae H, Hino M, et al. Electrocardiogram is very useful for predicting acute heart failure following myeloablative chemotherapy with hematopoietic stem cell transplantation rescue. *Bone Marrow Transplant*. Apr 2003;31(7):585-90. doi:10.1038/sj.bmt.1703890
40. Nakamae H, Hino M, Akahori M, et al. Predictive value of QT dispersion for acute heart failure after autologous and allogeneic hematopoietic stem cell transplantation. *Am J Hematol*. May 2004;76(1):1-7. doi:10.1002/ajh.20042
41. Armenian SH, Sun CL, Shannon T, et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood*. Dec 1 2011;118(23):6023-9. doi:10.1182/blood-2011-06-358226
42. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. Feb 15 1993;118(4):255-67. doi:10.7326/0003-4819-118-4-199302150-00003
43. Artz AS, Logan B, Zhu X, et al. The prognostic value of serum C-reactive protein, ferritin, and albumin prior to allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndromes. *Haematologica*. Nov 2016;101(11):1426-1433. doi:10.3324/haematol.2016.145847
44. Sivgin S, Nazlim S, Zararsiz G, et al. Increased Bone Marrow Iron Scores Are Strongly Correlated With Elevated Serum Ferritin Levels and Poorer Survival in Patients With Iron Overload That Underwent Allogeneic Hematopoietic

Stem Cell Transplantation: A Single Center Experience. *Clin Lymphoma Myeloma Leuk*. Oct 2016;16(10):582-587. doi:10.1016/j.clml.2016.08.002
45. Hwang DY, Kim SJ, Cheong JW, et al. High pre-transplant serum ferritin and busulfan-thiotepa conditioning regimen as risk factors for hepatic sinusoidal obstructive syndrome after autologous stem cell transplantation in patients with malignant lymphoma. *Leuk Lymphoma*. 2016;57(1):51-7. doi:10.3109/10428194.2015.1041387
46. Armand P, Kim HT, Virtanen JM, et al. Iron overload in allogeneic hematopoietic cell transplantation outcome: a meta-analysis. *Biol Blood Marrow Transplant*. Aug 2014;20(8):1248-51. doi:10.1016/j.bbmt.2014.04.024
47. Guo W, Dong A, He M, et al. A Meta-Analysis for Effects of Elevated Pre-Transplantation Serum Ferritin on the Outcomes in Patients Undergoing Hematopoietic Stem Cell Transplantation. *Cancer Invest*. Aug 8 2016;34(7):340-7. doi:10.1080/07357907.2016.1197236
48. Ramos CA, Saliba RM, de Padua L, et al. Impact of hepatitis C virus seropositivity on survival after allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Haematologica*. Feb 2009;94(2):249-57. doi:10.3324/haematol.13756
49. Hammond SP, Borchelt AM, Ukomadu C, Ho VT, Baden LR, Marty FM. Hepatitis B virus reactivation following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. Sep 2009;15(9):1049-59. doi:10.1016/j.bbmt.2009.05.001
50. Hamaguchi M, Yamada H, Gondo H, Takemoto Y, Morishima Y, Kodera Y. Retrospective study on the impact of hepatitis B and hepatitis C virus infection on hematopoietic stem cell transplantation in Japan. *Int J Hematol*. Apr 2002;75(3):324-31. doi:10.1007/BF02982051
51. Colecchia A, Ravaioli F, Sessa M, et al. Liver Stiffness Measurement Allows Early Diagnosis of Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome in Adult Patients Who Undergo Hematopoietic Stem Cell Transplantation: Results from a Monocentric Prospective Study. *Biol Blood Marrow Transplant*. May 2019;25(5):995-1003. doi:10.1016/j.bbmt.2019.01.019
52. Lau JE, Weber C, Earl M, et al. Outcomes after autologous SCT in lymphoma patients grouped by weight. *Bone Marrow Transplant*. May 2015;50(5):652-7. doi:10.1038/bmt.2014.327
53. Navarro WH, Loberiza FR, Jr., Bajorunaite R, et al. Effect of body mass index on mortality of patients with lymphoma undergoing autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. May 2006;12(5):541-51. doi:10.1016/j.bbmt.2005.12.033
54. Costa LJ, Micallef IN, Inwards DJ, et al. Effect of the dose per body weight of conditioning chemotherapy on severity of mucositis and risk of relapse after autologous haematopoietic stem cell transplantation in relapsed diffuse large B cell lymphoma. *Br J Haematol*. Oct 2008;143(2):268-73. doi:10.1111/j.1365-2141.2008.07342.x
55. Vogl DT, Wang T, Perez WS, et al. Effect of obesity on outcomes after autologous hematopoietic stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. Dec 2011;17(12):1765-74. doi:10.1016/j.bbmt.2011.05.005
56. Doney K, McMillen K, Buono L, Deeg HJ, Gooley T. Impact of Body Mass Index on Outcomes of Hematopoietic Stem Cell Transplantation in Adults. *Biol Blood Marrow Transplant*. Mar 2019;25(3):613-620. doi:10.1016/j.bbmt.2018.10.006
57. Gleimer M, Li Y, Chang L, et al. Baseline body mass index among children and adults undergoing allogeneic hematopoietic cell transplantation: clinical characteristics and outcomes. *Bone Marrow Transplant*. Mar 2015;50(3):402-10. doi:10.1038/bmt.2014.280
58. Baumgartner A, Zueger N, Bargetzi A, et al. Association of Nutritional Parameters with Clinical Outcomes in Patients with Acute Myeloid Leukemia Undergoing Haematopoietic Stem Cell Transplantation. *Ann Nutr Metab*. 2016;69(2):89-98. doi:10.1159/000449451
59. Yang J, Xue SL, Zhang X, et al. Effect of body mass index on overall survival of patients with allogeneic hematopoietic stem cell transplantation. *Eur J Clin Nutr*. Jun 2017;71(6):750-754. doi:10.1038/ejcn.2016.225
60. Sweiss K, Patel S, Culos K, Oh A, Rondelli D, Patel P. Melphalan 200 mg/m(2) in patients with renal impairment is associated with increased short-term toxicity but improved response and longer treatment-free survival. *Bone Marrow Transplant*. Oct 2016;51(10):1337-1341. doi:10.1038/bmt.2016.136
61. St Bernard R, Chodirker L, Masih-Khan E, et al. Efficacy, toxicity and mortality of autologous SCT in multiple myeloma patients with dialysis-dependent renal failure. *Bone Marrow Transplant*. Jan 2015;50(1):95-9. doi:10.1038/bmt.2014.226
62. Glavey SV, Gertz MA, Dispenzieri A, et al. Long-term outcome of patients with multiple [corrected] myeloma-related advanced renal failure following auto-SCT. *Bone Marrow Transplant*. Nov 2013;48(12):1543-7. doi:10.1038/bmt.2013.109

63. Ataei S, Hadjibabaie M, Moslehi A, et al. A double-blind, randomized, controlled trial on N-acetylcysteine for the prevention of acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation. *Hematol Oncol*. Jun 2015;33(2):67-74. doi:10.1002/hon.2141
64. Oshima K, Kanda Y, Nanya Y, et al. Allogeneic hematopoietic stem cell transplantation for patients with mildly reduced renal function as defined based on creatinine clearance before transplantation. *Ann Hematol*. Jan 2013;92(2):255-60. doi:10.1007/s00277-012-1584-1
65. Shimoi T, Ando M, Munakata W, et al. The significant impact of acute kidney injury on CKD in patients who survived over 10 years after myeloablative allogeneic SCT. *Bone Marrow Transplant*. Jan 2013;48(1):80-4. doi:10.1038/bmt.2012.85
66. Kagoya Y, Kataoka K, Nannya Y, Kurokawa M. Pretransplant predictors and posttransplant sequels of acute kidney injury after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. Mar 2011;17(3):394-400. doi:10.1016/j.bbmt.2010.07.010
67. Durey K, Patterson H, Gordon K. Dental assessment prior to stem cell transplant: treatment need and barriers to care. *Br Dent J*. May 9 2009;206(9):E19; discussion 478-9. doi:10.1038/sj.bdj.2009.304
68. Yamagata K, Onizawa K, Yanagawa T, et al. A prospective study to evaluate a new dental management protocol before hematopoietic stem cell transplantation. *Bone Marrow Transplant*. Aug 2006;38(3):237-42. doi:10.1038/sj.bmt.1705429
69. Akintoye SO, Brennan MT, Graber CJ, et al. A retrospective investigation of advanced periodontal disease as a risk factor for septicemia in hematopoietic stem cell and bone marrow transplant recipients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. Nov 2002;94(5):581-8. doi:10.1067/moe.2002.128960
70. Melkos AB, Massenkeil G, Arnold R, Reichart PA. Dental treatment prior to stem cell transplantation and its influence on the posttransplantation outcome. *Clin Oral Investig*. Jun 2003;7(2):113-5. doi:10.1007/s00784-003-0209-4
71. Elsawy M, Sorror ML. Up-to-date tools for risk assessment before allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. Oct 2016;51(10):1283-1300. doi:10.1038/bmt.2016.141
72. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chronic Dis*. Sep 1974;27(7-8):387-404. doi:10.1016/0021-9681(74)90017-4
73. Artz AS, Pollyea DA, Kocherginsky M, et al. Performance status and comorbidity predict transplant-related mortality after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. Sep 2006;12(9):954-64. doi:10.1016/j.bbmt.2006.05.015
74. Au BK, Gooley TA, Armand P, et al. Reevaluation of the pretransplant assessment of mortality score after allogeneic hematopoietic transplantation. *Biol Blood Marrow Transplant*. May 2015;21(5):848-54. doi:10.1016/j.bbmt.2015.01.011
75. Mori Y, Teshima T, Kamezaki K, et al. Validation of pretransplantation assessment of mortality risk score in the outcome of hematopoietic SCT in non-Caucasians. *Bone Marrow Transplant*. Aug 2012;47(8):1075-81. doi:10.1038/bmt.2011.229
76. Kishore BW, D.; Nikolousis, E.; Lovell, R.; Milligan, D.; Holder, K.; Bratby, L.; Murthy, V.; Paneesha, S. Pre-Transplantation Assessment Of Mortality (PAM) Score Is a Poor Predictor For Survival In The Highest Risk Group When Used In T Cell Depleted Myeloablative Allogeneic Transplants. *Blood*. 2013;122:5553.
77. Wiseman D, Nikolousis E, Lovell R, et al. Pre-Transplantation Assessment Of Mortality (PAM) Score Is a Poor Predictor For Survival In The Highest Risk Group When Used In T Cell Depleted Myeloablative Allogeneic Transplants. *Blood*. 2013;122(21):5553-5553.
78. Labonte L, Iqbal T, Zaidi MA, et al. Utility of comorbidity assessment in predicting transplantation-related toxicity following autologous hematopoietic stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. Sep 2008;14(9):1039-1044. doi:10.1016/j.bbmt.2008.06.019
79. Gratwohl A. The EBMT risk score. *Bone Marrow Transplant*. Jun 2012;47(6):749-56. doi:10.1038/bmt.2011.110
80. Lozano SO, E.; Iacobelli, S.; van Biezen, A.; Beelen, D.; Finke, J.; Mufti, G.; Niederwieser, D.;Ehninger, G., Ganser, A.; Stuhler, G.; Maertens, J.; Bacigalupo, A.; Volin, L.; Nagler, A.; Kobbe, G.; Schönland, S.; de Witte, T.; Kröger, N.; Robin, M. The EBMT Score Predicts Transplant Related Mortality and Overall Survival after Allogeneic Stem Cell Transplantation for Myelodysplastic Syndromes. *Blood*. 2015;126:3223.
81. Gul Z, Khan H, Bashir Q, et al. EBMT Risk Score for Pre Transplant Risk Assessment in Patients with Multiple Myeloma. *Blood*. 2012;120(21):3094-3094. doi:10.1182/blood.V120.21.3094.3094
82. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. Nov 1994;47(11):1245-51. doi:10.1016/0895-4356(94)90129-5
83. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. Oct 15 2005;106(8):2912-9. doi:10.1182/blood-2005-05-2004

84. Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer*. May 1 2008;112(9):1992-2001. doi:10.1002/cncr.23375
85. Michelis FV, Messner HA, Atenafu EG, et al. Patient age, remission status and HCT-CI in a combined score are prognostic for patients with AML undergoing allogeneic hematopoietic cell transplantation in CR1 and CR2. *Bone Marrow Transplant*. Nov 2015;50(11):1405-10. doi:10.1038/bmt.2015.165
86. Bokhari SW, Watson L, Nagra S, et al. Role of HCT-comorbidity index, age and disease status at transplantation in predicting survival and non-relapse mortality in patients with myelodysplasia and leukemia undergoing reduced-intensity-conditioning hemopoeitic progenitor cell transplantation. *Bone Marrow Transplant*. Apr 2012;47(4):528-34. doi:10.1038/bmt.2011.138
87. Nakaya A, Mori T, Tanaka M, et al. Does the hematopoietic cell transplantation specific comorbidity index (HCT-CI) predict transplantation outcomes? A prospective multicenter validation study of the Kanto Study Group for Cell Therapy. *Biol Blood Marrow Transplant*. Oct 2014;20(10):1553-9. doi:10.1016/j.bbmt.2014.06.005
88. Mo XD, Xu LP, Liu DH, et al. The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) is an outcome predictor for partially matched related donor transplantation. *Am J Hematol*. Jun 2013;88(6):497-502. doi:10.1002/ajh.23443
89. Veeraputhiran M, Yang L, Sundaram V, et al. Validation of the Hematopoietic Cell Transplantation-Specific Comorbidity Index in Nonmyeloablative Allogeneic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. Oct 2017;23(10):1744-1748. doi:10.1016/j.bbmt.2017.06.005
90. Berro M, Arbelbide JA, Rivas MM, et al. Hematopoietic Cell Transplantation-Specific Comorbidity Index Predicts Morbidity and Mortality in Autologous Stem Cell Transplantation. *Biol Blood Marrow Transplant*. Oct 2017;23(10):1646-1650. doi:10.1016/j.bbmt.2017.06.014
91. Jaglowski SM, Ruppert AS, Hofmeister CC, et al. The hematopoietic stem cell transplant comorbidity index can predict for 30-day readmission following autologous stem cell transplant for lymphoma and multiple myeloma. *Bone Marrow Transplant*. Oct 2014;49(10):1323-9. doi:10.1038/bmt.2014.155
92. Kassar MG, S.A.; Shell, K.; Venugopal, P.; Shammo, J.; Farhat, M.I.; Batus, M.; Law, A.; Fung, H.C.;. Assessing the impact of comorbidities on autologous hematopoietic cell transplant (AHCT) outcomes using the hematopoietic cell transplant-comorbidity index (HCT-CI) in lymphoma. *Journal of Clinical Oncology*. 2007;25(18_suppl)doi:10.1200/jco.2007.25.18_suppl.71
93. Saad A, Mahindra A, Zhang MJ, et al. Hematopoietic cell transplant comorbidity index is predictive of survival after autologous hematopoietic cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. Mar 2014;20(3):402-408 e1. doi:10.1016/j.bbmt.2013.12.557
94. Ousia S, Kalra A, Williamson TS, et al. Hematopoietic cell transplant outcomes after myeloablative conditioning with fludarabine, busulfan, low-dose total body irradiation, and rabbit antithymocyte globulin. *Clin Transplant*. Sep 2020;34(9):e14018. doi:10.1111/ctr.14018
95. Michelis FV, Messner HA, Uhm J, et al. The Modified Pre-Transplant EBMT Risk Score Is Superior To The HCT-CI Score In Predicting Overall Survival and Non-Relapse Mortality After Allogeneic Hematopoietic Cell Transplantation In Patients With Acute Myeloid Leukemia. *Blood*. 2013;122(21):2153-2153. doi:10.1182/blood.V122.21.2153.2153
96. Terwey TH, Hemmati PG, Martus P, et al. A modified EBMT risk score and the hematopoietic cell transplantation-specific comorbidity index for pre-transplant risk assessment in adult acute lymphoblastic leukemia. *Haematologica*. May 2010;95(5):810-8. doi:10.3324/haematol.2009.011809
97. Yamamoto W, Ogusa E, Matsumoto K, Maruta A, Ishigatsubo Y, Kanamori H. Predictive value of risk assessment scores in patients with hematologic malignancies undergoing reduced-intensity conditioning allogeneic stem cell transplantation. *Am J Hematol*. Sep 2014;89(9):E138-41. doi:10.1002/ajh.23764
98. NCCN. NCCN Guidelines - Older Adult Oncology.
99. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol*. Aug 1 2018;36(22):2326-2347. doi:10.1200/JCO.2018.78.8687
100. Cruz M, Covinsky K, Widera EW, Stijacic-Cenzer I, Lee SJ. Predicting 10-Year Mortality for Older Adults. *JAMA*. 2013;309(9):874-876. doi:10.1001/jama.2013.1184
101. Manuel DG, Perez R, Sanmartin C, et al. Measuring Burden of Unhealthy Behaviours Using a Multivariable Predictive Approach: Life Expectancy Lost in Canada Attributable to Smoking, Alcohol, Physical Inactivity, and Diet. *PLoS Med*. Aug 2016;13(8):e1002082. doi:10.1371/journal.pmed.1002082
102. Graf C. The Lawton instrumental activities of daily living scale. *Am J Nurs*. Apr 2008;108(4):52-62; quiz 62-3. doi:10.1097/01.NAJ.0000314810.46029.74

103. Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med*. Feb 24 1997;157(4):449-54.
104. Ketelaars L, Pottel L, Lycke M, et al. Use of the Freund clock drawing test within the Mini-Cog as a screening tool for cognitive impairment in elderly patients with or without cancer. *J Geriatr Oncol*. Apr 2013;4(2):174-82. doi:10.1016/j.jgo.2012.10.175
105. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *Am J Psychiatry*. Jun 1983;140(6):734-9. doi:10.1176/ajp.140.6.734
106. Muffly LS, Kocherginsky M, Stock W, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. *Haematologica*. Aug 2014;99(8):1373-9. doi:10.3324/haematol.2014.103655
107. Deschler B, Ihorst G, Schnitzler S, Bertz H, Finke J. Geriatric assessment and quality of life in older patients considered for allogeneic hematopoietic cell transplantation: a prospective risk factor and serial assessment analysis. *Bone Marrow Transplant*. May 2018;53(5):565-575. doi:10.1038/s41409-017-0021-4
108. Wildes TM, Tuchman SA, Klepin HD, et al. Geriatric Assessment in Older Adults with Multiple Myeloma. *J Am Geriatr Soc*. May 2019;67(5):987-991. doi:10.1111/jgs.15715
109. Richardson DR, Huang Y, McGinty HL, et al. Psychosocial risk predicts high readmission rates for hematopoietic cell transplant recipients. *Bone Marrow Transplant*. Nov 2018;53(11):1418-1427. doi:10.1038/s41409-018-0118-4
110. Hegde A, Murthy HS. Frailty: the missing piece of the pre- hematopoietic cell transplantation assessment? *Bone Marrow Transplant*. Jan 2018;53(1):3-10. doi:10.1038/bmt.2017.192
111. Salas MQ, Atenafu EG, Bascom O, et al. Pilot prospective study of Frailty and Functionality in routine clinical assessment in allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. Jan 2021;56(1):60-69. doi:10.1038/s41409-020-0979-1
112. Salas MQ, Solano MT, Baile González M, et al. The Frailty Syndrome As Predictor of Allogeneic Hematopoietic Cell Transplantation Outcomes. Prospective Study on Behalf of the Grupo Español De Trasplante Hematopoyético y Terapia Celular. *Blood*. 2023;142(Supplement 1):2346-2346. doi:10.1182/blood-2023-190352
113. Salas MQ, Atenafu EG, Pasic I, et al. Impact of hematopoietic cell transplant frailty scale on transplant outcome in adults. *Bone Marrow Transplant*. Mar 2023;58(3):317-324. doi:10.1038/s41409-022-01892-3
114. Salas MQ, Solano MT, Baile González M, et al. Frailty Syndrome in Adults Undergoing Autologous Hematopoietic Cell Transplantation. Prospective Study on Behalf of the Grupo Español De Trasplante Hematopoyético y Terapia Celular. *Blood*. 2023;142(Supplement 1):3702-3702. doi:10.1182/blood-2023-185679
115. Cook G, Pawlyn C, Royle K-L, et al. Dynamic Frailty Assessment in Transplant Non-Eligible Newly Diagnosed Myeloma Patients: Initial Data from UK Myeloma Research Alliance (UK-MRA) Myeloma XIV (FiTNEss): A Frailty-Adjusted Therapy Study. *Blood*. 2023;142(Supplement 1):4748-4748. doi:10.1182/blood-2023-188672
116. Hayden PJ, Sirait T, Koster L, Snowden JA, Yakoub-Agha I. An international survey on the management of patients receiving CAR T-cell therapy for haematological malignancies on behalf of the Chronic Malignancies Working Party of EBMT. *Curr Res Transl Med*. Aug 2019;67(3):79-88. doi:10.1016/j.retram.2019.05.002
117. Yakoub-Agha I, Chabannon C, Bader P, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Haematologica*. 2020;105(2):297-316. doi:10.3324/haematol.2019.229781
118. Penalba V, Asvat Y, Deshields TL, Vanderlan JR, Chol N. Rates and predictors of psychotherapy utilization after psychosocial evaluation for stem cell transplant. *Psychooncology*. Feb 2018;27(2):427-433. doi:10.1002/pon.4473
119. Foster LW, McLellan LJ, Rybicki LA, Dabney J, Welsh E, Bolwell BJ. Allogeneic BMT and patient eligibility based on psychosocial criteria: a survey of BMT professionals. *Bone Marrow Transplant*. Jan 2006;37(2):223-8. doi:10.1038/sj.bmt.1705219
120. Foster LW, McLellan L, Rybicki L, Tyler T, Bolwell BJ. Ethical reasoning about patient eligibility in allogeneic BMT based on psychosocial criteria. *Bone Marrow Transplant*. Nov 2009;44(9):607-12. doi:10.1038/bmt.2009.58
121. Bevans M, Wehrlen L, Prachenko O, Soeken K, Zabora J, Wallen GR. Distress screening in allogeneic hematopoietic stem cell (HSCT) caregivers and patients. *Psychooncology*. Jun 2011;20(6):615-22. doi:10.1002/pon.1906
122. Bultz BD, Groff SL, Fitch M, et al. Implementing screening for distress, the 6th vital sign: a Canadian strategy for changing practice. *Psychooncology*. May 2011;20(5):463-9. doi:10.1002/pon.1932
123. Giese-Davis J, Waller A, Carlson LE, et al. Screening for distress, the 6th vital sign: common problems in cancer outpatients over one year in usual care: associations with marital status, sex, and age. *BMC Cancer*. 2012/10/02 2012;12(1):441. doi:10.1186/1471-2407-12-441

124. Garcia C, Jr., Botega NJ, De Souza CA. A psychosocial assessment interview of candidates for hematopoietic stem cell transplantation. *Haematologica*. Apr 2005;90(4):570-2.
125. Foster LW, McLellan L, Rybicki L, Dabney J, Visnosky M, Bolwell B. Utility of the psychosocial assessment of candidates for transplantation (PACT) scale in allogeneic BMT. *Bone Marrow Transplant*. Sep 2009;44(6):375-80. doi:10.1038/bmt.2009.37
126. Olbrisch MEL, J.L.; Hamer, R. The PACT: A rating scale for the study of clinical decision-making in psychosocial screening of organ transplant candidates. *Clinical Transplantation*. 1989;3(3):164-169.
127. Hong S, Rybicki L, Corrigan D, et al. Psychosocial Assessment of Candidates for Transplant (PACT) as a tool for psychological and social evaluation of allogeneic hematopoietic cell transplantation recipients. *Bone Marrow Transplant*. Sep 2019;54(9):1443-1452. doi:10.1038/s41409-019-0455-y
128. Harashima S, Yoneda R, Horie T, et al. Psychosocial Assessment of Candidates for Transplantation scale (PACT) and survival after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. Jul 2019;54(7):1013-1021. doi:10.1038/s41409-018-0371-6
129. Hoodin F, Zhao L, Carey J, Levine JE, Kitko C. Impact of psychological screening on routine outpatient care of hematopoietic cell transplantation survivors. *Biol Blood Marrow Transplant*. Oct 2013;19(10):1493-7. doi:10.1016/j.bbmt.2013.07.019
130. Solh MM, Speckhart D, Solomon SR, et al. The Transplant Evaluation Rating Scale predicts overall survival after allogeneic hematopoietic stem cell transplantation. *Blood Adv*. Oct 13 2020;4(19):4812-4821. doi:10.1182/bloodadvances.2020002204
131. Kuba K, Esser P, Scherwath A, et al. Cancer-and-treatment-specific distress and its impact on posttraumatic stress in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). *Psychooncology*. Aug 2017;26(8):1164-1171. doi:10.1002/pon.4295
132. Liang J, Lee SJ, Storer BE, et al. Rates and Risk Factors for Post-Traumatic Stress Disorder Symptomatology among Adult Hematopoietic Cell Transplant Recipients and Their Informal Caregivers. *Biol Blood Marrow Transplant*. Jan 2019;25(1):145-150. doi:10.1016/j.bbmt.2018.08.002
133. Ehrlich KB, Miller GE, Scheide T, et al. Pre-transplant emotional support is associated with longer survival after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. Dec 2016;51(12):1594-1598. doi:10.1038/bmt.2016.191
134. Baliousis M, Rennoldson M, Snowden JA. Psychological interventions for distress in adults undergoing haematopoietic stem cell transplantation: a systematic review with meta-analysis. *Psychooncology*. Apr 2016;25(4):400-11. doi:10.1002/pon.3925
135. El-Jawahri A, Traeger L, Greer JA, et al. Effect of Inpatient Palliative Care During Hematopoietic Stem-Cell Transplant on Psychological Distress 6 Months After Transplant: Results of a Randomized Clinical Trial. *J Clin Oncol*. Nov 10 2017;35(32):3714-3721. doi:10.1200/jco.2017.73.2800
136. El-Jawahri A, Chen YB, Brazauskas R, et al. Impact of pre-transplant depression on outcomes of allogeneic and autologous hematopoietic stem cell transplantation. *Cancer*. May 15 2017;123(10):1828-1838. doi:10.1002/cncr.30546
137. Haynes RT, DW; Sackett, DL. Compliance in Health Care. Johns Hopkins University Press; 1979:1-2.
138. Bishop MM, Rodrigue JR, Wingard JR. Mismanaging the gift of life: noncompliance in the context of adult stem cell transplantation. *Bone Marrow Transplant*. Jun 2002;29(11):875-80. doi:10.1038/sj.bmt.1703523
139. Morrison CF, Martsolf DM, Wehrkamp N, Tehan R, Pai ALH. Medication Adherence in Hematopoietic Stem Cell Transplantation: A Review of the Literature. *Biol Blood Marrow Transplant*. Apr 2017;23(4):562-568. doi:10.1016/j.bbmt.2017.01.008
140. Gresch B, Kirsch M, Fierz K, et al. Medication nonadherence to immunosuppressants after adult allogeneic haematopoietic stem cell transplantation: a multicentre cross-sectional study. *Bone Marrow Transplant*. Feb 2017;52(2):304-306. doi:10.1038/bmt.2016.262
141. Pai ALH, Rausch J, Drake S, et al. Poor Adherence Is Associated with More Infections after Pediatric Hematopoietic Stem Cell Transplant. *Biol Blood Marrow Transplant*. Feb 2018;24(2):381-385. doi:10.1016/j.bbmt.2017.10.033
142. Mumby PB, Hurley C, Samsi M, Thilges S, Parthasarathy M, Stiff PJ. Predictors of non-compliance in autologous hematopoietic SCT patients undergoing out-patient transplants. *Bone Marrow Transplant*. Apr 2012;47(4):556-61. doi:10.1038/bmt.2011.129
143. Rodrigue JR, Pearman TP, Moreb J. Morbidity and mortality following bone marrow transplantation: predictive utility of pre-BMT affective functioning, compliance, and social support stability. *Int J Behav Med*. 1999;6(3):241-54. doi:10.1207/s15327558ijbm0603_3

144. Mishkin AD, Shapiro PA, Reshef R, Lopez-Pintado S, Mapara MY. Standardized Semi-structured Psychosocial Evaluation before Hematopoietic Stem Cell Transplantation Predicts Patient Adherence to Post-Transplant Regimen. *Biol Blood Marrow Transplant*. Nov 2019;25(11):2222-2227. doi:10.1016/j.bbmt.2019.06.019
145. Stagno S, Busby K, Shapiro A, Kotz M. Patients at risk: addressing addiction in patients undergoing hematopoietic SCT. *Bone Marrow Transplant*. Aug 2008;42(4):221-6. doi:10.1038/bmt.2008.211
146. Chang G, Antin JH, Orav EJ, Randall U, McGarigle C, Behr HM. Substance abuse and bone marrow transplant. *Am J Drug Alcohol Abuse*. May 1997;23(2):301-8. doi:10.3109/00952999709040948
147. Chang G, Orav EJ, Tong MY, Antin JH. Predictors of 1-year survival assessed at the time of bone marrow transplantation. *Psychosomatics*. Sep-Oct 2004;45(5):378-85. doi:10.1176/appi.psy.45.5.378
148. Graf SA, Vaughn JE, Chauncey TR, et al. Comorbidities, Alcohol Use Disorder, and Age Predict Outcomes after Autologous Hematopoietic Cell Transplantation for Lymphoma. *Biol Blood Marrow Transplant*. Sep 2016;22(9):1582-1587. doi:10.1016/j.bbmt.2016.06.007
149. Nelson AM, Juckett MB, Coe CL, Costanzo ES. Illness perceptions predict health practices and mental health following hematopoietic stem cell transplantation. *Psychooncology*. Jun 2019;28(6):1252-1260. doi:10.1002/pon.5075
150. Campo RA, Wu LM, Austin J, Valdimarsdottir H, Rini C. Personal resilience resources predict post-stem cell transplant cancer survivors' psychological outcomes through reductions in depressive symptoms and meaning-making. *J Psychosoc Oncol*. Nov-Dec 2017;35(6):666-687. doi:10.1080/07347332.2017.1342306
151. Barata A, Gonzalez BD, Sutton SK, et al. Coping strategies modify risk of depression associated with hematopoietic cell transplant symptomatology. *J Health Psychol*. Jul 2018;23(8):1028-1037. doi:10.1177/1359105316642004
152. Turcotte LM, Verneris MR. Is It Better to Be Rich or Relaxed? Sociobiology Meets Bone Marrow Transplant. *Clin Cancer Res*. Jan 01 2016;22(1):6-8. doi:10.1158/1078-0432.CCR-15-2112
153. Baker KS, Davies SM, Majhail NS, et al. Race and socioeconomic status influence outcomes of unrelated donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. Dec 2009;15(12):1543-54. doi:10.1016/j.bbmt.2009.07.023
154. Knight JM, Syrjala KL, Majhail NS, et al. Patient-Reported Outcomes and Socioeconomic Status as Predictors of Clinical Outcomes after Hematopoietic Stem Cell Transplantation: A Study from the Blood and Marrow Transplant Clinical Trials Network 0902 Trial. *Biol Blood Marrow Transplant*. Dec 2016;22(12):2256-2263. doi:10.1016/j.bbmt.2016.08.016
155. Fu S, Rybicki L, Abounader D, et al. Association of socioeconomic status with long-term outcomes in 1-year survivors of allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. Oct 2015;50(10):1326-30. doi:10.1038/bmt.2015.166
156. Silla L, Fischer GB, Paz A, et al. Patient socioeconomic status as a prognostic factor for allo-SCT. *Bone Marrow Transplant*. Apr 2009;43(7):571-7. doi:10.1038/bmt.2008.358
157. Hamilton BK, Rybicki L, Arai S, et al. Association of Socioeconomic Status with Chronic Graft-versus-Host Disease Outcomes. *Biol Blood Marrow Transplant*. Feb 2018;24(2):393-399. doi:10.1016/j.bbmt.2017.10.009
158. Knight JM, Rizzo JD, Logan BR, et al. Low Socioeconomic Status, Adverse Gene Expression Profiles, and Clinical Outcomes in Hematopoietic Stem Cell Transplant Recipients. *Clin Cancer Res*. Jan 1 2016;22(1):69-78. doi:10.1158/1078-0432.Ccr-15-1344
159. Brown-Iannuzzi JL, Payne BK, Rini C, DuHamel KN, Redd WH. Objective and subjective socioeconomic status and health symptoms in patients following hematopoietic stem cell transplantation. *Psychooncology*. Jul 2014;23(7):740-8. doi:10.1002/pon.3473
160. Hong S, Rybicki L, Abounader D, et al. Association of Socioeconomic Status with Outcomes of Autologous Hematopoietic Cell Transplantation for Multiple Myeloma. *Biol Blood Marrow Transplant*. Jun 2016;22(6):1141-1144. doi:10.1016/j.bbmt.2016.03.011
161. Fiala MA, Finney JD, Liu J, et al. Socioeconomic status is independently associated with overall survival in patients with multiple myeloma. *Leuk Lymphoma*. 2015;56(9):2643-9. doi:10.3109/10428194.2015.1011156
162. Posluszny DM, Bovbjerg DH, Syrjala KL, Agha M, Dew MA. Correlates of anxiety and depression symptoms among patients and their family caregivers prior to allogeneic hematopoietic cell transplant for hematological malignancies. *Support Care Cancer*. Feb 2019;27(2):591-600. doi:10.1007/s00520-018-4346-3
163. Colón EA, Callies AL, Popkin MK, McGlave PB. Depressed mood and other variables related to bone marrow transplantation survival in acute leukemia. *Psychosomatics*. Fall 1991;32(4):420-5. doi:10.1016/s0033-3182(91)72045-8
164. Tay J, Beattie S, Bredeson C, et al. Pre-Transplant Marital Status and Hematopoietic Cell Transplantation Outcomes. *Curr Oncol*. Dec 2020;27(6):e596-e606. doi:10.3747/co.27.6327

165. Gerull S, Denhaerynck K, Chalandon Y, et al. Lack of association between relationship status and clinical outcome in allogeneic stem cell transplantation—the Swiss Transplant Cohort Study. *Bone Marrow Transplantation*. 2017/12/01 2017;52(12):1686-1688. doi:10.1038/bmt.2017.204
166. Frick E, Motzke C, Fischer N, Busch R, Bumeder I. Is perceived social support a predictor of survival for patients undergoing autologous peripheral blood stem cell transplantation? *Psychooncology*. Sep 2005;14(9):759-70. doi:10.1002/pon.908
167. Sannes TS, Simoneau TL, Mikulich-Gilbertson SK, et al. Distress and quality of life in patient and caregiver dyads facing stem cell transplant: identifying overlap and unique contributions. *Support Care Cancer*. Jun 2019;27(6):2329-2337. doi:10.1007/s00520-018-4496-3
168. Beattie S, Lebel S, Petricone-Westwood D, et al. Balancing give and take between patients and their spousal caregivers in hematopoietic stem cell transplantation. *Psychooncology*. Dec 2017;26(12):2224-2231. doi:10.1002/pon.4340
169. Beattie S, Lebel S, Tay J. The influence of social support on hematopoietic stem cell transplantation survival: a systematic review of literature. *PLoS One*. 2013;8(4):e61586. doi:10.1371/journal.pone.0061586

Criteria for Donor Selection

Presented by: Kareem Jamani

Summary

- Donor selection will be based on human leukocyte antigen (HLA)-match and important non-HLA factors that influence transplant outcomes (e.g., age of donor, urgency of transplant, cytomegalovirus (CMV) serostatus) – see Figures 1-3.
- Syngeneic donors may be preferred for aplastic anemia other and diseases with minimal reliance on graft-versus-tumor effect.
- With HLA-mismatched donors, graft failure has been reported in patients with donor-specific HLA antibodies (DSA). HLA antibody testing should be performed prior to transplantation.
- For donor eligibility (acceptable health), refer to ABMTP Donor Eligibility and Suitability Standard Operating Procedures for allogeneic and cord blood donations, located on ABMTP Sharepoint, or the WMDA website https://share.wmda.info/display/DMSR/WMDA+Donor+Medical+Suitability+Recommendations

Selecting an Allogeneic Donor: Guiding Concepts

- Donor characteristics associated with improved overall survival are prioritized.
- When available, local data is incorporated into the selection algorithm.
- For patients with high-risk disease, time to transplant may influence physician choice of donor.

The donor selection algorithms presented in this chapter are mostly consistent with recently published CIBMTR/NMDP guidelines for selection of unrelated donors[2], with differences related to local data with respect to CMV matching.

Role of HLA Matching

Large registry studies have provided insight into the role of HLA matching in unrelated donor selection. Most recently, the NMDP/CIBMTR examined ~8000 donor-recipient pairs from almost 200 transplant centers[2]. Importantly, this analysis reflected modern transplant technique: patients were transplanted in 1999-2011 with predominantly peripheral blood stem cells for AML, ALL, MDS and CML. Further, ABMTP transplant technique was well represented in the study: all patients received myeloablative conditioning with ~50% receiving non-TBI based conditioning and ~30% receiving in-vivo T-cell depletion. Important findings included:

- Mismatch at HLA-A, -B, -C or –DR was associated with increased risk of death, grades 2-4 and grades 3-4 aGVHD, cGVHD and treatment-related mortality.
- HLA DQB1 and DPB1 mismatches: among 8/8 matched cases, DQB1 mismatches were only associated with grades 2-4 aGVHD (RR1.2) and DPB1 mismatches were associated with grades 2-4 aGVHD (RR 1.4), grades 3-4 aGVHD (RR 1.5), and decreased relapse (RR 0.71).

Importantly, DPB1 non-permissive mismatches were associated with a higher risk of death as compared to DPB1 permissive mismatches. There was no difference in survival between those receiving DPB1 permissive mismatch versus those receiving DPB1 matched donors, however DPB1 permissive mismatched donors were associated with an increased risk of grades 2-4 (RR 1.3) and 3-4 aGVHD (RR 1.4) and a lower risk of relapse (RR 0.7) as compared to DPB1 matched donors. These findings with respect to DPB1 replicated those of an earlier study in a less recent cohort of patients receiving primarily bone marrow grafts after conditioning with predominantly TBI-based myeloablative conditioning with only 16% receiving in-vivo T-cell depletion[3].

- In contrast, regarding HLA-DPB1 matching, local data did not demonstrate significant differences in relapse and GVHD outcomes among donor-recipient pairs matched or permissive/non-permissive mismatched at HLA-DPB1 in a small cohort without multivariable adjustment[4]. The local data requires further follow-up in a larger cohort with multivariable modelling.

Older Matched Sib (MSD) vs. Younger MUD Donors

Among MUDs, younger age has been repeatedly found to be the most important donor characteristic associated with recipient overall survival. Thus, investigators have sought to evaluate outcomes of allo-HCT with a young MUD (typically defined as <35 y.o.) vs. an older MSD (typically defined as >50 y.o.). Retrospective analyses seeking to answer this question can be summarized as follows:

- AML/MDS: In two separate CIBMTR analyses MUDs were associated with a lower risk of relapse and improved disease-free survival vs. MSDs, but this was countered by an increased risk of acute and chronic GVHD and non-relapse mortality. No difference in overall survival was noted. (Guru Murthy 2022 PMID 35024768 & Abid 2023 PMID 37406882). These results could not be replicated in a more contemporary large single-centre analysis where no difference in any outcome was noted (Kim 2024 PMID 38703824).
- B-cell ALL: In a CIBMTR analysis, MUDs were associated with a lower risk of relapse vs. MSDs, but a greater risk of cGVHD and NRM, leading to no difference in overall- or leukemia-free-survival (Abid 2023 PMID 37481243).

Summary: Older MSDs and young MUDs are associated with similar outcomes. Select the donor that allows for fastest time to transplant.

HLA-Mismatched Donors

In a 2024 unpublished analysis: haploidentical HCT is associated with similar overall survival to MUD and matched sib HCT in Alberta while mismatched unrelated HCT is associated with significantly worse overall survival, driven by increased acute GVHD and NRM as well as marginally higher cGVHD. Haploidentical donors are the preferred donor in Alberta when a matched donor is not available. Haploidentical related donors are widely and quickly available and excellent outcomes have

been reported in the literature using the post-transplant cyclophosphamide platform. Umbilical cord HCT has not been a typical choice for alternative donor HCT for adults in Alberta. Nevertheless, umbilical cord HCT may be pursued in circumstances where proceeding to allo-HCT is felt to be critically important and 7/8 unrelated or haploidentical donors are unavailable.

In both 7/8 unrelated donor HCT and haploidentical HCT, it is critical to identify donor-specific antibodies (DSAs) against the locus/loci of mismatch. DSAs have been strongly associated with graft failure, poor graft function and reduced overall survival[6]. Donors without the corresponding HLA antigens should be selected. If the latter are unavailable, recipients should undergo desensitization prior to HCT.

With respect to selecting a 7/8 HLA matched unrelated donor, the recent CIBMTR/NMDP analysis noted the following[2]:

- When comparing locus of HLA mismatch, there were no large differences in outcomes.
- The exception to this was mismatch at HLA-C 03:03/03:04, which was associated with similar survival to 8/8 matched transplants, a finding that replicated that of a previous study[7].
- Among 7/8 donors, no significant effect of mismatch at DQB1 or DPB1 mismatch were observed. This stands in contrast to findings of other studies, i.e. the literature does not provide clear guidance with respect to matching DQB1 and DPB1 in 7/8 matched donors. However, an as of yet unreplicated single study suggests that >2 mismatches of low expression HLA loci (HLA-DP, -DQ, -DRB3/4/5) in 7/8 transplants is associated with increased mortality (HR 1.45), predominantly in the form of treatment-related mortality (HR 1.68)[8].

Selection of donors for haploidentical HCT has been reviewed by the EBMT along with the publication of consensus recommendations[9]. Overall, the literature regarding haploidentical donor selection with the PTCy platform is sparse as compared to the literature regarding unrelated donor selection. The following haplo HCT donor characteristics have been associated with improved survival in >1 published study[9]:

- Younger donor age (particularly less than 40 y.o.).
- Sibling or offspring donor as opposed to parent donor (however, this was not replicated in the large CIBMTR study discussed below).
- Avoid major ABO incompatibility only in bone marrow transplantation (no effect of ABO mismatch in peripheral blood stem cell transplant).

The following donor characteristics may be associated with improved recipient outcomes but require further verification. These characteristics may be considered if the above donor criteria are met and there remains >1 suitable haploidentical donor choice[9]:

- Male donor for male recipient.
- If using a parent donor, father donor preferred over mother.

The following donor characteristics have not consistently been shown to affect recipient outcome in haploidentical HCT[9]:

- Degree of HLA mismatch.

A recent CIBMTR study examined the largest cohort to date (>1400) of haploidentical HCTs transplanted with a PTCy platform and provided significant insight with respect to haploidentical HCT donor selection, particularly with respect to the role of HLA matching[10]. Major findings included:

- Improvement in overall survival was associated with younger donor (particularly age <40), match at HLA-B leader, nonpermissive mismatch at HLA-DPB1 and CMV seronegative donor for seronegative recipient.
- Improvement in disease-free survival was associated with match at HLA-B leader, non-permissive mismatch at HLA-DPB1, CMV seronegative donor for CMV seronegative recipient and mismatch at HLA-DRB1 in conjunction with match at HLA-DQB1.
- Donor-recipient relationship was not associated with any major outcome studied.
- Because of the difficulty of simultaneously considering clinical and HLA factors, the authors developed a disease-free survival calculator that considers all factors associated with disease-free survival noted above. The calculator can be used to compare multiple donor options. The calculator is located at: http://haplodonorselector.b12x.org/v1.0/
- Importantly, no further HLA typing is required to determine HLA-B leader matching as leaders are known for most HLA-B alleles and may be sought out by entering donor-recipient HLA-B alleles in the following calculator: https://bleader.nmdp.org

A suggested approach is to type all potential haploidentical donors under age 40 given the recurrently found strong association between donor age and overall survival. If there are >1 potential donors under age 40, the above calculator may be used to select the donor that will result in the best disease-free survival. If there are no potential donors under age 40 but >1 over age 40, the calculator may be used to select the donor that may result in the best disease-free survival.

Donor-Specific Antibodies (DSA)

For recipients with potential HLA-mismatched unrelated donors and haploidentical donors, HLA antibody screening will be performed. If HLA antibody screening is positive then Single Antigen Bead analysis will be performed to assess the presence of donor-specific HLA antibodies (HLA-DSA). In recipients positive for HLA-DSA, a T and B cell flow crossmatch will be performed using donor lymphocytes and recipient serum.

Non-HLA Factors

Three modern studies have confirmed that age is indeed the only non-HLA donor factor that is consistently associated with recipient survival. The first study examined two cohorts of several thousand patients each with the intention of producing a donor selection score: three donor characteristics predicted recipient mortality in the first cohort: CMV mismatch (negative impact for D-R+, HR 1.14), non-permissive DPB1 mismatch (negative impact, HR 1.13) and older donor age (negative impact, HR 1.07 per decade increase in age). In the second cohort, only donor age predicted recipient survival (negative impact, HR 1.11 per decade increase in age). In absolute terms,

choosing a donor 2 years older was associated with a 1% decrease in 2 year survival, 5 years older a 2% decrease, 10 years older a 3% decrease and 20 years older a 7% decrease[13].

In a second large study, donor age was the only non-HLA donor factor that was associated with survival. As in the former study, donor age was continuously associated with recipient survival: for every 10 year increment in donor age, there was a 5.5% increase in hazard ratio for overall mortality[14].

In a third study, a machine learning model using ~12 000 patients reported to CIBMTR provided further insight into the degree of donor age that leads to an optimal outcome: donors aged 30 or younger lead to optimal overall survival with little additional benefit going further. A male donor leads to optimal event-free survival. All other donor characteristics were not associated with EFS or OS. Thus, male donors aged 30 or younger are preferred. (Spellman 2024 PMID 39368807)

CMV serostatus. Selecting a CMV seronegative donor for a CMV seronegative recipient is a commonly accepted practice based on multiple reports of worse survival of seronegative recipients receiving grafts from seropositive donors[15, 16], but this is generally based on studies in which GVHD prophylaxis did not include rabbit ATG (anti-thymocyte globulin). Kalra *et al*. published the outcomes in 928 Alberta patients who underwent myeloblative HSCT in hematological malignancies between 1999 and 2014 who received ATG as part of the conditioning regimen, and focused on the impact of donor and recipient CMV serostatus on transplant outcomes[17]. In this study, donor CMV serostatus had no impact on recipients who were CMV sero-negative, whereas there was a substantially lower survival in the D^-R^+ patient group versus D^+R^+ (41% vs. 59% at five years, p=0.001). Survival rates were also lower in D^-R^+ HLA-matched sibling transplant recipients compared with D^+R^+ HLA matched unrelated donor transplant recipients (44% vs. 66%) at 5 years, p=0.009). The differences in survival were being attributed to higher non-relapse mortality. The conclusion from this study was that, when using ATG for patients with malignancies, choosing a CMV seropositive donor for a CMV seropositive recipient is important, even if this requires an unrelated graft. In an updated analysis, the difference in survival between the the D^-R^+ group versus D^+R^+ group appeared to be limited to those with lymphoid malignancies[5]. Thus, CMV matching for R^+ recipients need only be considered for those undergoing allo-HCT for lymphoid malignancies.

Thus, after matching for factors that influence recipient survival: HLA-A, -B, -C and –DR matching, CMV serostatus in those with lymphoid malignancies, younger age of donor, avoidance of HLA-DPB1 non-permissive mismatching, and other less important factors (e.g., gender, ABO compatibility, donor size, in no particular order) can be considered.

Syngeneic Donors

There is no need for GVHD prophylaxis. These transplants are associated with a higher relapse rate compared to matched sibling transplants in malignancies where a graft-versus-leukemia effect is

important; such as acute myeloid leukemia (AML) (52 versus 16%), CML (40 versus 7%), and acute lymphoblastic leukemia (ALL) (36 versus 26% at 3 years)[11]. No graft-versus-lymphoma effect has been seen in non-Hodgkin lymphoma syngeneic versus allogeneic registry data, and syngeneic transplant may be a good option for lymphomas or benign disorders.

Donor Eligibility and Suitability

According to the Health Canada lymphohematopoetic cells for transplant standards manual, the following donors are **not suitable** for peripheral blood stem cell or bone marrow donation:

- persons with prion-related disease
- persons with a potentially transmittable neurological disease of an unestablished etiology
- persons with active encephalitis or meningitis of infectious or unknown etiology
- persons with rabies or persons who, within the past 6 months, were bitten by an animal and treated as if the animal was rabid
- persons with a history of infection with HIV, clinically active HCV or HBV
- persons with a family hx of Creutzfeldt-Jakob disease
- persons who have received human-derived pituitary growth hormone
- persons who have received dura matter
- persons with HTLV-I or HTLV-II, active WNV, or syphilis
- persons who have known or suspected sepsis at the time of donation
- persons previously diagnosed with a hematologic malignancy or with melanoma
- persons previously diagnosed with other types of cancer, unless they have been evaluated and deemed suitable to donate by a physician

Further, the WMDA Donor Medical Suitability Wiki can be used as a resource regarding further suitability issues, particularly with respect to donor medical conditions. This can be found on WMDA's website at
https://share.wmda.info/display/DMSR/WMDA+Donor+Medical+Suitability+Recommendations

Finally, potential donors may screen positive on the ABMTP Donor Personal History Questionnaire (for example, related to travel, habits, sexual history etc.). In the case of a positive screen, donor clearance will be at the donor physician's discretion. If a clinically relevant risk of disease transmission is identified, an exceptional release may be requested by the donor physician in case of urgent medical need. Further guidance with respect to positive screens on the ABMTP Donor Personal History Questionnaire and their implications are found in the Donor Personal History Questionnaire Guidance Document found here:

Donor Questionnaire Guidance Document

Figure 1. Algorithm for Selection of a Donor for Recipients with Non-Lymphoid Malignancies or Recipients with Lymphoid Malignancies who are CMV Seronegative**.**

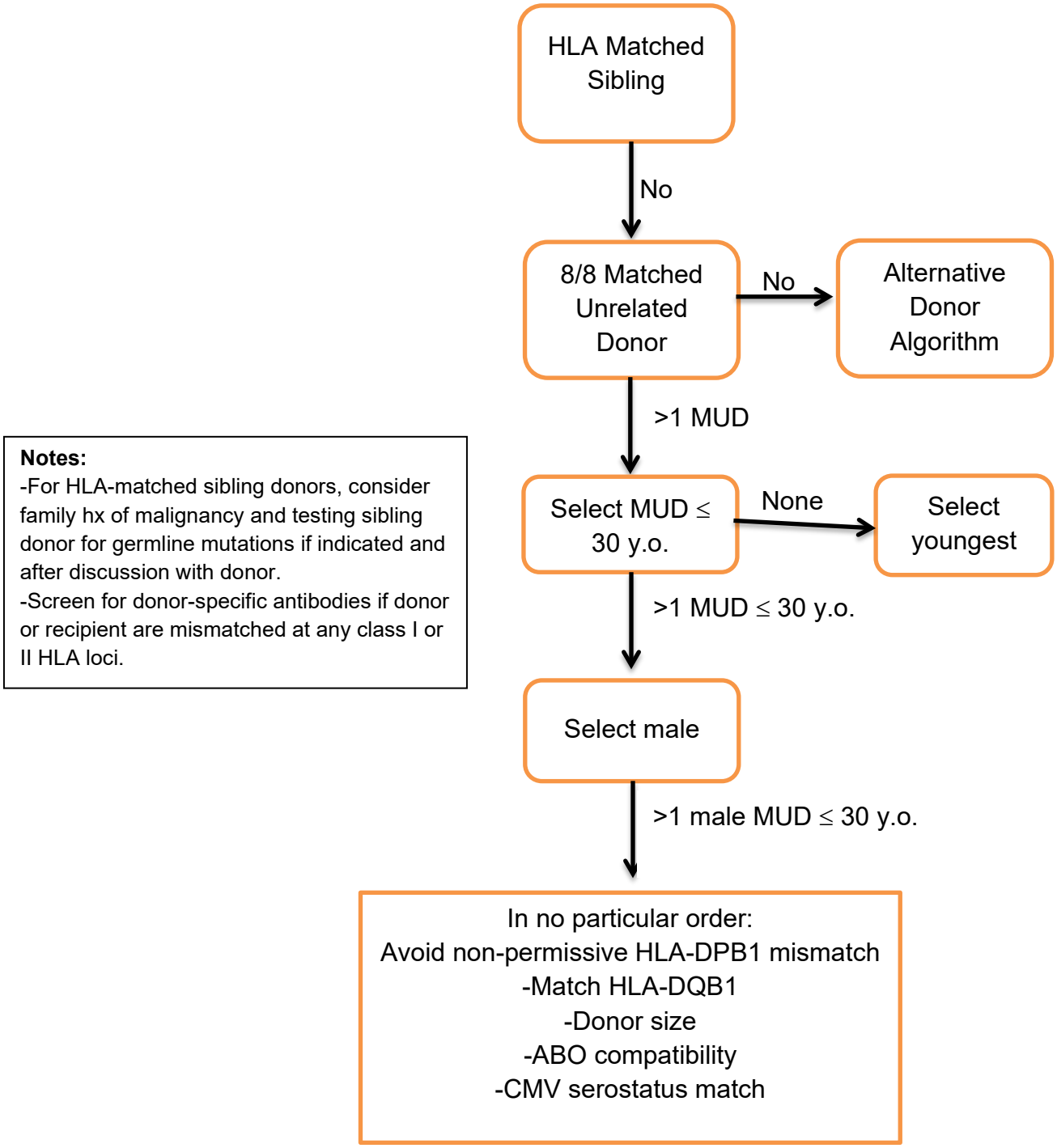
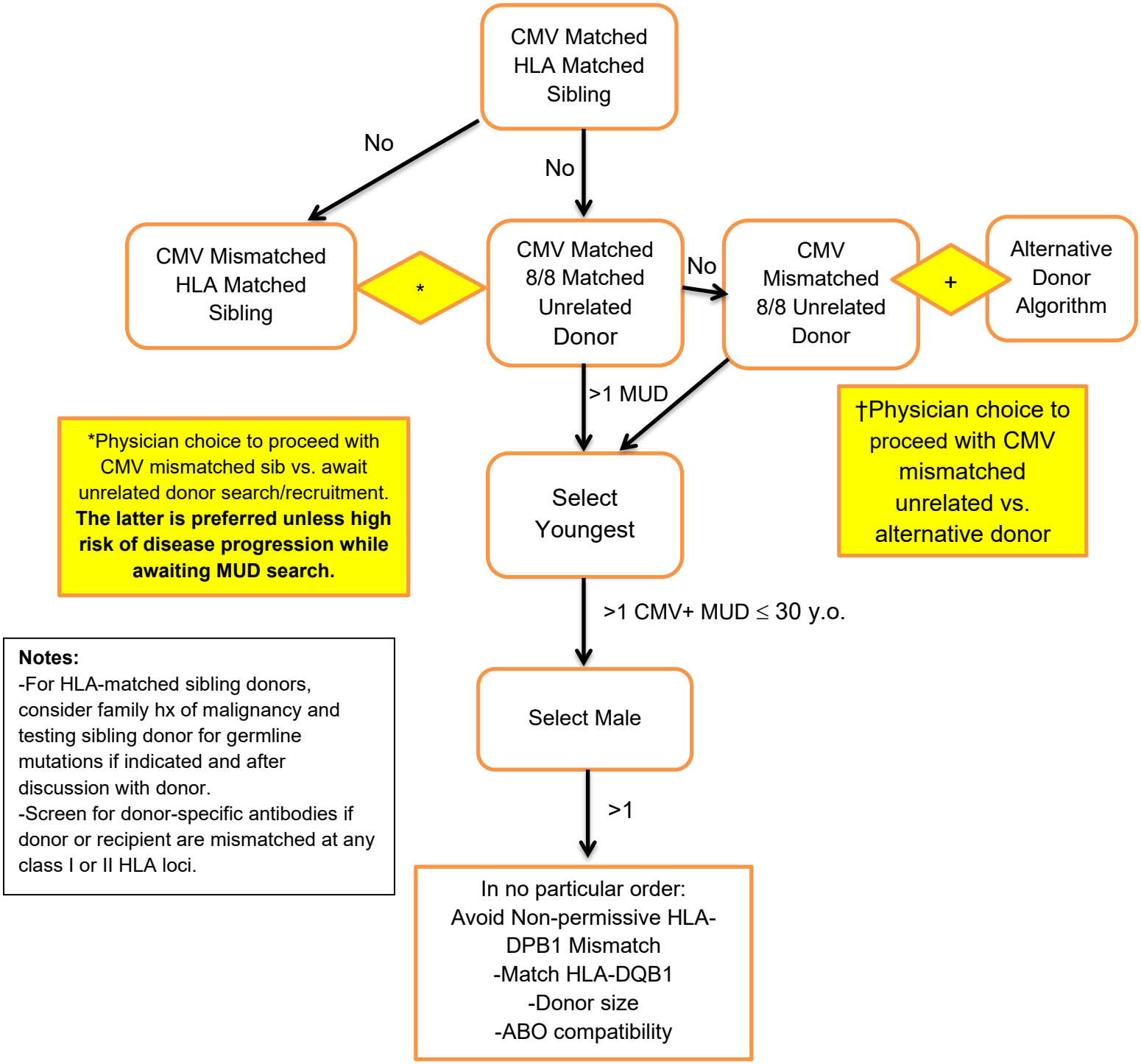
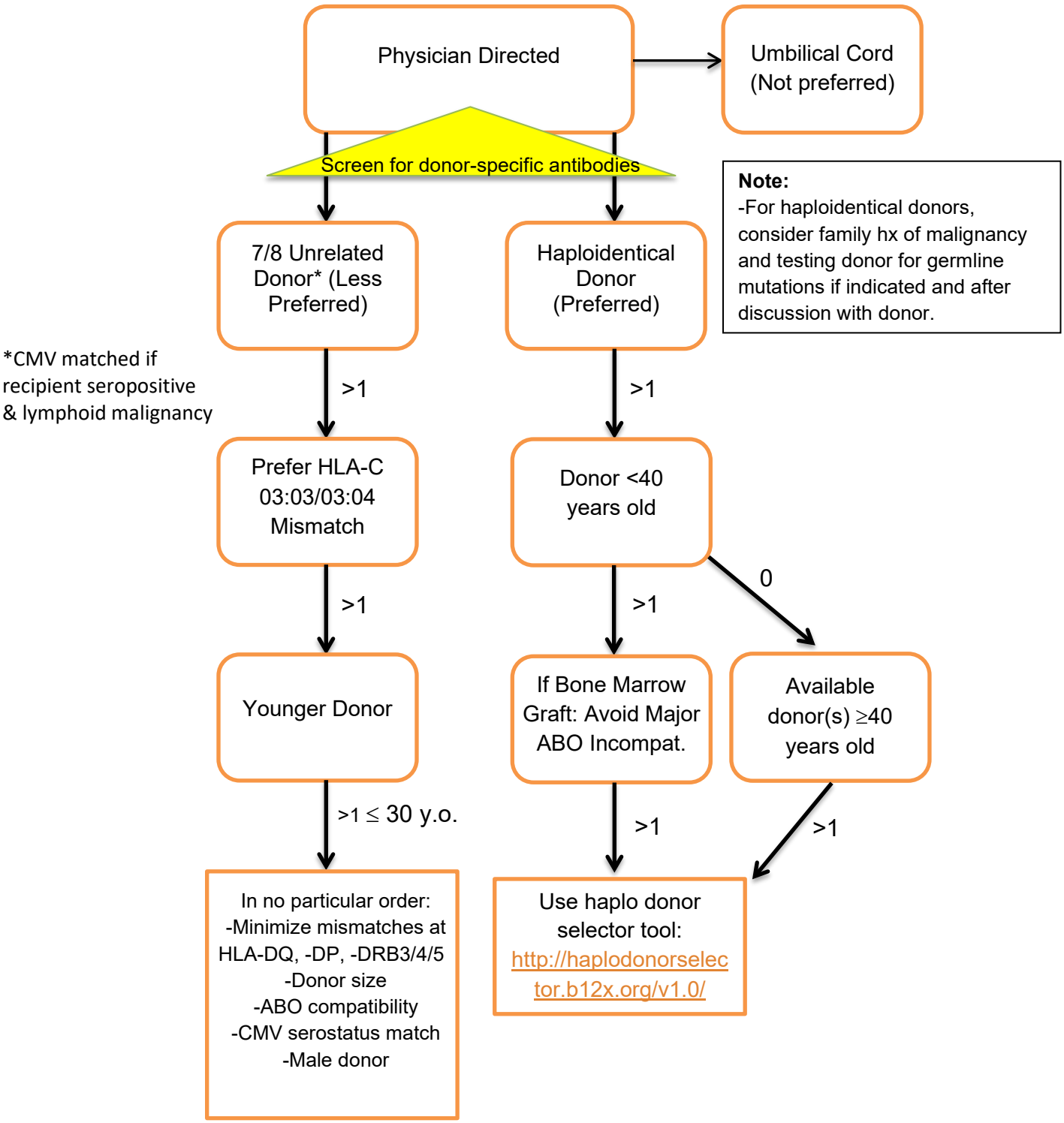


Figure 2. Algorithm for Selection of a Donor for CMV Seropositive Recipients with Lymphoid Malignancies and Receiving ATG-based GVHD Prophylaxis



Notes:
-For HLA-matched sibling donors, consider family hx of malignancy and testing sibling donor for germline mutations if indicated and after discussion with donor.
-Screen for donor-specific antibodies if donor or recipient are mismatched at any class I or II HLA loci.

Figure 3. Algorithm for Selection of an Alternative Donor



References

1.
2. Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. Blood. 2019;134:924-934.
3. Fleischhauer K, Shaw BE, Gooley T, et al. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study. Lancet Oncol. 2012;13:366-374.
4. Noureddine Berka DK, Abdelhamid Liacini, Faisal Khan, Rehan Mujeeb Faridi, Kemp J. Taylor, Jan Storek, Victor Lewis. HLA-DP Matching is Not Clinically Relevant in 10/10 HLA Matched Transplants: A Single Center Study. Biol Blood Marrow Transplant. 2013;19:S343.
5. Ousia S, Kalra A, Williamson TS, et al. Hematopoietic cell transplant outcomes after myeloablative conditioning with fludarabine, busulfan, low-dose total body irradiation, and rabbit antithymocyte globulin. Clin Transplant. 2020;34:e14018.
6. Gladstone DE, Bettinotti MP. HLA donor-specific antibodies in allogeneic hematopoietic stem cell transplantation: challenges and opportunities. Hematology Am Soc Hematol Educ Program. 2017;2017:645-650.
7. Fernandez-Vina MA, Wang T, Lee SJ, et al. Identification of a permissible HLA mismatch in hematopoietic stem cell transplantation. Blood. 2014;123:1270-1278.
8. Fernandez-Vina MA, Klein JP, Haagenson M, et al. Multiple mismatches at the low expression HLA loci DP, DQ, and DRB3/4/5 associate with adverse outcomes in hematopoietic stem cell transplantation. Blood. 2013;121:4603-4610.
9. Ciurea SO, Al Malki MM, Kongtim P, et al. The European Society for Blood and Marrow Transplantation (EBMT) consensus recommendations for donor selection in haploidentical hematopoietic cell transplantation. Bone Marrow Transplant. 2019.
10. Fuchs EJ, McCurdy SR, Solomon SR, et al. HLA Informs Risk Predictions after Haploidentical Stem Cell Transplantation with Post-transplantation Cyclophosphamide. Blood. 2021.
11. Gale RP, Horowitz MM, Ash RC, et al. Identical-twin bone marrow transplants for leukemia. Ann Intern Med. 1994;120:646-652.
12.
13. Shaw BE, Logan BR, Spellman SR, et al. Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most. Biol Blood Marrow Transplant. 2018;24:1049-1056.
14. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2016;127:260-267.
15. Boeckh M, Nichols WG. The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy. Blood. 2004;103:2003-2008.
16. Boeckh M, Nichols WG, Papanicolaou G, Rubin R, Wingard JR, Zaia J. Cytomegalovirus in hematopoietic stem cell transplant recipients: Current status, known challenges, and future strategies. Biol Blood Marrow Transplant. 2003;9:543-558.
17. Kalra A, Williamson T, Daly A, et al. Impact of Donor and Recipient Cytomegalovirus Serostatus on Outcomes of Antithymocyte Globulin-Conditioned Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2016;22:1654-1663.

Stem Cell Mobilization

Presented by: Peter Duggan

Summary

Autologous Stem Cell Collections

- For autologous stem cell collection, mobilization options include G-CSF alone (for patients who have not had prior chemo- or radio-therapy), plerixafor plus G-CSF, or combined chemotherapy and G-CSF mobilization (for those who have had prior chemo- or radio-therapy).
- Filgrastim or biosimilars may be used for autologous stem cell mobilization.
- Plerixafor is indicated for patients who are at risk for poor mobilization, those who have failed a previous mobilization attempt, for salvage during a suboptimal mobilization attempt, and for planned collection in combination with G-CSF.
- Peripheral blood is the recommended source of stem cells for autologous transplantation. Bone marrow harvests are not recommended.
- Ex-vivo purging of malignant cells from autologous stem cell products (eg, by CD34 enrichment) in patients with malignancies is not recommended.
- For CD34 enriched autografts (for autoimmune diseases), CD34 collection targets will be set at 8 x 10^6/kg and collected in a single full day apheresis. Plerixafor may be required if a sufficient peripheral blood CD34 count is not achieved with GCSF alone.

Allogeneic Stem Cell Collections

- Allogeneic donors undergoing mobilization will receive G-CSF daily for five days. Additional dose(s) should be given on day 5 and/or day 6 if fewer than 3 x 10^6 CD34+ cells/kg are collected, and a second day of collection should be arranged.
- Unrelated donors: Per WMDA, biosimilars may only be used for donors if there is an approved indication for this use. There are currently no filgrastim biosimilars available in Canada that have this labelled indication. Therefore, Neupogen is the only brand of G-CSF that can be used for allogeneic donors.
    - The Canadian Blood Services Stem Cell Donor Registry has indicated that *plerixafor* should not be given to unrelated donors who fail to mobilize with G-CSF. In the case of unrelated donors who are not mobilizing as expected, early communication to CBS is essential. The transplant center should be contacted in order to confirm that bone marrow would be acceptable prior to arranging a bone marrow harvest in these cases.
- Related allogeneic donors who mobilize poorly with G-CSF alone (blood CD34 count 5-10 per microliter) will be offered off-label plerixafor. Those refusing plerixafor will undergo surgical bone marrow harvest on day +6 of G-CSF. Those who fail mobilization (CD34 count < 5) will undergo surgical marrow harvest on day +6.

Autologous Stem Cell Mobilization Options

The preferred stem cell source for autologous SCT is mobilized peripheral blood stem cells collected by apheresis. This is based upon small RCTs that demonstrated improved quality of life, shorter engraftment times, decreased blood and platelet transfusions, decreased hospital stays, and reduced costs relative to traditional bone marrow harvests[1-8]. Chemotherapy (a salvage regimen or cyclophosphamide 2-4g/m^2) plus G-CSF 5-10 mcg/kg/day is an acceptable standard method of stem cell mobilization[9-19]. Predictors of poor mobilization include: advancing age, prior treatment with chlorambucil, fludarabine, melphalan, radiotherapy to >25% of bone marrow, or repeated cycles of chemotherapy plus G-CSF within the past 6 months, as well as those with low blood platelet counts prior to mobilization treatment, or those who have experienced prior failure of stem cell mobilization.

A chemotherapy free regimen using GCF plus plerixafor has been utilized. There are no randomized controlled trials comparing chemotherapy-based mobilization regimens to mobilization with plerixafor and growth factors. Retrospective comparisons do show higher total and day one CD34+counts following chemotherapy-based mobilization, but this is associated with higher risk of febrile neutropenia. There is no significant difference in the number of patients able to proceed to transplant, the number of apheresis days and transplant outcomes[33-35]. Those mobilized with plerixafor and GCSF are almost always collected on their planned day of apheresis. This approach is most widely described in the setting of multiple myeloma, and can be considered when disease targeted chemotherapy is not required, and the collection target is modest (e.g. single transplant). It may not be a successful approach if collection for multiple transplants is planned.

The role of graft purging of malignant cells in patients with malignancies. Registry (CIBMTR and EBMT) data suggest there may be a role for purging based on the extremely low relapse rates following syngeneic SCT, followed by higher relapse rates with purged autologous SCT and then significantly higher relapse rates with unpurged autologous SCT[20]. This data, however, is potentially biased, and randomized controlled trials evaluating ex-vivo autograft tumor purging techniques have not been reported in the setting of autologous transplantation for lymphoma. In addition, autograft purging results in stem cell loss and delays hematopoietic and immunological engraftment[21—23]. Because of these facts, routine ex-vivo autograft purging is not recommended.

Option 1. Granulocyte Colony Stimulating Factor (G-CSF) Alone, or G-CSF with Plerixafor.

Indications:

- Mobilization of peripheral blood stem cells for autologous stem cell transplant patients who *have not* had prior chemotherapy or radiotherapy.
- G-CSF with or without plerixafor is preferred over chemotherapy + growth factors for mobilizing patient with multiple myeloma and amyloidosis. Chemotherapy may be considered for those who are expected to mobilize poorly, who have a high CD34 target, or who have significant residual myeloma in marrow.

- Plerixafor may be given “on demand” for those with a low CD34 count after 4-5 days of GCSF alone, or planned on day 4, prior to apheresis the following day.

G-CSF dosing - autologous donor:

- G-CSF 5-10 µg/kg/day for 4 days, rounded to nearest vial size and fewest injections (see Table 1).

Plerixafor dosing

- 0.24mg/kg/day, to maximum dose of 24mg/day.

Option 2. Combined Chemotherapy and G-CSF Stem Cell Mobilization

Indications:

- Mobilization of peripheral blood stem cells for autologous stem cell transplant patients who *have* had prior chemotherapy or radiotherapy.

Standard intensity regimen indications:

- Myeloma, when growth factor only mobilization is not preferred.
- Germ cell tumours
- Lymphoma with largest tumour mass less than 5 cm and negative marrow biopsies
- Most other miscellaneous indications

Standard intensity regimens include:

- Cyclophosphamide 2.5 g/m^2 day 1 OR standard dose regimen such as DHAP, high dose cytarabine, VIP, or TIP
- Add Rituximab 1400mg sc on first day chemotherapy for CD20+ B-cell lymphomas
- G-CSF starting on Wednesday of the following week (~day 7-9)
- Apheresis scheduled for Monday-Wednesday 2 weeks after chemo (~days 12 to 14)

High intensity regimen indications:

- Lymphoma with mass greater than 5 cm, bone marrow involvement, or refractory disease

High intensity regimen example:

- DICEP regimen
  - Cyclophosphamide 1.75 g/m^2/day x 3 days
  - Etoposide 350 mg/m^2/day x 3 days
  - Cisplatin 35 mg/m^2/day x 3 days
- Add Rituximab 375mg/m^2 IV (or 1400mg sc) for CD20+ B-cell lymphomas (decrease dose of all chemo by 20% for patients >60yrs)
- G-CSF starting day 14
- Apheresis ~days 19 to 21

G-CSF dosing:

Patients without risk factors for poor mobilization should receive G-CSF 5-10 µg/kg/day, rounded to nearest vial size and fewest injections, beginning on the day indicated in the protocol and continuing until completion of apheresis (see Table 1)

Table 1. Dosing for granulocyte colony stimulating factor based on weight for autologous stem cell mobilization

Donor Weight (kg)	G-CSF Dose (µg)*
< 60kg	300
60 - 75	480
75.1 – 100	600
> 100	780

*dose ranges yield 5 to 8 mcg/kg

Option 3. Plerixafor for Stem Cell Mobilization

Risk Factors for poor mobilization:

1. Advanced disease (≥2 lines of chemotherapy)
2. Extensive BM involvement or cellularity <30% at time of mobilization
3. Age >60
4. Prior radiotherapy to >25% of bone marrow surface area
5. Prior treatment with fludarabine and other purine analogues, lenalidomide, melphalan
6. Platelets less than 100x 10^9/L prior to mobilization
7. Prior failed mobilization attempt

Plerixafor use should be considered in the following settings:

1. Preemptively for patients predicted to mobilize poorly based on the risk factors above. It should be used in combination with G-CSF with or without chemotherapy.
2. For salvage immediately prior to apheresis for patients with suboptimal mobilization. Plerixafor should be given if the post nadir WBC count is >5 x 10^9/L and CD34 count is >5 but <20 x 10^6/L or if <50% of the target CD34 yield was achieved on the first day of apheresis.
3. Re-mobilization for patients with a prior failed attempt at mobilization with G-CSF with or without chemotherapy.
4. As part of a planned chemotherapy-free collection strategy using plerixafor with GCSF.

Plerixafor dosing:

- The recommended dose of Plerixafor is 0.24 mg/kg body weight (0.16 mg/kg for creatinine clearance <50 mL/min) by subcutaneous injection, injection with the dose capped at 24mg, given the day before apheresis is planned, and then daily until apheresis is complete.

Apheresis:

- Performed on the day when the post-chemotherapy nadir blood counts have recovered to:
  - Platelet greater than 30 x 10^9/L and hemoglobin >70 g/L
  - CD34+ count greater than 20 x 10^6/L
- Plan for large volume apheresis (≥3 blood volumes, approximately 15 L) using a central venous catheter for autologous donors. Minimum apheresis volume of 8L.
- Target CD34+ collection:
  - Minimum target all patients: 2 x 10^6 CD34+ cells/kg/transplant
  - Ideal target 5 to 10 x 10^6 CD34+ cells/kg/transplant (preferred)

Mobilization and Collection for CD34 Enriched Autologous Transplants

For patients requiring CD34 enriched autologous stem cell products, such as those undergoing ASCT for autoimmune disease, CD34 collection targets will be higher in order to compensate for losses during processing and to obtain a final product containing 5 x 10^6 CD34 cells. This target is to be collected on a single day of apheresis to avoid needing more than one day of CD34 selection. Based on these requirements, the following collection parameters are recommended:

1. Requested CD34 cell dose for collection will be set at 8 x 10^6/kg
2. Total CD34 cell target must be collected in a single full day apheresis
3. Sufficient peripheral blood CD34 count is necessary to meet these parameters. Plerixafor may be required if a sufficient peripheral blood CD34 count is not achieved with GCSF alone.
   a. If PB CD34 ≥ 150, regardless of target, proceed with collection.
   b. If PB CD34 ≥ 60 and CD34 collection target is ≤ 700, proceed with collection.
   c. If PB CD34 ≥ 60 and <150 but CD34 collection target ≥ 700, arrange for plerixafor and collect on the following day.
   d. If PB CD34 ≤ 60, arrange for plerixafor and collect the following day. Exceptions to this may include those with CD34 < 60 but a low collection target based on weight that is expected to be collected based on the current CD34 count without the addition of plerixafor.

Allogeneic Stem Cell Transplant Donors

G-CSF dosing - allogeneic donor

- For donors weighing more than 48 kg, G-CSF 8-10 µg/kg/day, rounded to nearest vial size (see table). Individualize dosing for donors weighing < 48 kg or > 120 kg, irrespective of vial sizes. Doses are given daily for five days (days 1 to 5) with apheresis collection on day 5.

Table 2. Dosing for granulocyte colony stimulating factor based on weight for allogeneic donor stem cell mobilization

Donor Weight (kg)	G-CSF Dose (µg)
< 48	300
48-60	480
60.1-78	600
78.1-100	780
100.1-120	960

Additional doses of G-CSF for allogeneic donors:

- Order additional doses of G-CSF to be administered after collection and the following morning if fewer than 3 x 10^6 CD34+ cells/kg were collected in the first apheresis session.

Apheresis:

- Plan large volume apheresis (≥3 blood volumes) on day 5 using peripheral venous access. A second collection day may be required if the minimum dose is not reached on one day of apheresis.
    - Donor apheresis using central venous access devices (CVAD) will be used only in exceptional circumstances. In the case of unrelated donors, the need for CVAD use will be discussed with CBS.
- Minimum of 8L apheresis
- Target CD34+ Collection: 5 - 10 x 10^6/kg recipient weight
- Minimum target: 3 x 10^6 CD34+ cells/kg recipient weight

Failed Mobilization of an Allogeneic Donor

Failure to collect a sufficient number of stem cells to transplant an allogeneic recipient has very significant implications for that recipient. Options for the transplant center include approaching a backup donor or approaching an alternative family member for haploidentical donation; in most cases, however, the recipient has already been conditioned and approaching a second donor may result in significant delays and prolonged aplasia. In Alberta, if a related donor mobilizes poorly (blood CD34 count 5-10 per microliter) after five days of G-CSF they will be offered a dose of plerixafor off label and will undergo collection by apheresis on day 6 if CD34 count increases to ≥ 15. Donors who decline to receive plerixafor or whose blood CD34 count is < 5 per microliter on the fifth day of G-CSF will be asked to undergo surgical bone marrow harvest urgently on day 6.

For unrelated donors, in the event that there is a failed mobilization, the collection center must have the ability to collect marrow as an emergency procedure. The collection center must inform the CBS if the donor expresses concerns or would not be willing and/or eligible for marrow HPC as a contingency collection. The CBS Stem Cell Registry has advised that plerixafor should not be administered to unrelated donors. The WMDA also does not recommend the use of plerixafor but

recognizes that there may be situations where its use is appropriate. In the case of failed mobilization of an unrelated donor, early notification of the transplant center is essential. The collection center will work closely with CBS to determine the next steps in the collection plan.

Cytokine-Stimulated Bone Marrow

The use of G-CSF stimulated bone marrow for hematopoietic cell transplantation was proposed as a way of providing a product with the rapid engraftment potential of G-CSF mobilized peripheral blood grafts but with the low risk of GVHD associated with bone marrow. Studies have shown that GVHD rates are lower with bone marrow (including G-CSF stimulated marrow) but no consistent advantage of G-CSF stimulated marrow over unstimulated marrow has been demonstrated either in terms of overall- or progression-free survival[24]. The ABMTP will not routinely administer G-CSF to bone marrow donors.

Donors from Vulnerable Groups

Minor Donors: <18 years of age may be selected if:

a. There is no equivalent histocompatible adult donor who is willing and readily available for donation
b. It is deemed the recipient will benefit from transplantation
c. The clinical, emotional and psychological risks to the donor are minimized and are reasonable in relation to the benefits expected to the donor and the recipient as outlined in the pediatric donor eligibility and suitability evaluation SOP (BMTS20005)
d. Following a psychological evaluation, the staff has deemed that there is a strong personal and emotionally positive relationship between the donor and recipient as outlined in the Pediatric Donor Eligibility and Suitability Evaluation SOP (BMTS20005)
e. Parental permission/consent and child assent will be obtained as per Pediatric Blood and Marrow Transplant Consent Procedure (BMTS20009)
f. A donor advocate trained in pediatrics will be assigned as outlined in the Pediatric Donor Eligibility and Suitability Evaluation SOP (BMTS20005)
g. The donor must weigh a sufficient amount to safely undergo collection

Older Donors: >65 years of age:

a. Must be able to complete standard donor testing outlined in Standard Protocol Allogeneic Donor Collection Workup (BMTW34092).
b. Must meet suitability and eligibility criteria as defined in Donor Eligibility and Suitability SOP (BMTS10212)
c. Must have general good health as determined by physician assessment.
d. Comorbidities are identified and evaluated by donor physician
e. Must have a performance status that will permit the safe collection of cells as determined by physician assessment

f. Resources will be provided for disabilities, including the visual or hearing impairments
g. Donors may access a third-party advocate as they feel appropriate as per "Interaction Between Alberta Health Services and Third Party Advocates PRR-04"

Hemoglobinopathies:

G-CSF is not advised for mobilization in donors with sickle cell disease.

Hemoglobinopathy assessment is required for all donors (autologous and allogeneic) as administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity (e.g. veno- occlusive crisis) and mortality in donors with sickle cell disease (HBSS), (HPSC), and also with compound hemoglobinopathies such as sickle-beta-thalassemia (S/β Thal). Patients with hemoglobinopathy will be identified based on their medical history. Testing of donors with no history of hemoglobinopathy and with a normal hemoglobin is not required, but is an acceptable method.

Of note, medical literature reports that donors with sickle cell trait have been safely mobilized and collected[32-34]. Although donors with the sickle cell trait did have higher symptom scores than control donors, there were no symptoms suggestive of sickle crisis. Thus, in this group the risk is limited.

Repeat Donations

The Alberta BMT Program permits donors to donate on more than one occasion, provided the risk of donating is justified by the condition of the recipient. Donors will only be permitted to donate stem cells (bone marrow and/or G-CSF stimulated peripheral blood stem cells) twice, although the program will not limit the number of donations of non-mobilized cells such as donor lymphocyte infusions.

Weekend Apheresis

If a Weekend Apheresis Collection is probable or confirmed, the most responsible physician shall contact personnel in Flow Cytometry, Apheresis and Cellular Therapy Laboratory by Friday at noon.

- Apheresis Manager: (403) 944-4059
- Flow Cytometry, Tech III: (403) 944-4765
- Cellular Therapy Lab: (403) 944-4439

Use of G-CSF Biosimilars

Biosimilars are approved biologics with comparable quality, safety, and efficacy to a reference product for which patent protection has expired. Biosimilar regulatory approval is provided on the basis of a robust comparability exercise demonstrating similarity with the original product, rather than on the need to show a positive risk-benefit assessment, which it is assumed has already been proven. The degree

of clinical similarity required to achieve biosimilar status is considered on a case-by case basis by the regulatory authorities.

Biosimilars of G-CSF, based on the original filgrastim product Neupogen, have been available for a number of years and are now widely used, often exceeding the use of the original product. For the currently approved biosimilar G-CSFs (e.g., Nivestym), extrapolation to all indications of the reference product has been granted, given the comparable receptor site kinetics and mode of action. This includes mobilization of peripheral blood stem cells in patients undergoing autologous stem cell transplantation as well as for stem cell mobilization in patients and healthy donors.

For autologous stem cell mobilization, the overall effectiveness of biosimilar G-CSF has been evaluated in several open-label studies, some of which have include the reference product as a comparator. All of these studies have shown no significant differences in efficacy (e.g., median number of CD34+ cells collected, number of G-CSF injections required, apheresis days, etc.), and safety, with similar incidence and severity of common adverse events such as bone or muscles pain and headache, and no severe or unexpected AEs[25-27]. There are a few reports of biosimilar G-CSF use for PBSC mobilization in healthy donors that suggest these agents are effective and well tolerated, with similar mobilization outcomes in comparison to Neupogen, with no clinically significant differences between groups[28-30]. There is an ongoing long-term safety study over 10 years, which will contribute data for up to 2000 person-years and add to the cumulative assessment of the long-term safety of G-CSF as a mobilizing agent[31].

The safety considerations for healthy donors differ from those for patients since donors do not benefit from the treatment. The safety threshold for donors is therefore extremely low, and until more efficacy and safety data have been collected, CBS has recommended against the use of biosimilar G-CSFs in healthy donors at this time.

References

Stem Cell Graft

1. Kanteti R, Miller K, McCann J, Roitman D, Morelli J, Hurley C, et al. Randomized trial of peripheral blood progenitor cell vs bone marrow as hematopoietic support for high-dose chemotherapy in patients with non-Hodgkin's lymphoma and Hodgkin's disease: a clinical and molecular analysis. Bone Marrow Transplant 1999 Sep;24(5):473-81.
2. Vose JM, Sharp G, Chan WC, Nichols C, Loh K, Inwards D, et al. Autologous transplantation for aggressive non-Hodgkin's lymphoma: results of a randomized trial evaluating graft source and minimal residual disease. J Clin Oncology 2002 May;20(9):2344-52.
3. Lewis A. Autologous stem cells derived from the peripheral blood compared to standard bone marrow transplant; time to engraftment: a systematic review. Int J Nurs Studies 2005 Jul;42(5):589-96.
4. van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. A prospective randomized trial. Eur J Cancer 2001 Sep;37(14):1781-9.
5. Vellenga E, van Agthoven M, Croockewit AJ, Verdonck LF, Wijermans PJ, van Oers MH, et al. Autologous peripheral blood stem cell transplantation in patients with relapsed lymphoma results in accelerated haematopoietic reconstitution improved quality of life and cost reduction compared with bone marrow transplantation: the Hovon 22 study. Br J Haematol 2001 Aug;114(2):319-26.

6. Smith TJ, Hillner BE, Schmitz N, Linch DC, Dreger P, Goldstone AH, et al. Economic analysis of a randomized clinical trial to compare filgrastim-mobilized peripheral-blood progenitor-cell transplantation and autologous bone marrow transplantation in patients with Hodgkin's and non-Hodgkin's lymphoma. J Clin Oncol 1997 Jan;15(1):5-10.
7. Weisdorf DJ, Verfaille CM, Miller WJ, Blazar BR, Perry E, Shu XO, et al. Autologous bone marrow versus non-mobilized peripheral blood stem cell transplantation for lymphoid malignancies: a prospective, comparative trial. Am J Hematol 1997 Mar;54(3):202-8.
8. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, et al. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet 1996 Feb;347(8998):353-7.

Mobilization

9. Stewart DA, Guo D, Morris D, Poon MC, Ruether BA, Jones AR, et al. Superior autologous blood stem cell mobilization from dose-intensive cyclophosphamide, etoposide, cisplatin plus G-CSF than from less intensive chemotherapy regimens. Bone Marrow Transplant 1999 Jan;23(2):111-7.
10. Duggan PR, Guo D, Luider J, Auer I, Klassen J, Chaudhry A, et al. Predictive factors for long-term engraftment of autologous blood stem cells. Bone Marrow Transplant 2000 Dec;26(12),1299-1304.
11. Stewart DA, Guo D, Luider J, Auer I, Klassen J, Morris D, et al. A low CD34+ cell dose predicts relapse and death early following autologous blood stem cell transplantation. Hematology 2001;6:19-27.
12. Narayanasami U, Kanteti R, Morelli J, Klekar A, Al-Olama A, Keating C, et al. Randomized trial of filgrastim versus chemotherapy and filgrastim mobilization of hematopoietic progenitor cells for rescue in autologous transplantation. Blood 2001 Oct;98(7):2059-64.
13. Demirer T, Ayli M, Ozcan M, Gunel N, Haznedar R, Dagli M, et al. Mobilization of peripheral blood stem cells with chemotherapy and recombinant human granulocyte colony-stimulating factor (rhG-CSF): a randomized evaluation of different doses of rhG-CSF. Br J Haematol 2002 Feb;116(2):468-74.
14. Andre M, Baudoux E, Bron D, Canon JL, D'Hondt V, Fassotte MF, et al. Phase III randomized study comparing 5 or 10 microg per kg per day of filgrastim for mobilization of peripheral blood progenitor cells with chemotherapy, followed by intensification and autologous transplantation in patients with nonmyeloid malignancies. Transfusion 2003 Jan;43(1):50-7.
15. Pavone V, Gaudio F, Guarini A, Perrone T, Zonno A, Curci P, et al. Mobilization of peripheral blood stem cells with high-dose cyclophosphamide or the DHAP regimen plus G-CSF in non-Hodgkin's lymphoma. Bone Marrow Transplant 2002 Feb;29(4):285-90.
16. Blystad AK, Delabie J, Kvaloy S, Holte H, Vålerhaugen H, Ikonomou I, et al. Infused CD34 cell dose, but not tumour cell content of peripheral blood progenitor cell grafts, predicts clinical outcome in patients with diffuse large B-cell lymphoma and follicular lymphoma grade 3 treated with high-dose therapy. Br J Haematol 2004 Jun;125(5):605-12.
17. Stiff P, Gingrich R, Luger S, Wyres MR, Brown RA, LeMaistre CF, et al. A randomized phase 2 study of PBPC mobilization by stem cell factor and filgrastim in heavily pretreated patients with Hodgkin's disease or non-Hodgkin's lymphoma. Bone Marrow Transplant 2000 Sep;26(5):471-81.
18. Humpe A, Riggert J, Munzel U, Repas-Humpe LM, Vehmeyer K, Brunner E, et al. A prospective, randomized, sequential, crossover trial of large-volume versus normal-volume leukapheresis procedures: effect on progenitor cells and engraftment. Transfusion 1999 Oct;39(10):1120-7.
19. Weaver CH, Zhen B, Schwartzberg L, Walker C, Upton S, Buckner CD. A randomized trial of mobilization of peripheral blood stem cells with cyclophosphamide, etoposide, and granulocyte colony-stimulating factor with or without cisplatin in patients with malignant lymphoma receiving high-dose chemotherapy. Am J Clin Oncol 1998 Aug;21(4):408-12.

Purging

20. Gisselbrecht C, Mounier N. Rituximab: enhancing outcome of autologous stem cell transplantation in non-Hodgkin's lymphoma. Semin Oncol 2003 Feb;30(1 Suppl 2):28-33.
21. Alvarnas JC, Forman SJ. Graft purging in autologous bone marrow transplantation: a promise not quite fulfilled. Oncology Jun 2004;18(7):867-76.
22. Heeckeren WJ, Vollweiler J, Fu P, Cooper BW, Meyerson H, Lazarus HM, et al. Randomised comparison of two B-cell purging protocols for patients with B-cell non-Hodgkin lymphoma: in vivo purging with rituximab versus ex vivo purging with CliniMACS CD34 cell enrichment device. Br J Haematol 2006 Jan;132(1):42-55.

23. Maeda S, Kagami Y, Ogura M, Taji H, Suzuki R, Kondo E, et al. CD34+-selected autologous peripheral blood stem cell transplantation conditioned with total body irradiation for malignant lymphoma: increased risk of infectious complications. Int J Hematol 2001 Aug;74(2):214-21.

G-CSF Stimulated Marrow

24. Deotare U, Al-Dowsare G, Couban S and Lipton J. G-CSF primed bone marrow as a source of stem cells for allografting. Revisiting the Concept. Bone Marrow Transplant (2015); 50: 1150-56

Biosimilars

25. Lefrere F, Brignier AC, Elie C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. Adv Ther 2011; 28: 304-10
26. Manko J, Walter-Cronck A, Jawniak D, et al. A clinical comparison of the efficacy and safety of biosimilar G-CSF and originator G-CSF in haematopoietic stem cell mobilization. Pharmacol Rep 2014 66:239-42
27. Yafour N, Brahimi M, Osmani S, et al. Biosimilar G-CSF (filgrastim) is effective for peripheral blood stem cell mobilization and non-cryopreserved autologous transplantation. Transfus Clin Biol 2013 20:502-4
28. Azar N, Choquet S, Garnier A, et al. Use of a biosimilar G-CSF in allogeneic stem cell mobilization. Bone Marrow Transplant 2012 47 (suppl 1):S316 (P727)
29. Antelo M, Zabalza A, Sanchez P, et al. Safety and efficacy of a G-CSF biosimilar (Zarzio®) for haematopoietic progenitor cell mobilization in allogeneic healthy donors. Bone Marrow Transplant 2013 48(Sppl1 2):S102 (P491)
30. Schmitt M, Xu X, Hilgendorf I, et al. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. Bone Marrow Transplant 2013 48:922-5
31. Becker P, Brauninger S, Bialleck H, et al. Biosimilar filgrastim mobilizes haematopoietic stem cells in healthy volunteer donors with expected efficiency and typical acute adverse effects: interim results of a post-authorization safety study. Bone Marrow Transplant 2013; 48(Suppl 2):S28 (O177)

Sickle cell disease

32. Fitzugh Cd, etal. Granulocyte colony stimulating factor (G-CSF) administration and individuals with sickle cell disease: Time for a moratorium? Cytotherapy 2009;11(4):464-471
33. Rosenbaum C et al. Granulocyte colony stimulating factor based stem cell mobilization in patients with sickle cell disease. Biology of blood and marrow transplantation 2008; 14: 719-723
34. Kang et al. Mobilization, collection, and processing of peripheral blood stem cells and individuals with sickle cell trait. Blood 2002; 99: 850

33. Yang et al. Are we choosing mobilization regimens for autologous stem cell transplant station in multiple myeloma wisely: a single center comparison of GCSF +/- plerixafor versus cyclophosphamide +/- plerixafor. J Clin Apher. 2022; 37(4): 348 – 353

34 Shaughnessy P etal. Cost and clinical analysis of autologous *hematopoietic stem cell mobilization* with GCSF and plerixafor compared to GCSF and cyclophosphamide. Biology of blood and marrow transplantation. 2011 May; 17(5): 729 – 36

35. Costa LJ et al. Growth factor and patient adapted use of flexor is superior to CY and growth factor for Autologous hematopoietic stem cell mobilization. Bone marrow transplant. 2011 Apr; 46(4): 523-8.

Vaccination

Presented by: Kareem Jamani

Summary

- Transplant recipients should be immunized according to the Guidelines of Community and Population Health Division ("Public Health"), Alberta Health and Wellness, posted at https://www.alberta.ca/alberta-immunization-policy.aspx#toc-4 (under 'Special situations for immunization).

Highlights of the Schedule:

- 6 mo posttransplant, start non-live vaccines (given at 6, 7, 8, 12, 14 and 24 mo)
- 24 mo posttransplant, start live vaccines (given at 24 and 27 mo) – contraindicated in patients with relapse or active cGVHD – wait until ≥3 mo after discontinuation of immunosuppressive therapy (systemic and topical) and no cGVHD activity. Discontinue valacyclovir 1 day before first VZV vaccine dose.
- Autologous HCT recipients will be vaccinated for varicella/zoster with Shingrix (rather than live VZV vaccine) at 6 and 7 months post-HCT. Valacyclovir will be discontinued 1 month after the second Shingrix dose. Continuation of VCV can be considered in cases of immunosuppressive therapy during/after the Shingrix vaccination.
- CAR-T recipieints will be vaccinated according to the post allogeneic HCT vaccination schedule.
- 36 mo posttransplant, check antibody levels to tetanus, hepatitis B, measles and rubella, and order boosters if needed.

Background

The Albertan Guidelines were developed based on international guidelines[1], keeping simplicity in mind. For example, the same schedule was developed for autologous and allogeneic transplant recipients, and similar schedule was developed for children and adults. The reason for simplicity is to minimize confusion that could arise from the fact that many parties are involved in the vaccination process, including the transplant physician, the hematologist/oncologist to whom an autologous transplant recipient is referred after autologous transplantation, the Public Health vaccination clinic administering the vaccines and, in special scenarios, Infectious Disease specialist, Public Health specialist ("Medical Officer of Health") or Travel Clinic physician.

Practical Considerations

- Antibody levels to vaccine-preventable diseases decline during 1-10 years posttransplant if the recipient is not revaccinated.
  - The decline is more substantial in allogeneic compared to autologous HCT recipients. Therefore, and because influenza, pneumococcal disease and shingles are less frequent

after autologous than allogeneic HCT, vaccination is less important after autologous than allogeneic HCT.

Why Vaccinate?

- Let transplant recipients enjoy the same protection from vaccine-preventable diseases as the general population.
  - Haemophilus influenzae type b
  - Neisseria meningitidis
  - Diphteria
  - Tetanus
  - Pertussis
  - Poliomyelitis
  - Hepatitis B
- Protect against infectious diseases that occur more frequently in transplant recipients than in the general population, or are more severe in transplant recipients, in particular:
  - Influenza virus
  - Covid-19
  - Streptococcus pneumoniae
  - Varicella zoster virus

When to Revaccinate?

- Depends on multiple considerations, which were taken into account when creating the schedule and should be taken into account by clinicians when adjusting the schedule to a specific patient
- B cell counts recover to normal at 3-6 mo, memory B cells later
  - In case of B cell depleting antibodies (eg, rituximab), B cell counts are near-zero for 6 mo after last dose. If a patient was treated with a B cell depleting antibody posttransplant, delay start of vaccination till at least 6 mo after the last antibody dose.
- CD4 T cell counts recover to normal at >1 year, but T cell responses are detectable earlier
  - In case of T cell depleting antibodies (eg, rabbit ATG for GVHD), T cell counts are very low for 6 mo after last dose. If a patient was treated with a T cell depleting antibody posttransplant, delay start of vaccination till at least 6 mo after the last antibody dose.
- Antigen consideration
  - Ab responses to recall protein antigens (eg, diphtheria toxoid, tetanus toxoid) recover early
  - Ab responses to neoantigens (eg, hepatitis B vaccine in individuals not vaccinated and not infected pre-transplant) and to polysaccharides (eg, pneumococcal polysaccharide vaccine [Pneumovax]) recover late, particularly late in patients with GVHD
    - For polysaccharides, the response occurs earlier and even in patients with GVHD if conjugated to a recall protein (eg, pneumococcal polysaccharide-protein conjugate vaccine [Prevnar])

- Need for immediate vs long-term immunity
  - The later the start of immunization, the higher and probably more durable Ab responses
  - On the other hand, low response early postHCT may be better than no response to confer at least some protection against influenza, Covid-19, and S.pneumoniae.
- Live vaccine consideration
  - Safety documented in patients at 2 y posttransplant
    - If no relapse
    - If no active GVHD
    - Off of immunosuppressive drugs for at least 3 mo
    - Off of IVIG for 7 months (efficacy of live vaccines is decreased with IVIG; wash-out of 3 months is probably sufficient; however, Public Health official recommendation is to wait 7-11 months)
  - Probably safe as early as 1 year posttransplant, so could be used during outbreak
- GVHD status consideration
  - Patients with active GVHD and/or treated with systemic immunosuppressive drugs mount lower antibody responses to vaccines than patients without GVHD/off of immunosuppressive drugs. However, even the low response is thought to protect at least some patients from influenza, Covid-19, or pneumococcal disease. Given that protection against influenza, Covid-19, and pneumococcus is more important in these patients (compared to patients without GVHD/off of immunosuppressive drugs), immunization with non-live vaccines should not be delayed due to GVHD/immunosuppressive therapy. Live vaccines are contraindicated.
- Malignancy status consideration
  - Patients with relapsed original malignancy or second malignancy treated with chemotherapy, radiation or comfort measures only should not get any vaccine. Live vaccines are contraindicated and non-live vaccines are probably ineffective and/or futile.
- Maintenance therapies consideration
  - Patients on post-transplant maintenance therapies may receive non-live & live vaccines at the discretion of attending physician.
    - For maintenance rituximab or T-cell depleting antibodies, start of vaccination with non-live vaccines should be delayed until ≥6 months after the last dose of rituximab or T-cell depleting antibodies[2].
    - Live vaccines can be started at ≥12 months after the last dose of rituximab (opinion, no data exist).
    - Maintenance lenalidomide and bortezomib are not contraindications to vaccination
      - Non-live vaccine safety and efficacy is not jeopardized by lenalidomide[3].
      - Live vaccines are safe (if given ≥2 y postHCT and no relapse) but no data exist on efficacy[4]. Given that multiple myeloma patients are always at risk of

relapse, it is recommended to continue valacyclovir indefinitely and forego live vaccines.

Donor Vaccination:

- Theoretically useful and possibly practical only for
  - Pneumococcal Conjugate Vaccine and Influenza Vaccine, unknown for Covid-19
  - Related donors
  - If vaccine can be given at least 10 days before stem cell collection
  - Consider immunizing the donor if recipient at high risk of GVHD

Close Contact Vaccination (eg, Vaccination of Family Members):

- Important for influenza and Covid-19
- Recommended for VZV if no history of chickenpox or shingles or vaccination, or for seronegative family members; however, practicability is limited
  - If a family member or a health care worker vaccinated with a VZV vaccine (live) develops a vesicular rash, there is a small chance of transmitting the virus and, theoretically, causing VZV disease in the immunocompromised patient. Thus, it may be prudent to advise VZV vaccinees that if they develop a rash within 6 weeks post-vaccination, they should avoid contact with immunocompromised patients, particularly VZV seronegative immunocompromised patients.

Non-Routine Vaccines:

- Funding
  - If used for medical/occupational reason, funded by Alberta Public Health. Examples:
    - Hepatitis A for illicit drug users or patients with chronic liver disease
    - Rabies for handlers of potentially rabid animals
    - Salmonella typhi for close contacts of carriers or lab workers
  - If used for travel reason, NOT funded by Alberta Public Health. Examples:
    - Hepatitis A
    - Salmonella typhi
    - Tick-borne encephalitis
    - Japanese encephalitis
    - Yellow fever (live)
- Timing
  - Non-live vaccines can be given already at 6-24 mo posttransplant; however, immunogenicity is limited. If travel is planned at 2 ½ y posttransplant or later, vaccinate at 24 mo. In case of GVHD, wait until at least 3 mo after immunosuppressive drugs have been discontinued and GVHD inactive.
  - Live vaccines (yellow fever) can be given at 24 mo (if off of immunosuppressive & maintenance therapy drugs)
    - Disclaimer: Probably safe, however, data is limited.

Shingrix (Recombinant Zoster Vaccine):

- Based on the results of a large, international randomized placebo-controlled trial, Shingrix is safe and effective in autologous-HCT recipients when given 50-70 days post HCT, with a second dose 1-2 months later[6]. In Alberta, Shingrix will be given at 6 and 7 months post-HCT to align with current non-live vaccine clearance practices. Those receiving post-HCT maintenance therapies for multiple myeloma (ex. bortezomib/lenalidomide) were included in the trial, although detailed outcomes for these patients have not been presented. Non B-cell or T-cell depleting maintenance therapies, therefore, are not a contraindication to vaccination with Shingrix.
- There are no safety or efficacy data in allo-HCT recipients.
- Allo-HCT and CAR-T recipients late (≥3 years) post-transplant/therapy may choose to receive Shingrix per general population guidelines. This is probably safe but the incremental efficacy of receiving Shingrix after completing the ABMTP VZV vaccination strategy is unknown. If patients choose to receive Shingrix, Shingrix should be administered at least 1 year after completing live Varicella vaccination per the ABMTP vaccination schedule. As in the general population, Shingrix in this setting is not publicly funded.

Recommendations for HCT Recipients that have Missed Post-HCT Vaccinations:

- Those who had vaccination delayed due to ongoing immunosuppressive therapy and/or chronic GVHD should receive all vaccines per the post-HCT immunization schedule.
- Those who missed vaccination for other reasons (for example, receipt of HCT before routine immunization protocol developed (pre-2008) or non-compliance/missed appointments with public health) should receive routine vaccinations per the general population:
    - 2 Td and 1 dTap
    - 2 MMR
    - 2 live attenuated Varicella
    - Hep B series if born in 1981 or later
    - One Pneumo-P for 65 years and over
    - Covid-19 per current Public Heath recommendations

Special Topics:

COVID-19 Vaccines and HCT Recipients.

Allo- and auto-HCT as well as CAR-T recipients experience poor outcomes after COVID-19 infection[7]. Existing COVID-19 vaccines are non-live and utilize either an mRNA or a replication-incompetent adenovirus vector platform. National and international HCT groups have endorsed COVID-19 vaccination for auto- and allo-HCT recipients. Thus:

- In Alberta, HCT recipients will be vaccinated for COVID-19 when criteria for other non-live vaccinations, as outlined above, are met.
- Caregivers of HCT and CAR-T cell recipients are strongly recommended to be vaccinated for COVID-19.

Vaccination for COVID and Influenza Earlier than 6 months Post-HCT.

- COVID and Influenza infections are associated with morbidity and mortality, especially in the first 6 months post-HCT[8]. Similar humoral and cellular immune responses to COVID mRNA vaccines have been noted in those vaccinated at <4 months versus 4-12 months post allo-HCT[9]. Responses to influenza vaccination have also been documented as early as 3 months post-HCT[10]. With both vaccines, thus, there is support to begin vaccination at 3 months post-HCT depending on current season (for influenza) or current epidemiology (for COVID). Physicians will have discretion to clear auto/allo-HCT and CAR-T recipients as early as 3 months post-transplant for these vaccines.

Vaccination in the Setting of an Outbreak.

- The resurgence of a vaccine-preventable illness in the community is possible. In the case of an outbreak, vaccination for the relevant pathogen may be considered earlier than recommended in the routine post-transplant schedule. For example, MMR vaccination at 1 year post-transplant has been found to be safe in retrospective cohorts of HCT recipients in the context of measles outbreak[11]. The decision to vaccinate earlier than planned should be made as a program and in consultation with public health and infectious diseases.

Vaccination after CAR-T Cell Therapies

Developing recommendations for vaccination after CAR-T therapies is challenging because:

- There are no studies detailing the immunogenicity, efficacy, or safety of vaccination after CAR-T therapy.
- There are a lack of consensus guidelines and limited expert opinion.
- Patients have received varying pre-CAR-T therapies that will affect post-CAR-T risk of infection as well as immunogenicity, efficacy and safety of vaccines (i.e. allogeneic-HCT vs. autologous-HCT vs no HCT before CAR-T cell therapy).
- Patients will receive varying post-CAR-T therapies that will affect risk of infection as well as immunogenicity, efficacy and safety of vaccines (i.e. no therapy vs. allogeneic-HCT).
- Varying CAR-T cell constructs/targets (i.e. CD19 vs. BCMA vs. others) will lead to varying quantity/quality of immunodeficiency and varying paces of immune reconstitution. Relevant but limited data are available for CD19 CAR-T therapies and no data are available for other constructs/targets.

- Specifically after CD19 CAR-T therapy, nearly all responding patients will rapidly develop B-cell aplasia which may persist >1 year post-therapy. However, ~50% of recipients will experience B-cell recovery beginning at 6-12 months post-therapy[12].
- Despite B-cell aplasia, pre-existing humoral immunity to vaccine-related antigens may be preserved in CD19 CAR-T recipients due to the persistence of CD19 negative plasma cells[13].

Despite the limitations noted above, infections remain the leading cause or late mortality after CAR-T[14] and it is reasonable to vaccinate patients empirically until further data become available. In Alberta, we will vaccinate patients according to the schedule developed for allo-HCT recipients.

References

1. Ljungman P, Cordonnier C, Einsele H, Englund J, Machado CM, Storek J, Small T; Center for International Blood and Marrow Transplant Research; National Marrow Donor Program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Disease Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Diseases Canada; Centers for Disease Control and Prevention. Vaccination of hematopoietic cell transplant recipients. Bone Marrow Transplant 2009 Oct;44(8):521-6.
2. Horwitz SM, Negrin RS, Blume KG, Breslin S, Stuart MJ, Stockerl-Goldstein KE, et al. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. Blood. 2004 Feb;103(3):777-83.
3. Palazzo M, Shah GL, Copelan O, Seier K, Devlin SM, Maloy M, et al. Revaccination after autologous hematopoietic stem cell transplantation is safe and effective in patients with multiple myeloma receiving lenalidomide maintenance. Biol Blood Marrow Transplant 2018 Apr;24(4):871-876.
4. Pandit A, Leblebjian H, Hammond SP, Laubach JP, Richardson PG, Baden LR, et al. Safety of live-attenuated measles-mumps-rubella and herpes zoster vaccination in multiple myeloma patients on maintenance lenalidomide or bortezomib after autologous hematopoietic cell transplantation. Bone Marrow Transplant 2018 Feb 9 [Epub ahead of print].
5. Jamani K, MacDonald J, Lavoie M, Williamson TS, Brown CB, Chaudhry A, et al. Zoster prophylaxis after allogeneic hematopoietic cell transplantation using acyclovir/valacyclovir followed by vaccination. Blood Adv. 2016 Nov;1(2):152-159.
6. Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, Lopez-Jimenez J, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. JAMA. 2019; 322(2): 123.
7. Sharma et al. Lancet Haematol 2021. PMCID 7816949.
8. Pinana et al. Transplant Infectious Disease. PMID 37585370
9. Hill et al. eClinicalMedicine. PMID 37128256
10. Engelhard et al. Transplant Infectious Disease. PMID 23363310
11. Pergam et al. BBMT. PMID: 31394271
12. Hill et al. Blood. PMCID 7441168
13. Bhoj et al. Blood. PMCID 4957161.
14. Puckrin et al. Eur J Haematol. PMID 37767547.

Umbilical Cord Blood Transplantation

Presented by: Adam Bryant

Summary

- For adults, cord blood as a stem cell source can be considered when no HLA-matched or haploidentical donor is available.
- Total nucleated dose and degree of HLA-matching are the most important factors when selecting units for cord blood transplantation
- For single umbilical cord blood transplantation in malignant conditions:
    - TNC at freezing must be ≥2.5 x10^7/kg
    - In comparing available units with TNC ≥ 3.0 x10^7/kg, prioritize highest degree of HLA match. Increased TNC dose beyond this threshold is not associated with improved outcomes
    - In comparing smaller dose units (TNC < 3.0 x10^7/kg) prioritize dosing over HLA match
    - HLA matches must be 4/6, 5/6, or 6/6 at HLA-A or -B antigen and -DRB1 allele level matching
    - Where possible, higher TNC doses (ie ≥ 3.5 x 10^7) are preferred for units with 4/6 HLA disparity
    - HLA-A or –B mismatch is preferable over DRB1 mismatch
    - Donor specific antibodies are preferred to be absent
    - Other factors to consider if multiple units available (see text)
        - Unit quality based on collection center characteristics
        - High-resolution allele-level HLA-matching
        - Availability of RBC-depleted units
        - Unit CD34+ count
- For non-malignant conditions
    - Higher TNC doses are required (≥5.0 X 10^7/kg)
    - Wherever possible a high degree of HLA matching is preferred
    - Absence of HLA-antibodies likely has greater importance than in transplant for malignant disease
- Double unit cord blood transplantation is feasible if no adequate single unit is available. Selection of DUCBT units involves
    - Selection two best available cord blood units, each with minimum TNC ≥ 1.5 x10^7/kg (preferred ≥ 2.0 x 10^7/kg) and best HLA match to recipient
    - Unit-unit HLA match should not be considered in selection of double unit graft since there is no association with sustained engraftment or speed of neutrophil engraftment
- Conditioning for UCBT is myeloablative and uses our center's preferred regimen (Flu/Bu/low dose TBI). This and many other myeloablative regimens have been reported without clear superiority of one regimen over another

- GVHD prophylaxis after UCBT is with mycophenolate mofetil (~15 mg/kg bid) to day 35 and cyclosporine to day 84 and. Standard dose methotrexate is not used as it has been associated with delayed engraftment/graft failure. Our center may however consider exploring low dose methotrexate regimens in the future based on reports of promising outcomes with respect to engraftment and toxicity (see text). ATG is not used as it has been associated with prohibitively high rates of posttransplant infection.
- Red blood cell replete units will be thawed and washed to remove cellular debris prior to infusion. Buffy coat and red blood cell depleted units will be thawed and diluted. DMSO content for thawed and diluted products will not exceed 5 mL/kg of 20% DMSO solution per day.

Background

The first successful umbilical cord blood transplantation was performed in 1989, on a 5-year old male with severe Fanconi's anemia who received cord blood stem cells from an HLA-identical sibling[1]. Decades later his graft remains durable with no evidence of disease. Since that time, umbilical cord blood stem cells have become a well-established source of hematopoietic stem cells for allogeneic stem cell transplantation. More than 40,000 patients have undergone UCBT for malignant and non-malignant conditions. Owing to the increased use of haploidentical transplants donors as stem cell sources the use of umbilical cord transplants has been on a steady decline in Calgary and North America since the early 2010s.

When selecting a donor source for hematopoietic stem cell transplantation, haploidentical related donors and mismatched unrelated donors are feasible options for those without matched related or unrelated donors, as outlined in the AHS BMT Standard Practice Manual chapter on Donor Selection. In cases where a search for matched related, unrelated, or haploidentical donors is or is suspected to be unfruitful a simultaneous cord blood search should be performed, especially if transplantation is urgent.

Advantages of umbilical cord blood transplantation include:

- Rapid availability – median 25-36 days sooner than unrelated volunteer marrow/blood stem cells
- Larger donor pool – tolerance of 1-2/6 HLA mismatches (i.e. 4-6/6 HLA-A, -B antigen, and DRB1 allele)
- Lower incidence and severity of acute graft-versus-host-disease (GVHD)
- Lower incidence of chronic GVHD
- Lower risk of viral transmission (e.g. CMV, EBV)
- Lack of donor attrition
- Lack of risk to donor

Disadvantages of umbilical cord blood transplantation include:

- Lower number of progenitor cells and stem cells – higher risk of graft failure, delayed engraftment
- Delayed immune reconstitution – increased risk of infection leading to death
- Not possible to obtain more cells for future treatment (e.g. donor lymphocyte infusion, second transplant)
- Genetic history of donor unknown

Umbilical Cord Blood Transplantation

There is little randomized clinical trial data comparing transplantation of umbilical cord blood (UCB) vs. related or unrelated marrow or peripheral blood stem cell donors. The best data available comes from retrospective single center and registry data available for both children and adults.

In adults, the large retrospective EBMT/CIBMTR (European Group for Blood and Marrow Transplantation / Center for International Blood and Marrow Transplant Research) study compared leukemia-free survival for umbilical cord blood, peripheral blood progenitor cell, and marrow transplantation in 1525 patients aged 16 or older[5]. When compared to 7-8/8 allele-matched peripheral blood or marrow (matched unrelated [MUD] and mismatched unrelated donor [MMUD]) transplantation, UCB transplantation had comparable leukemia-free survival, higher transplant-related mortality, and lower rates of graft-vs-host disease. The authors concluded that data support UCB transplantation (UCBT) for adults with acute leukemia when no HLA-matched donor is available for urgent transplants. Similarly a large 2020 Japanese registry study including 4150 adult patients comparing 7/8 MMUD (n = 488) to UCB (n= 3662) acute myeloid leukemia (AML) transplant recipients from 2008 to 2017 reported comparable OS (46 v 54 %; HR 1.01; p= 0.89), NRM (HR 1.16; p=0.16), and relapse rates (HR 0.85; p = 0.08) in both groups, and decreased grade II-IV aGVHD (HR 0.76; p<0.001) cGVHD (HR 0.77, p = 0.002) in UCBT patients[27].

Other comparisons have reported advantages of MMUD transplant over UCBT. A 2019 retrospective EBMT registry study including 2963 total MUD, MMUD, and UCB transplant recipients recently reported lower relapse incidence (HR = 0.8, p = 0.02) lower NRM (HR = 0.7, p = 0.008), improved GRFS (HR = 0.8, p = 0.01), and improved OS (HR = 0.7, p < 0.001) in 9/10 MMUD (n=677) compared to UCB recipients (n=285)[28]. Given the absence of consistent data favoring MMUD over UCB transplant, selection between these donor sources be should done a case by case basis factoring in donor, disease, and patient characteristics.

Retrospective comparisons, meta-analyses, and small prospective trials have recently reported data supporting improved transplant outcomes with haploidentical (haplo) donor hematopoietic cell transplant (HCT) when compared to UCBT[29-33]. In two meta-analyses from 2020[29] and 2019[32] with overlapping study inclusion reporting on 2,793 (1,432 haplo; 1,361 UCB) and 3,434 (1,759 haplo, and

1,675 UCB) mostly adult transplant recipients for hematologic malignancies, haplo HCT was associated with decreased rates of acute GVHD, increased rates of chronic GHVD, decreased non-relapse mortality, improved relapse-free survival, and improved overall survival.

Umbilical cord allotransplantation at our center is thus considered in cases where a suitable matched related, unrelated, or haploidentical donor is not available. Mismatched unrelated donors are preferred over cord blood sources, but this selection should nonetheless be reviewed on a case-by-case basis.

Selection of Cord Blood Unit for Single Unit Cord Blood Transplantation

Cell Dose & HLA Match

Both the total nucleated cell dose and degree of HLA-match of the umbilical cord blood unit in single cord blood transplantation have a strong impact on survival via effect on transplant-related mortality. In a large 2010 retrospective single center analysis of 1061 predominantly pediatric recipients of single-unit myeloablative UCBT for the treatment of hematological malignancies from 1993 to 2006, the best transplantation outcomes were in recipients of 6/6 units regardless total nucleated cell (TNC) dose, though median dose was notably 4.0×10^7/kg[6]. Recipients of 4/6 HLA-matched units required a TNC $\geq 5.0 \times 10^7$/kg to achieve comparable TRM and RFS to that of recipients of 5/6 units with a TNC of $\geq 2.5 \times 10^7$/kg. This study may suggest that that the greater the degree of HLA disparity, the higher the required TNC dose to ensure transplantation survival[6].

More recent reports have suggested that beyond a minimum TNC threshold, HLA disparity may not have adverse impact of NRM or other transplant outcomes. A 2019 Japanese registry study of 1,355 adults receiving UCB allogeneic HCT (alloHCT) between 2003 and 2016, including only those with minimum TNC dose of 2×10^7/kg compared pairings above or below the median TNC dose (2.68×10^7/kg) and with either 1 or 2 mismatches[34]. No advantage was seen in those with the least degree of mismatch and higher cell dose when compared to other pairings with greater mismatch, smaller cell dose, or both. TNC in the highest quartile was associated with improved ANC engraftment rates when compared to the lowest quartile, but higher TNC dose quartiles were otherwise not associated with improved engraftment, relapse, or survival outcomes, suggesting against benefit of increased TNC dosing beyond a given minimum threshold. In the large 2014 EBMT and Eurocord study addressing the impact of allele-level matching on outcomes, in multivariate analysis, the effect of a TNC count $\geq 3 \times 10^7$ kg on NRM was independent of HLA disparity, and held true when patients were analyzed as pediatric and adult subcohorts[35]. In a phase 3, 320-patient multicenter randomized controlled trial (RCT) comparing single UCB (SUCB) to double UCB (DUCB) alloHCT, single units were eligible if above a TNC of $2.5 \geq \times 10^7$/kg regardless of HLA mismatch, included 39% 4/6 mismatches, and demonstrated similar outcomes with respect to neutrophil engraftment, relapse, PFS, and OS when compared to DUCBTs[36]. The 2019 NMDP/CIBMTR Guidelines on cord unit selection suggest a

minimum 2.5 x 10^7/kg minimum dose per single unit and do not specifcy higher minium doses for differing degrees of HLA disparity[37].

Other studies[7-12] consistently demonstrate cell dose to be the most important factor on survival outcomes, and the EBMT and NMDP/CIBMTR guidelines have recommended using ≥2.5-3x10^7 total nucleated cells/kg at collection for patients with malignant disease and ≥5.0x10^7 nucleated cells/kg for those with non-malignant disease[7, 37].

An increasing number of HLA mismatches is associated with delayed engraftment, higher treatment-related mortality, higher rates of chronic GVHD, and in malignant diseases, decreased relapse rates[7]. As greater HLA disparity is not associated with improved relapse outcomes in nonmalignant diseases, optimal HLA matching is important in these cases. When choosing between multiple cord units that meet the minimum cell dose requirement, optimal HLA matching should be prioritized. Memorial Sloan-Kettering Cancer Center (MSKCC) guidelines for single UCBT suggest a minimum nucleated cell dose of 2.5 x 10^7/kg with 1 or 2 mismatches at the HLA-A, -B antigen, or –DRB1 allele[13]. There is no data to guide dosing of TNC by actual versus ideal or adjusted body weight, thus the dose should be based on the patient's actual weight at time of transplantation.

Based on the above data, at our center selection of a single umbilical cord blood transplantation in malignant conditions requires a minimum TNC at freezing of ≥2.5 x 10^7/kg. When comparing available units with TNC ≥3.0 x10^7/kg, the highest degree of HLA match should be prioritized, as increasing TNC dose beyond this threshold is not associated with improved outcomes. In comparing smaller dose units (TNC < 3.0 x10^7/kg) we prioritize dosing over HLA match. Where possible higher TNC doses (i.e. ≥ 3.5 x 10^7) are preferred for units with greater (i.e. 4/6) HLA disparity.

HLA matching in UCBT is based on HLA antigen typing for –A and –B, and allelic typing for HLA-DRB1. A single institution retrospective analysis of 79 adults with AML who received single unit UCBT was analyzed for the impact of directional donor-recipient HLA disparity using allele-typing at HLA-A, -B, -C, and DRBI[14]. With the extended high-resolution typing, the donor-recipient compatibility ranged from 2/8 to 8/8, but this did not have a negative impact on non-relapse mortality, GVHD or engraftment. The 5-year cumulative incidence of relapse was 44% vs. 22% for patients receiving UCB units matched ≥6/8 or <6/8, respectively (p=0.01). On multivariate analysis higher HLA-disparity in the GVH direction and first complete remission at time of transplantation were the only variables significantly associated with an improved DFS. The effect of allele-level matching on non-relapse mortality in 1568 single umbilical cord blood transplantations for hematological malignancy was published in 2014[15]. Only 7% of donor-recipient pairs were matched at HLA-A, -B, -C, and DRB1; 15% were mismatched at one, 26% at two, 30% at three, 16% at four, and 5% at five alleles. Only 54% of units matched at HLA-A, -B, and –DRB1 were actually matched at the allele-level at all loci. Non-relapse mortality was higher with units mismatched at one (26%), two (26%), three (34%), four (37%), or five alleles (41%) compared to HLA-matched units (9%). Cell dose <3.0 x10^7/kg was

associated with higher NRM independent of HLA-match. Neutrophil recovery was lower with mismatches at 3-5 alleles but not at 1 or 2 alleles. These data support allele-level HLA-matching in the selection of single UCB units whenever possible.

Donor Specific Antibodies (DSA)

Since most UCBT are performed with HLA-mismatched UCB units, the presence of anti-HLA donor-specific antibodies in the patients against the UCB can result in failure or delay of engraftment. Anti-HLA antibodies before transplant may occur due to alloimmunization to HLA through blood transfusions, pregnancy, and also in some unexposed individuals. In the UCBT setting, few studies with controversial results are available on the impact of DSA on outcomes. One analysis showed an increased risk of graft failure and lower survival for patients with positive DSA undergoing single (n=386) or double (n=73) UCBT[16]. Another report showed no association between the presence of DSA and transplant outcomes in 126 double UCBT recipients[17]. Presence of DSA was found to be associated with higher 1-year TRM (46 v 32%; p=0.06) and lower engraftment (44% vs. 81%, p=0.006) in patients with or without antibodies, respectively[18]. Based on these data, whenever possible, it is important to avoid selecting a unit when the patient has donor specific anti-HLA antibodies.

Other factors to consider in selecting cord blood units:

- Unit quality, measured by practices of the bank with from which is it originates, is associated with increased unit potency including post-thaw CD34+ cell recovery and viability. Where possible it is desirable to obtain cord blood units that were more recently cryopreserved, from banks that are FACT-accredited, that store RBC-depleted cord units, at adequate volume (≥25 cc thawed volume per unit), and that are closer in location[37].

- CD34+ cell count can be considered when choosing between multiple cord units that are otherwise similar from the same bank. NMDP/CIBMTR guidelines suggest a minimum $CD34^+$ count of ≥ 1.5×10^5 kg[37]. Given variation in and non-standardization of $CD34^+$ count and viability measurements, interpretation of reported $CD34^+$ count should be done cautiously, particularly if it appears discrepant from TNC dose[37,38].

- Red blood cell (RBC) content of the unit. Buffy coat enriched and RBC depleted units should be considered over RBC replete units. RBC replete units contain red cell debris and free hemoglobin, which can be associated with infusion reaction and washing of these RBC replete units can result in progenitor cell loss.

- Natural killer cell immunoglobulin-like receptor mismatch, non-inherited maternal antigens and inherited paternal antigens may influence decisions about which units to select in the future

Double Unit Umbilical Cord Blood Transplantation

The use of single unit UCBT is limited since many adults do not have access to a single cord blood unit with the recommended TNC dose. Strategies for ex-vivo expansion of UCB units are being actively explored in the literature with some early phase I/II trials showing promise[39-42]. These strategies have yet to be standardized or widely adopted and warrant further exploration.

Double unit UCBT as a strategy to augment cell dose of the graft has been successful with improved sustained donor engraftment and post-transplantation survival compared with historic SUCBT controls[19]. Sustained hematopoiesis is accounted for by only one of the two units, with demonstration of dominance as early as Day +21 post-transplant. Higher $CD3^+$ cell dose and percentage of $CD34^+$ cell viability was associated with unit dominance[19]. The exact biological mechanism responsible for single-donor predominance after double unit CBT remain incompletely understood. Accumulating reports support the use of DUCBT to overcome the cell dose barrier in adults. In one study with 177 patients who underwent myeloablative UCBT, DUCBT recipients experienced lower relapse rates (19 vs 34% at 5-years), higher rates of GVHD (acute GVHD 48 vs 29%; chronic GVHD 18 vs 10%), and higher RFS (51 vs 40%) when compared to SUCBT recipients[20].

Given that either unit may engraft after a double unit UCBT, each unit of a double-unit graft is equally important and the same unit selection principles should apply to both units. Optimal strategies for balancing cell dose against HLA match are not well established. Of note there is no relationship between unit-unit HLA match and the likelihood of sustained donor engraftment[19]. When analyzing HLA-A or -B antigen or -DRB1 allele mismatches or 10/10 HLA-allele matches in 84 recipients of double unit UCBT, there was no association between unit-unit HLA match and sustained engraftment, speed of neutrophil engraftment, or unit dominance[19]. Thus, unit-unit HLA match should not be considered in the selection of a double-unit graft, particularly at the expense of available grafts with higher cell doses. MSKCC guidelines recommend each DUCBT have a minimum TNC of $\geq 2.0 \times 10^7$ /kg, with preference for HLA matching above this TNC threshold, and unit-unit HLA match is not considered[13]. NMDP/CIBMTR guidelines and most DUCBT studies in adult and pediatric populations recommend or require a minimum TNC dose of $\geq 1.5 \times 10^7$/kg for DUCBT, suggesting a less stringent TNC threshold may be safe and effective[37,43].

Whether DUCBT is preferable SUCBT when the cell dose in one unit is acceptable is unknown in the adult setting. In The Blood and Marrow Transplant Clinical Trials Network randomized trial (BMT CTN 0501) was a phase III trial that randomized patients to receive a single (n=113) or double (n=111) UCBT, with median pre-cyroperserved TNC dose of 4.8 and 8.9 $\times 10^7$/kg, respectively[21]. The results of this study showed no survival advantage after DUCBT compared to SUCBT in children with hematological malignancies (1 year OS 65% vs. 71%, p=0.13). Except for a higher risk of grade III-IV acute GVHD in recipients of a double UCBT, all outcomes were similar between the two groups. Similar findings were reported in a large 2019 systematic review comparing DUCBT to SUCBT that included the above RCT and 24 additional retrospective and prospective reports. A total of 6571 total

patients were included, with 12 of 25 studies enrolling adults exclusively[43]. DUCBT was associated with higher incidence of acute and extensive cGVHD but with lower relapse incidence, and outcomes were ultimately similar between DUCBT and SUCBT for NRM, RFS, and OS. Authors suggested the increased GVH and presumed GVL effect reported here may suggest that DUCBT could be considered in patients with higher risk disease, but this possibility has yet to be explored in a prospective randomized fashion.

Schema for Unrelated Cord Blood Unit Selection

Step 1

Evaluate search reports for units 4-6/6 HLA-matched with TNC ≥2.5 x 10^7/kg.

Step 2

Review information and bank of origin for each unit.
Obtain missing unit information.
Prepare cord blood search summary report.

Step 3

For units with TNC ≥ 3.0
1 Rank units according to HLA-A, -B antigen, -DRB1 allele match.
2 List highest to lowest TNC within each HLA-match grade.

For units with TNC<3.0
1 Rank units according highest TNC first
2 List highest to lowest with comparable TNC by HLA-A, -B antigen, -DRB1 allele match

- Where possible higher TNC doses (ie ≥3.5 x 10^7) are preferred for units with 4/6 HLA disparity
- Where available, unit CD34+ count, allelic HLA matching, RBC content, and unit quality (see text) can further inform unit selection

Step 4

If suitable cord unit available, proceed with single unit UCBT.

If no suitable cord unit available, proceed with double unit UCBT
- Minimum dosing each unit ≥2.0 x 10^7/kg
- For units ≥ 2.0 x 10^7/kg, preference given to units with greater HLA match
- Unit-unit HLA match does not need to be considered

Infusion of Cord Blood Units

Cord blood units are processed and infused according to established standard operating procedures. Processing requirements for Cord Blood Units are determined by transplant physician, in consultation with the Cellular Therapy Laboratory (CTL), prior to planned infusion. The following considerations are taken into account when determining processing requirements:

1. Red Cell Content
   - Buffy coat and Red Cell Depleted units are typically thawed and diluted for Adult Recipients[22]
   - Red Cell Replete units are thawed and washed for Adult Recipients[22]
2. DMSO content
   - DMSO content in thawed & diluted products should not exceed 5 mL/kg/day of 20% DMSO
3. Infusion of Double Cords for transplant
   - For double cord blood transplants, the first unit must be thawed, processed and administered safely prior to thaw and processing of the second unit.

Conditioning

Non-relapse mortality has historically been an important contributor to adverse outcomes in UCBT. In the aim of reducing NRM, many studies have explored reduced intensity conditioning regimens. The largest and most recent comparison of conditioning approaches was reported in a 2016 EBMT Eurocord registry study involving adults transplanted for AML with SUCBT or DUCBT from 2004 to 2013[44]. A total 894 adults who underwent myeloablative (MAC, n = 479) or reduced intensity conditioning (RIC, n = 415) were included. MAC regimens were varied and included 40 (8%) patients receiving Flu/Bu based ablative conditioning. Compared to MAC UCBMT recipients, RIC recipients had similar neutrophil engraftment and rates of acute and chronic GVHD. RIC recipients also had a higher incidence of disease relapse, but lower NRM, ultimately resulting in comparable PFS, GRFS, and OS between both groups. MAC regimens were not compared amongst each other.

Given these findings, our center prefers a myeloablative Flu/Bu/low dose TBI conditioning platform, the same regimen as that used for MRD, MUD, MMUD and haploidentical alloHCT at our center, and a regimen with which we have extensive experience.

GVHD Prophylaxis

Use of ATG has been associated with decreased survival primarily due to infections[23-25]. Use of methotrexate has been associated with delayed engraftment and graft failure[26]. Some evidence suggests that delayed or failed engraftment is lower with a mycophenlate mofetil/calcineurin inhibitor (MMF/CNI) based regimen than with methotrexate[45]. Exploration of reduced-dose methotrexate, often less than half the standard dose, has in some reports been also associated with lower NRM, infectious complications, and improved engraftment [45,46] and in one retrospective three arm study,

comparable engraftment to that seen with MMF/CNI based prophylaxis[47]. Further comparative and prospective studies are required to establish the optimal GVHD prophylaxis regimen in UCBT.

The most frequent GVHD prophylaxis reported in UCBT (including in the US BMT CTN study 1101) remains MMF/Cyclosporine (CSA), which in the absence of clear evidence pointing to an optimal regimen, is the prophylaxis regimen we prefer at our center (MMF to day 35, CSA to day 84).

Calgary Results

Among 22 pts who received UCB between 2004 and 2013 (using CSA+ATG GVHD prophylaxis), 8 patients are alive at ≥5 y posttransplant. Of the 14 patients who died, 4 died due to an infection (not associated with GVHD), 3 due to GVHD, 3 due to relapse and 4 due to other (typically multi-organ failure).

References

1. Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Devergie A, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical cord blood from an HLA-identical sibling. N Engl J Med 1989;321(17):1174-78
2. Rocha V, Wagner JE Jr, Sobocinski KA, Klein JP, Zhang MJ, Horowitz MM, et al. Graft-versus-host disease in children who have received a cord blood or bone marrow transplant from an HLA-identical sibling. N Engl J Med 2000 Jun;342(25):1846-54.
3. Herr AL, Kabbara N, Bonfim CM, Teira P, Locatelli F, Tiedemann K, et al. Long-term follow-up and factors influencing outcomes after related HLA-identical cord blood transplantation for patients with malignancies: an analysis on behalf of Eurocord-EBMT. Blood 2010 Sep;116(11):1849-56.
4. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet 2007 Jun;359(9577):1947-54.
5. Eapen M, Rocha V, Sanz G, Scaradavou A, Zhang MJ, Arcese W, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. Lancet Oncol 2010 Jul;11(7):653-60.
6. Barker JN, Scaradavou A, Stevens CE. Combined effect of total nucleated cell dose and HLA match on transplantation outcome in 1061 cord blood recipients with hematologic malignancies. Blood 2010 Mar;115(9):1843-9.
7. Gluckman E, Rocha V. Donor selection for unrelated cord blood transplants. Curr Opin Immunol 2006 Oct;18(5):565-70.
8. Rocha V, Broxmeyer HE. New approaches for improving engraftment after cord blood transplantation. Bio Blood Marrow Transplant 2010 Jan;16(1 Suppl):S216-32.
9. Gluckman E, Rocha V, Arcese W, Michel G, Sanz G, Chan KW, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. Exp Hematol 2004 Apr;32(4):397-407.
10. Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, Adamson J, Migliaccio AR, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med 1998 Nov;339(22):1565-77.
11. Wagner JE, Barker JN, DeFor TE, Baker KS, Blazar BR, Eide C, et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. Blood 2002 Sep;100(5):1611-8.
12. Laughlin MJ, Barker J, Bambach B, Koc ON, Rizzieri DA, Wagner JE, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N Engl J Med 2001;344:1815-22.
13. Barker JN, Byam C, Scaradavou A. How I treat: the selection and acquisition of unrelated cord blood grafts. Blood 2011 Feb;117(8):2332-9.
14. Sanz J, Jaramillo FJ, Planelles D, Montesinos P, Lorenzo I, Moscardo F, et al. Impact on outcomes of human leukocyte antigen matching by allele-level typing in adults with acute myeloid leukemia undergoing umblicial cord blood transplantation. Biol Blood Marrow Transplant 2014 Jan;20(1):106-10.
15. Eapen M, Klein JP, Ruggeri A, Spellman S, Lee SJ, Anasetti C, et al. Impact of allele-level HLA matching on outcomes after myeloblative single unit umbilical cord blood transplantation for hematologic malignancy. Blood 2014 Jan;123(1):133-40.
16. Cutler C, Kim HT, Sun L, Sese D, Glotzbecker B, Armand P, et al. Donor-specific anti-HLA antibodies predict outcome in double umbilical cord blood transplantation. Blood 2011 Dec;118(5):6691-7.
17. Brunstein CG, Noreen H, DeFor TE, Maurer D, Miller JS, Wagner JE. Anti-HLA antibodies in double umbilical cord blood transplantation. Biol Blood Marrow Translant. 2011 Nov;17(11):1704-8.
18. Ruggeri A, Rocha V, Gluckman E, Loiseau P. Anti-HLA antibodies and outcomes after cord blood transplantation. 11th Annual International Cord Blood Symposium. 2013.
19. Avery S, Shi W, Lubin M, Gonzales AM, Heller G, Castro-Malaspina H, et al. Influence of infused cell dose and HLA match on engraftment after double-unit cord blood allografts. Blood 2001 Mar;117(12):3277-85.

20. Verneris MR, Brunstein CG, Barker J, MacMillan ML, DeFor T, McKenna DH, et al. Relapse risk after umbilical cord blood transplantation: enhanced graft-versus-leukemia effect in recipients of 2 units. Blood 2009 Nov;114(9):4293-9.
21. Wagner JE, Eapen M, Carter SL, Haut PR, Peres E, Schultz KR, et al. No survival advantage after double umbilical cord blood (UCB) compared to single UCB transplant in children with hematological malignancy: Results of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN0501) randomized trial. ASH Meeting December. 2012;120:Abstract 359.
22. Omaha NE. FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fifth Edition, Foundation for Accreditation of Cellular Therapy. March 2012;4:38.
23. Zheng C et al: Comparison of conditioning regimens with or without ATG for unrelated cord blood transplantation in children with advanced hematologic malignancies. BBMT 2015, 21:707.
24. Pascal L et al: Impact of ATG-containing reduced-intensity conditioning after single or double unit allogeneic cord blood transplantation. Blood 2015, 126:1027.
25. Pascal L: Impact of rabbit ATG-containing myeloablative conditioning regimens on the outcome of patients undergoing unrelated single-unit cord blood transplantation for hematological malignancies. BMT 2015, 50:45.
26. Herr AL et al: Long-term follow up and factors influencing outcomes after related HLA-identical cord blood transplantation for patients with malignancies. Blood 2010, 116:1849.

ADD-ON 2021 REFERENCES

27. Miyao K, Terakura S, Kimura F, Konuma T, Miyamura K, Yanada M, et al. Updated Comparison of 7/8 HLA Allele-Matched Unrelated Bone Marrow Transplantation and Single-Unit Umbilical Cord Blood Transplantation as Alternative Donors in Adults with Acute Leukemia. *Biol Blood Marrow Transplant.* 2020;26(11):2105-2114.
28. Baron F, Labopin M, Ruggeri A, Ehninger G, Bonifazi F, Stelljes M, et al. Umbilical cord blood versus unrelated donor transplantation in adults with primary refractory or relapsed acute myeloid leukemia: a report from Eurocord, the Acute Leukemia Working Party and the Cord Blood Committee of the Cellular Therapy and Immunobiology Working Party of the EBMT. *Blood Cancer J.* 2019;9(4):46.
29. Wu R, Ma L. Haploidentical Hematopoietic Stem Cell Transplantation Versus Umbilical Cord Blood Transplantation in Hematologic Malignancies: A Systematic Review and Meta-Analysis. *Cell Transplant.* 2020;29:963689720964771.
30. Sanz J, Montoro J, Solano C, Valcárcel D, Sampol A, Ferrá C, et al. Prospective Randomized Study Comparing Myeloablative Unrelated Umbilical Cord Blood Transplantation versus HLA-Haploidentical Related Stem Cell Transplantation for Adults with Hematologic Malignancies. *Biol Blood Marrow Transplant.* 2020;26(2):358-366.
31. Esquirol A, Querol S, Garcia-Cadenas I, Novelli S, Garrido A, Saavedra S, et al. When an HLA identical donor is not available in adults with hematological neoplasms: single-center comparison of single-unit cord blood transplantation and haploidentical-related PBSC transplantation with PTCy using a standardized conditioning platform (thiotepa-busulfan-fludarabine). *Ann Hematol.* 2020;99(1):157-165.
32. Poonsombudlert K, Kewcharoen J, Prueksapraopong C, Limpruttidham N. Post transplant cyclophosphamide based haplo-identical transplant versus umbilical cord blood transplant; a meta-analysis. *Jpn J Clin Oncol.* 2019;49(10):924-931.
33. Giannotti F, Labopin M, Shouval R, Sanz J, Arcese W, Angelucci E, et al. Haploidentical transplantation is associated with better overall survival when compared to single cord blood transplantation: an EBMT-Eurocord study of acute leukemia patients conditioned with thiotepa, busulfan, and fludarabine. *J Hematol Oncol.* 2018;11(1):110.
34. Yanada M, Konuma T, Kuwatsuka Y, Kondo T, Kawata T, Takahashi S, et al. Unit selection for umbilical cord blood transplantation for adults with acute myeloid leukemia in complete remission: a Japanese experience. *Bone Marrow Transplant.* 2019;54(11):1789-1798.
35. Sanz J, Jaramillo FJ, Planelles D, Montesinos P, Lorenzo I, Moscardó F, et al. Impact on outcomes of human leukocyte antigen matching by allele-level typing in adults with acute myeloid leukemia undergoing umbilical cord blood transplantation. *Biol Blood Marrow Transplant.* 2014;20(1):106-110.
36. Wagner JE, Jr., Eapen M, Carter S, Wang Y, Schultz KR, Wall DA, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. *N Engl J Med.* 2014;371(18):1685-1694.

37. Dehn J, Spellman S, Hurley CK, Shaw BE, Barker JN, Burns LJ, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood.* 2019;134(12):924-934.
38. Nakasone H, Tabuchi K, Uchida N, Ohno Y, Matsuhashi Y, Takahashi S, et al. Which is more important for the selection of cord blood units for haematopoietic cell transplantation: the number of CD34-positive cells or total nucleated cells? *Br J Haematol.* 2019;185(1):166-169.
39. Papa L, Djedaini M, Hoffman R. Ex Vivo Expansion of Hematopoietic Stem Cells from Human Umbilical Cord Blood-derived CD34+ Cells Using Valproic Acid. *J Vis Exp.* 2019(146).
40. Mehta RS, Rezvani K, Shpall EJ. Cord Blood Expansion: A Clinical Advance. *J Clin Oncol.* 2019;37(5):363-366.
41. Horwitz ME, Wease S, Blackwell B, Valcarcel D, Frassoni F, Boelens JJ, et al. Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide. *J Clin Oncol.* 2019;37(5):367-374.
42. Lund TC. Umbilical Cord Blood Expansion: Are We There Yet? *Biol Blood Marrow Transplant.* 2018;24(7):1311-1312.
43. Wang L, Gu ZY, Liu SF, Ma DX, Zhang C, Liu CJ, et al. Single- Versus Double-Unit Umbilical Cord Blood Transplantation for Hematologic Diseases: A Systematic Review. *Transfus Med Rev.* 2019;33(1):51-60.
44. Baron F, Ruggeri A, Beohou E, Labopin M, Sanz G, Milpied N, et al. RIC versus MAC UCBT in adults with AML: A report from Eurocord, the ALWP and the CTIWP of the EBMT. *Oncotarget.* 2016;7(28):43027-43038.
45. Yoshida S, Ohno Y, Nagafuji K, Yoshimoto G, Sugio T, Kamimura T, et al. Comparison of calcineurin inhibitors in combination with conventional methotrexate, reduced methotrexate, or mycophenolate mofetil for prophylaxis of graft-versus-host disease after umbilical cord blood transplantation. *Ann Hematol.* 2019;98(11):2579-2591.
46. Shiratori S, Ohigashi H, Takahashi S, Ara T, Goto H, Nakagawa M, et al. Reduced dose of MTX for GVHD prophylaxis promotes engraftment and decreases non-relapse mortality in umbilical cord blood transplantation. *Ann Hematol.* 2020;99(3):591-598.
47. Adachi Y, Ozeki K, Ukai S, Sagou K, Fukushima N, Kohno A. Optimal dosage of methotrexate for GVHD prophylaxis in umbilical cord blood transplantation. *Int J Hematol.* 2019;109(4):440-450.

ABO Incompatible Graft and Recipient

Presented by Nicole Prokopishyn

Summary

- Donor/recipient pairs of different blood groups may exhibit major ABO incompatibility (the recipient has pre-formed hemagglutinin antibodies reactive against donor red blood cells), minor ABO incompatibility (the donor has pre-formed hemagglutinin antibodies reactive against recipient red blood cells), or bidirectional (the donor and recipient both have hemagglutinin antibodies reactive against the other).
- There is no consistent evidence that ABO incompatibility unduly influences clinically relevant outcomes (e.g., survival, GVHD).
- An ABO compatible donor is preferred over an ABO incompatible donor to minimize the risk of non-lethal complications like hemolytic anemia or pure red cell aplasia.
- Major ABO incompatibility, including bidirectional incompatibility:
    - For adult recipients, if the red cell volume is >30mL, the product is split into aliquots with no greater than 30mL red cells per unit. If the initial incompatible red cell volume is <30mL, no further action is taken. No more than 30mL of incompatible red blood cells should be infused in a 6-hour period.
    - For pediatric recipients, the accepted range for ABO incompatible blood volume transfused is 0.2 to 0.5 mL/kg. The transplant physician will be contacted with the volume of incompatible red blood cells and will direct Cellular Therapy Lab (CTL) on desired final red blood cell content per infusion bag. CTL will aliquot and/or red cell reduce product as necessary for infusion into the patient.
    - For products with very large volumes of red cells, where dividing into several aliquots is not practical, red cell reduction by centrifugation or Hespan can be considered.
- Minor ABO incompatibility:
    - No action is taken as local validation data at CTL has indicated no adverse reactions associated with minor ABO incompatibilities.

Background

Up to 50% of related and 50% of unrelated donor transplants involve an ABO incompatible donor and recipient, not including differences between minor red cell antigens[1, 2, 3]. Donor- recipient pairs with the same ABO blood type are said to be compatible. Minor incompatibility occurs when the donor has antibodies against recipient ABO antigens, and major incompatibility occurs when the recipient carries antibodies against donor red cells. When both occur in the same donor-recipient pair, a bi-directional incompatibility is present, as shown in Table 1 below[3, 4]. Major incompatibility can result in acute hemolytic transfusion reaction at the time of stem cell infusion and delayed red cell engraftment. Minor incompatibility rarely causes at the time of transplant hemolysis from infusion of incompatible donor plasma, but can result in delayed transfusion reaction 7-14 days post-transplant

from production of isohemagglutinins by lymphocytes infused with the graft. ABO antigens are the primary concern in graft compatibility, though non-ABO antigens such as Rh and Kidd have been reported to cause post-transplant hemolysis[5, 6].

Table 1. Donor-recipient ABO compatibility[3, 4].

Mismatch Type	ABO Blood Type		Potential Clinical Consequence	Etiology
	Recipient	Donor		
Major	O	A,B	-Acute hemolytic episode	-Transfusion of incompatible red blood cells
		AB	-Delayed RBC engraftment	-Recipient anti-donor isohemagglutinins
Major	A	AB	-Pure red blood cell aplasia	-Loss of immature stem cells from processing with ABO antigens expressed on granulocytes and platelets
Major	B	AB	-Delayed granulocyte and platelet engraftment	
Minor	A	O	-Acute hemolytic episode	-Donor plasma with elevated isohemagglutinin titers/small blood volume recipient
Minor	B	O	-Delayed hemolysis secondary to passenger lymphocyte syndrome	
Minor	AB	O,A,B		-Passenger lymphocytes producing isohemagglutinins
Bidirectional	A	B	-Combination of major and minor consequences	-Combination of major and minor etiologies
Bidirectional	B	A		

Consequences of ABO Incompatible Transplant

The relative importance and discordant consequences of ABO incompatible transplants (as described below) is dependent on the era of transplants, underlying disease, type of transplants (Haplo-identical, Cord), graft source (marrow, PBSC etc.), conditioning (e.g. reduced intensity) as well as the availability of superior supportive measures.

Historically, there have been a number of single center reports as well as four large registry reports[2,7-9] describing the impact of ABO incompatibility on transplant outcomes. Overall, the results are inconsistent though some show a negative effect on neutrophil engraftment[2,7], acute graft versus host disease[2, 7], non-relapse mortality[2,8], and overall survival[2,8]. Moreover, an individual patient data-based meta-analysis conducted in 2009 suggests that there is no adverse association between any ABO mismatching and survival[10].

Acute Hemolytic Reaction
Acute hemolytic reactions occur in 15% of transplants with major ABO incompatibility[11], and in almost half of those receiving a high volume (>50mL) of incompatible red cells[12] resulting in renal failure and even death in some patients. Transplants with minor ABO compatibility will rarely cause acute hemolysis from the transfusion of donor isoagglutinins against recipient red cells.

Delayed Red Cell Engraftment and Pure Red Cell Aplasia (PRCA)
Recipient antibodies directed against donor red cells (isoagglutinins) are usually cleared rapidly following transplant, with the only consequence being a slight increase in transfusion requirements compared to ABO compatible grafts[13]. Isoagglutinins disappear more rapidly following unrelated donor compared to related donor transplants[1, 14], and in those with graft versus host disease[1, 15], and more slowly following non-myeloablative transplant[16]. Persistent anti-donor red cell isoagglutinins can cause delayed red cell engraftment that may persist for months or even years following transplant. In some cases, bone marrow biopsy will show normal erythroid precursors up to the point of expression of the incompatible antigen, with absence of precursors beyond that point reflecting the expression of ABO antigens at different stages of red cell development[17]. There is an increase in transfusion requirements contributing to iron overload.

Delayed Transfusion Reaction
Infusion of grafts with minor ABO incompatibility has rarely resulted in a delayed transfusion reaction, thought to be due to production of anti-host red cell antibodies by donor B-cells infused with the graft. These have mostly occurred 7-10 days after the transplant in red cell group A recipients of group O grafts[18]. Almost all patients had GVHD prophylaxis consisting of cyclosporine without methotrexate.

Neutrophil and Platelet Engraftment
It is not clear if ABO incompatibility can affect neutrophil and platelet engraftment, or contribute to graft failure. Major incompatibility was associated with delayed neutrophil engraftment in 3 registry studies[2, 7, 19]. but was not observed in several other studies, including a recent large CIBMTR/NMDP evaluation of donor characteristics[8, 9, 20-23]. Even if there is a difference, a median 1-2-day delay in engraftment is not likely to be clinically relevant. One registry study suggests delayed platelet recovery with major incompatible grafts[2]. Some single center studies have reported both platelet and neutrophil engraftment issues, but the majority of studies find no impact of incompatibility[18]. A significantly higher rate of graft failure was reported in major or bidirectional incompatible transplants (6/83 vs 0/141 compatible transplants)[24], though one or more HLA mismatches was also present in 3 of the 6 cases. Two small series also suggested a risk of graft failure that was not seen in a number of other reports[18].

Graft Versus Host Disease (GVHD)

Red blood cell membranes are rich in proteins of great structural diversity. Polymorphisms of these antigens, incompatible ABO antigens, and allelic variations of ABO antigens could serve as minor histocompatibility antigens influencing rates of GVHD. Expression of similar antigens on endothelial and epithelial tissues could serve targets for the donor immune system, inciting a GVH response.

Acute GVHD

Increased rates of grade II-IV aGVHD were reported in two cohort studies[25, 26] as well as two registry studies[2, 7], but were not seen in most other reports[18, 23, 27-30].

Interesting, bi-directional mismatching (but not major mismatch) was associated with increased risk of grade II-IV acute graft-versus-host disease in a recent EBMT registry study evaluating leukemia patients undergoing haplo-identical transplants with a HR 2.387; 95% CI: 1.22-4.66; P=0.01[19]. However, the same authors note that patients with minor mismatching transplanted with bone marrow grafts experienced increased grade II-IV acute graft-versus-host disease rates (HR 2.03; 95% CI: 1.00-4.10; P=0.04)[19]. In contrast, the effect of ABO mismatch on transplant outcomes and transfusion requirements in 594 patients undergoing reduced-intensity conditioned (RIC) HSCT with alemtuzumab was evaluated in three UK transplant centres and did not demonstrate any association with aGVHD risk[31]. Further, a registry study from CIBMTR evaluating 1,013 AML patients who underwent MMURD transplantation between 2005 and 2014 suggest that the incidence of grade II-IV acute graft versus host disease was marginally lower in patients with major ABO mismatching (HR 0.7, 95% CI, 0.5-1; P = .049)[21]. In the absence of clear biologic plausibility and conflicting evidence, such positive associations maybe due to chance.

Chronic GVHD

There are minimal studies that link chronic GVHD with ABO incompatibility. In the before mentioned UK study, the incidence of extensive chronic GVHD was higher in patients with minor and major mismatch compared with those who were ABO matched (hazard ratio (HR) 1.74, P=0.032 for minor, HR 1.69 P=0.0036 for major mismatch)[31].

Relapse, Non-Relapse Mortality, and Survival

There is little evidence to suggest an influence of ABO incompatibility on relapse. None of the four registry studies found this association. One case series reported a decrease in relapse when minor or bidirectional incompatible grafts were used compared to major incompatible or ABO matched grafts on univariate analysis, but this association was not significant on multivariate analysis[32]. By contrast, cohort and registry studies have found an increase in NRM and decrease in overall survival[2, 8, 18, 33, 34], though these findings were not confirmed by other studies[7, 20-23, 27-29, 31, 35].

More recently, Kollman et al[20]. re-examined the association of donor characteristics associated with post-HSCT outcomes in the modern HSCT era using data from CIBMTR/NMDP. Utilizing 2

independent datasets: 1988 to 2006 (N = 6349; training cohort) and 2007 to 2011 (N = 4690; validation cohort), they noted a potential association of ABO compatibility with survival in HSCT prior to 2007 with ABO minor mismatch conferring a HR 1.10 (95%CI 1.01-1.18) and ABO major mismatch a HR 1.13 (95%CI 1.05-1.21). However, this association was not seen in the HSCT after 2007 (validation cohort) where the mortality risks associated with minor and major ABO mismatched transplants were HR, 1.09 (95%CI, 0.98-1.23) and HR 1.09 (95% CI, 0.91-1.21) respectively. They also considered the effect of ABO match separately for bone marrow and peripheral grafts and did not see a significant effect of ABO mismatching on overall mortality. Further, ABO compatibility was not associated with NRM, Relapse Mortality, acute or chronic GVHD.

Similarly, the EBMT evaluated the influence of ABO compatibility in 837 patients who underwent haploidentical transplantation and did demonstrate differences in Non-relapse mortality, relapse incidence, leukemia-free survival, overall survival, and chronic graft-versus-host disease rates between ABO-matched and -mismatched patients. However, patients with *major ABO mismatching and bone marrow grafts* had decreased survival (HR=1.82; CI 95%: 1.048 - 3.18; P=0.033). This finding was not observed in a CIBMTR study evaluating the impact of ABO mismatch on transplant outcomes with various graft types[22].

In contrast, the Chinese developed a risk score utilizing data from 1199 consecutive subjects receiving transplants from an HLA-haplotype-matched relative using granulocyte colony-stimulating factor and anti-thymocyte globulin (n=685) or an HLA-identical sibling (n=514). They suggest that ABO mismatch was 1 of 3 (others were older donor/recipient age, female-to-male transplants) independent risk factors that conferred risk of TRM and LFS[36].

Summary

An ABO compatible donor is preferred over ABO incompatible donor, but priority is given to HLA matching, donor age. The relative importance of ABO compatibility over CMV status and female gender/parity is less clear with respect to post-HSCT outcomes[37].

Management

The red cell content of graft is partially depending on whether the graft is from bone marrow or peripheral blood collection by apheresis. In the later, the red cell content is normally <10ml per collection while is higher and more variable with bone marrow.

The safe volume of transfused incompatible red cells has not been established in large studies. In one case series, sixteen of 36 patients receiving over 50 mL of incompatible red cells experienced signs or symptoms of an acute hemolytic reaction, 10 had renal failure, and 6 died, compared to no deaths, no renal failure, and only 3 hemolytic reactions in 12 patients transfused less than 50 mLs[12]. Thresholds of 20mL and 30mL have been reported as associated with

minimal toxicity. The risk of acute hemolytic reactions can be reduced by decreasing the 1) red cell content of the graft, or 2) the isoagglutinin titers of the recipient.

Red cell depletion of the HPC product can reduce the total nucleated cell count[38]. It has been suggested that this may be of importance if the HPC content is low or if additional cells are not readily available, as with cord blood units or volunteer unrelated donor grafts[39]. In addition, because unrelated donor HPC products can come from anywhere in the world, and prolonged intervals between collection and infusion into the recipient are associated with decreased likelihood of engraftment and increased mortality[40], further product manipulation in these circumstances could be undesirable.

An alternative approach to red cell depletion is to consider isohemagglutinin reduction by plasma exchange for major ABO-incompatible bone marrow grafts. Sheppard et. al report their single centre experience suggests that engraftment times, transfusion requirements, incidence and severity of graft-versus-host disease, and 100-day treatment-related mortality did not differ between the patients with a major ABO donor mismatch and those with an ABO-compatible donor. Further, no hemolytic transfusion reactions were observed during product infusion.[41] This approach has been counter-challenged[42] as antibody titering is a laboratory technique shown to be difficult to standardize across institutions[43, 44]. Therefore, it may be difficult to determine whether a concentration of incompatible antibody can be universally considered to be protective against a hemolytic reaction.

The Calgary Approach

In Calgary, the Alberta Bone Marrow Transplant Program (ABMTP) work-up obtains donor and recipient blood type information prior to selection of suitable donor for transplant. The transplant physician reviews the donor and recipient blood type information and is responsible for determining compatibility and indicating on the order for stem cell collection the compatibility status of the donor product. Compatibility is determined based on Table 25-1 in AABB Technical Manual (Table 1 above). The Cellular Therapy Laboratory will determine the product compatibility at the time of receipt of a cellular therapy product. If there is major incompatibility, the red cell volume is then determined (SOP: CTL.725 Preparing Cellular Therapy Products for Infusion or Processing).

1. For pediatric recipients, the accepted range for ABO incompatible blood volume transfused is 0.2 – 0.5 mL/kg. The transplant physician will be contacted with the volume and will direct CTL on desired final RBC content per infusion bag (based on hydration status and renal function of the recipient). CTL will aliquot and/or red cell reduce product as necessary.

2. For adult recipients, less than or equal to 30 mL +/- 1 mL of incompatible red cells will be allowed per infusion bag of apheresis product (HPC(A)). If product contains greater than 31 mL of incompatible red cells the product will be split into aliquots. HPC(M) will be red cell reduced to achieve ≤ 30 mL/infusion aliquot. If the initial incompatible red cell volume is < 30mL, no further action is taken.

3. For products with very large volumes of red cells, where dividing into aliquots is not practical, red cell reduction by centrifugation, Hespan, or apheresis can be considered.

4. For plasma incompatible transplants (minor incompatibility), no action is taken for any recipient as it has been determined by CTL validation studies that there is no association with adverse infusion reactions and minor incompatibility of products.

Following transplants with minor ABO incompatible grafts, the appropriate red cell type to be transfused cannot be determined by the usual blood bank techniques. Blood bank is notified about these transplants in order to provide appropriate blood product support (see Table 2).[3]

There is little evidence to guide the management of pure red cell aplasia (PRCA) beyond transfusion support until red cell engraftment occurs. There have been case reports of improvement following administration of erythropoietin[45-47], though this was unsuccessful in other reports[16, 48]. There are also case reports of successful treatment of PRCA with rituximab[49, 50], plasma exchange[48, 49], anti-thymocyte globulin[51-53], bortezomib[54] and donor lymphocyte infusion[55, 56]. There is insufficient evidence to support the routine use of these treatments for PRCA following ABO incompatible transplant.

There is a suggestion that methotrexate based GVHD prophylactic regimens will result in fewer cases of delayed transfusion reactions. However, given that this is so rare, its clinical impact is negligible compared to that of GVHD. The choice of GVHD regimen should therefore reflect optimal management/prevention of graft versus host disease.

Table 2. Recommended blood products for compatible and incompatible transplant recipients.

Recipient	Donor	Compatibility	1st Choice red cells	2nd Choice red cells	1st choice platelets	2nd choice platelets	FFP
A	A	Compatible	A	O	A, AB	B, O	A, AB
B	B	Compatible	B	O	B, AB	A, O	B, AB
AB	AB	Compatible	AB	A, B, O	AB	A, B, O	AB
O	O	Compatible	O	N/A	O, A, A, B, B	N/A	O, A, A, B, B
A	O	Minor inc	O	N/A	A, AB	B, O	A, AB
B	O	Minor inc	O	N/A	B, AB	A, O	B, AB
AB	O	Minor inc	O	N/A	AB	A, B, O	AB
AB	A	Minor inc	A	O	AB	A, B, O	AB
AB	B	Minor inc	B	O	AB	B, A, O	AB
O	A	Major inc	O	N/A	A, AB	B, O	A, AB
O	B	Major inc	O	N/A	B, AB	A, O	B, AB
O	AB	Major inc	O	N/A	AB	A, B, O	AB
A	AB	Major inc	A	O	AB	A, B, O	AB
B	AB	Major inc	B	O	AB	B, A, O	AB
A	B	Bidirectional	O	N/A	AB	A, B, O	AB
B	A	Bidirectional	O	N/A	AB	B, A, O	AB
Rh+	Rh-		Rh-	N/A	N/A	N/A	N/A
Rh-	Rh+		Rh-	N/A	N/A	N/A	N/A

References

1. Mielcarek M, Leisenring W, Torok-Storb B, Storb R. Graft-versus-host disease and donor-directed hemagglutinin titers after ABO-mismatched related and unrelated marrow allografts: evidence for a graft-versus-plasma cell effect. Blood 2000; 96(3): 1150-1156.
2. Kimura F, Sato K, Kobayashi S, Ikeda T, Sao H, Okamoto S et al. Impact of AB0-blood group incompatibility on the outcome of recipients of bone marrow transplants from unrelated donors in the Japan Marrow Donor Program. Haematologica 2008; 93(11): 1686-1693. doi: 10.3324/haematol.12933
3. Worel N. ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation. Transfus Med Hemother 2016; 43(1): 3-12
4. Cushing M, Hendrickson J. Transfusion Support for Hematopoietic Stem Cell Transplant Recipients . In: Fung M, Eder A, Spitalnik S, Westhoff C (eds). Technical Manual, 19th edn. AABB, 2017, p 683.
5. Booth GS, Gehrie EA, Bolan CD, Savani BN. Clinical guide to ABO-incompatible allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2013; 19(8): 1152-1158. doi: 10.1016/j.bbmt.2013.03.018
6. Franchini M, de Gironcoli M, Gandini G, Vassanelli A, Rocca P, Benedetti F et al. Transmission of an anti-RhD alloantibody from donor to recipient after ABO-incompatible BMT. Bone Marrow Transplant 1998; 21(10): 1071-1073. doi: 10.1038/sj.bmt.1701226
7. Leo A, Mytilineos J, Voso MT, Weber-Nordt R, Liebisch P, Lensing C et al. Passenger lymphocyte syndrome with severe hemolytic anemia due to an anti-Jk(a) after allogeneic PBPC transplantation. Transfusion 2000; 40(6): 632-636.
8. Seebach JD, Stussi G, Passweg JR, Loberiza FR, Jr., Gajewski JL, Keating A et al. ABO blood group barrier in allogeneic bone marrow transplantation revisited. Biol Blood Marrow Transplant 2005; 11(12): 1006-1013. doi: 10.1016/j.bbmt.2005.07.015
9. Michallet M, Le QH, Mohty M, Prebet T, Nicolini F, Boiron JM et al. Predictive factors for outcomes after reduced intensity conditioning hematopoietic stem cell transplantation for hematological malignancies: a 10-year retrospective analysis from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Exp Hematol 2008; 36(5): 535-544. doi: 10.1016/j.exphem.2008.01.017
10. Kollman C, Howe CW, Anasetti C, Antin JH, Davies SM, Filipovich AH et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood 2001; 98(7): 2043-2051.
11. Kanda J, Ichinohe T, Matsuo K, Benjamin RJ, Klumpp TR, Rozman P et al. Impact of ABO mismatching on the outcomes of allogeneic related and unrelated blood and marrow stem cell transplantations for hematologic malignancies: IPD-based meta-analysis of cohort studies. Transfusion 2009; 49(4): 624-635. doi: 10.1111/j.1537-2995.2008.02043.x
12. Canals C, Muniz-Diaz E, Martinez C, Martino R, Moreno I, Ramos A et al. Impact of ABO incompatibility on allogeneic peripheral blood progenitor cell transplantation after reduced intensity conditioning. Transfusion 2004; 44(11): 1603-1611. doi: 10.1111/j.1537-2995.2004.04106.x
13. Janatpour KA, Kalmin ND, Jensen HM, Holland PV. Clinical outcomes of ABO-incompatible RBC transfusions. Am J Clin Pathol 2008; 129(2): 276-281. doi: 10.1309/VXY1ULAFUY6E6JT3
14. Rowley SD, Liang PS, Ulz L. Transplantation of ABO-incompatible bone marrow and peripheral blood stem cell components. Bone Marrow Transplant 2000; 26(7): 749-757. doi: 10.1038/sj.bmt.1702572
15. Blin N, Traineau R, Houssin S, Peffault de Latour R, Petropoulou A, Robin M et al. Impact of donor-recipient major ABO mismatch on allogeneic transplantation outcome according to stem cell source. Biol Blood Marrow Transplant 2010; 16(9): 1315-1323. doi: 10.1016/j.bbmt.2010.03.021
16. Lee JH, Lee JH, Choi SJ, Kim S, Seol M, Kwon SW et al. Changes of isoagglutinin titres after ABO-incompatible allogeneic stem cell transplantation. Br J Haematol 2003; 120(4): 702-710.
17. Bolan CD, Leitman SF, Griffith LM, Wesley RA, Procter JL, Stroncek DF et al. Delayed donor red cell chimerism and pure red cell aplasia following major ABO-incompatible nonmyeloablative hematopoietic stem cell transplantation. Blood 2001; 98(6): 1687-1694.
18. Southcott MJ, Tanner MJ, Anstee DJ. The expression of human blood group antigens during erythropoiesis in a cell culture system. Blood 1999; 93(12): 4425-4435.
19. Rowley SD, Donato ML, Bhattacharyya P. Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. Bone Marrow Transplant 2011; 46(9): 1167-1185. doi: 10.1038/bmt.2011.135
20. Canaani J, Savani BN, Labopin M, Huang XJ, Ciceri F, Arcese W et al. Impact of ABO incompatibility on patients' outcome after haploidentical hematopoietic stem cell transplantation for acute myeloid leukemia - a report from the

Acute Leukemia Working Party of the EBMT. Haematologica 2017; 102(6): 1066-1074. doi: 10.3324/haematol.2016.160804
21. Kollman C, Spellman SR, Zhang MJ, Hassebroek A, Anasetti C, Antin JH et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood 2016; 127(2): 260-267. doi: 10.1182/blood-2015-08-663823
22. Canaani J, Savani BN, Labopin M, Michallet M, Craddock C, Socie G et al. ABO incompatibility in mismatched unrelated donor allogeneic hematopoietic cell transplantation for acute myeloid leukemia: A report from the acute leukemia working party of the EBMT. Am J Hematol 2017; 92(8): 789-796. doi: 10.1002/ajh.24771
23. Damodar S, Shanley R, MacMillan M, Ustun C, Weisdorf D. Donor-to-Recipient ABO Mismatch Does Not Impact Outcomes of Allogeneic Hematopoietic Cell Transplantation Regardless of Graft Source. Biol Blood Marrow Transplant 2017; 23(5): 795-804. doi: 10.1016/j.bbmt.2017.02.009
24. Kudek MR, Shanley R, Zantek ND, McKenna DH, Smith AR, Miller WP. Impact of Graft-Recipient ABO Compatibility on Outcomes after Umbilical Cord Blood Transplant for Nonmalignant Disease. Biol Blood Marrow Transplant 2016; 22(11): 2019-2024. doi: 10.1016/j.bbmt.2016.07.019
25. Remberger M, Watz E, Ringden O, Mattsson J, Shanwell A, Wikman A. Major ABO blood group mismatch increases the risk for graft failure after unrelated donor hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2007; 13(6): 675-682. doi: 10.1016/j.bbmt.2007.01.084
26. Keever-Taylor CA, Bredeson C, Loberiza FR, Casper JT, Lawton C, Rizzo D et al. Analysis of risk factors for the development of GVHD after T cell-depleted allogeneic BMT: effect of HLA disparity, ABO incompatibility, and method of T-cell depletion. Biol Blood Marrow Transplant 2001; 7(11): 620-630. doi: 10.1053/bbmt.2001.v7.pm11760150
27. Bacigalupo A, Van Lint MT, Occhini D, Margiocco M, Ferrari G, Pittaluga PA et al. ABO compatibility and acute graft-versus-host disease following allogeneic bone marrow transplantation. Transplantation 1988; 45(6): 1091-1094.
28. Grube M, Wolff D, Ahrens N, Herzberg PY, Herr W, Holler E. ABO blood group antigen mismatch has an impact on outcome after allogeneic peripheral blood stem cell transplantation. Clin Transplant 2016; 30(11): 1457-1465. doi: 10.1111/ctr.12840
29. Gutierrez-Aguirre CH, Gomez-De-Leon A, Alatorre-Ricardo J, Cantu-Rodriguez OG, Gonzalez-Llano O, Jaime-Perez JC et al. Allogeneic peripheral blood stem cell transplantation using reduced-intensity conditioning in an outpatient setting in ABO-incompatible patients: are survival and graft-versus-host disease different? Transfusion 2014; 54(5): 1269-1277. doi: 10.1111/trf.12466
30. Konuma T, Kato S, Ooi J, Oiwa-Monna M, Ebihara Y, Mochizuki S et al. Effect of ABO blood group incompatibility on the outcome of single-unit cord blood transplantation after myeloablative conditioning. Biol Blood Marrow Transplant 2014; 20(4): 577-581. doi: 10.1016/j.bbmt.2013.12.563
31. Romee R, Weisdorf DJ, Brunstein C, Wagner JE, Cao Q, Blazar BR et al. Impact of ABO-mismatch on risk of GVHD after umbilical cord blood transplantation. Bone Marrow Transplant 2013; 48(8): 1046-1049. doi: 10.1038/bmt.2013.8
32. Brierley CK, Littlewood TJ, Peniket AJ, Gregg R, Ward J, Clark A et al. Impact of ABO blood group mismatch in alemtuzumab-based reduced-intensity conditioned haematopoietic SCT. Bone Marrow Transplant 2015; 50(7): 931-938. doi: 10.1038/bmt.2015.51
33. Erker CG, Steins MB, Fischer RJ, Kienast J, Berdel WE, Sibrowski W et al. The influence of blood group differences in allogeneic hematopoietic peripheral blood progenitor cell transplantation. Transfusion 2005; 45(8): 1382-1390. doi: 10.1111/j.1537-2995.2005.00214.x
34. Hefazi M, Litzow M, Hogan W, Gastineau D, Jacob E, Damlaj M et al. ABO blood group incompatibility as an adverse risk factor for outcomes in patients with myelodysplastic syndromes and acute myeloid leukemia undergoing HLA-matched peripheral blood hematopoietic cell transplantation after reduced-intensity conditioning. Transfusion 2016; 56(2): 518-527. doi: 10.1111/trf.13353
35. Logan AC, Wang Z, Alimoghaddam K, Wong RM, Lai T, Negrin RS et al. ABO mismatch is associated with increased nonrelapse mortality after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015; 21(4): 746-754. doi: 10.1016/j.bbmt.2014.12.036
36. Watz E, Remberger M, Ringden O, Lundahl J, Ljungman P, Mattsson J et al. Analysis of donor and recipient ABO incompatibility and antibody-associated complications after allogeneic stem cell transplantation with reduced-intensity conditioning. Biol Blood Marrow Transplant 2014; 20(2): 264-271. doi: 10.1016/j.bbmt.2013.11.011
37. Wang Y, Wu DP, Liu QF, Xu LP, Liu KY, Zhang XH et al. Donor and recipient age, gender and ABO incompatibility regardless of donor source: validated criteria for donor selection for haematopoietic transplants. Leukemia 2018; 32(2): 492-498. doi: 10.1038/leu.2017.199
38. Tay J, Allan D, Tinmouth A, Coyle D, Hebert P. Donor selection for patients undergoing allogeneic hematopoietic SCT: assessment of the priorities of Canadian hematopoietic SCT physicians. Bone Marrow Transplant 2013; 48(2): 314-316. doi: 10.1038/bmt.2012.137

39. Rowley SD. Hematopoietic stem cell transplantation between red cell incompatible donor-recipient pairs. Bone Marrow Transplant 2001; 28(4): 315-321. doi: 10.1038/sj.bmt.1703135
40. Sheppard D, Huebsch LB, Bredeson C. What is the optimal approach to major ABO-incompatible allogeneic stem cell transplantation? Biol Blood Marrow Transplant 2013; 19(12): 1760. doi: 10.1016/j.bbmt.2013.09.019
41. Lazarus HM, Kan F, Tarima S, Champlin RE, Confer DL, Frey N et al. Rapid transport and infusion of hematopoietic cells is associated with improved outcome after myeloablative therapy and unrelated donor transplant. Biol Blood Marrow Transplant 2009; 15(5): 589-596. doi: 10.1016/j.bbmt.2009.01.017
42. Sheppard D, Tay J, Bryant A, McDiarmid S, Huebsch L, Tokessy M et al. Major ABO-incompatible BMT: isohemagglutinin reduction with plasma exchange is safe and avoids graft manipulation. Bone Marrow Transplant 2013; 48(7): 953-957. doi: 10.1038/bmt.2012.264
43. Booth GS, Gehrie EA, Savani BN. Response to "What is the optimal approach to major ABO-incompatible allogeneic stem cell transplantation". Biol Blood Marrow Transplant 2013; 19(12): 1760-1761. doi: 10.1016/j.bbmt.2013.10.005
44. Kobayashi T, Saito K. A series of surveys on assay for anti-A/B antibody by Japanese ABO-incompatible Transplantation Committee. Xenotransplantation 2006; 13(2): 136-140. doi: 10.1111/j.1399-3089.2006.00296.x
45. Kumlien G, Wilpert J, Safwenberg J, Tyden G. Comparing the tube and gel techniques for ABO antibody titration, as performed in three European centers. Transplantation 2007; 84(12 Suppl): S17-19. doi: 10.1097/01.tp.0000296019.85986.af
46. Heyll A, Aul C, Runde V, Arning M, Schneider W, Wernet P. Treatment of pure red cell aplasia after major ABO-incompatible bone marrow transplantation with recombinant erythropoietin. Blood 1991; 77(4): 906.
47. Santamaria A, Sureda A, Martino R, Domingo-Albos A, Muniz-Diaz E, Brunet S. Successful treatment of pure red cell aplasia after major ABO-incompatible T cell-depleted bone marrow transplantation with erythropoietin. Bone Marrow Transplant 1997; 20(12): 1105-1107. doi: 10.1038/sj.bmt.1701012
48. Paltiel O, Cournoyer D, Rybka W. Pure red cell aplasia following ABO-incompatible bone marrow transplantation: response to erythropoietin. Transfusion 1993; 33(5): 418-421.
49. Benjamin RJ, Connors JM, McGurk S, Churchill WH, Antin JH. Prolonged erythroid aplasia after major ABO-mismatched transplantation for chronic myelogenous leukemia. Biol Blood Marrow Transplant 1998; 4(3): 151-156. doi: 10.1053/bbmt.1998.v4.pm9923413
50. Helbig G, Stella-Holowiecka B, Krawczyk-Kulis M, Wojnar J, Markiewicz M, Wojciechowska-Sadus M et al. Successful treatment of pure red cell aplasia with repeated, low doses of rituximab in two patients after ABO-incompatible allogeneic haematopoietic stem cell transplantation for acute myeloid leukaemia. Haematologica 2005; 90 Suppl: ECR33.
51. Maschan AA, Skorobogatova EV, Balashov DN, Pashanov ED, Trakhtman PE, Schipitzina IP et al. Successful treatment of pure red cell aplasia with a single dose of rituximab in a child after major ABO incompatible peripheral blood allogeneic stem cell transplantation for acquired aplastic anemia. Bone Marrow Transplant 2002; 30(6): 405-407. doi: 10.1038/sj.bmt.1703668
52. Labar B, Bogdanic V, Nemet D, Kovacevic-Metelko J, Mrsic M, Pavletic Z et al. Antilymphocyte globulin for treatment of pure red cell aplasia after major ABO incompatible marrow transplant. Bone Marrow Transplant 1992; 10(5): 471-472.
53. Bierman PJ, Warkentin P, Hutchins MR, Klassen LW. Pure red cell aplasia following ABO mismatched marrow transplantation for chronic lymphocytic leukemia: response to antithymocyte globulin. Leuk Lymphoma 1993; 9(1-2): 169-171. doi: 10.3109/10428199309148522
54. Roychowdhury DF, Linker CA. Pure red cell aplasia complicating an ABO-compatible allogeneic bone marrow transplantation, treated successfully with antithymocyte globulin. Bone Marrow Transplant 1995; 16(3): 471-472.
55. Khan F, Linden MA, Zantek ND, Vercellotti GM. Subcutaneous bortezomib is highly effective for pure red cell aplasia after ABO-incompatible haematopoietic stem cell transplantation. Transfus Med 2014; 24(3): 187-188. doi: 10.1111/tme.12121
56. Verholen F, Stalder M, Helg C, Chalandon Y. Resistant pure red cell aplasia after allogeneic stem cell transplantation with major ABO mismatch treated by escalating dose donor leukocyte infusion. Eur J Haematol 2004; 73(6): 441-446. doi: 10.1111/j.1600-0609.2004.00320.x
57. Ebihara Y, Manabe A, Tsuruta T, Ishikawa K, Hasegawa D, Ohtsuka Y et al. The effect of donor leukocyte infusion on refractory pure red blood cell aplasia after allogeneic stem cell transplantation in a patient with myelodysplastic syndrome developing from Kostmann syndrome. Int J Hematol 2007; 86(5): 446-450. doi: 10.1532/IJH97.07111

Long-Term Follow-Up

Presented by: Kareem Jamani

Summary

Frequency of Follow-Up

- The recommended follow-up interval for allo-HCT recipients between day 80 and 1 year post-HCT is every 4-6 weeks.
- Long-term follow-up visits for allo-HCT recipients should be at least annually.

Cardiovascular Disease

- All patients should be counselled with respect to lifestyle modifications that reduce the risk of cardiac events, such as tobacco avoidance, adequate physical activity, maintaining a healthy weight and a healthy diet.
- All patients should have yearly evaluation of blood pressure with treatment per established Canadian guidelines (CHEP; http://guidelines.hypertension.ca/, essentially target <135/85 for most patients and <130/80 for those with diabetes).
- HCT recipients with established arterial disease should resume secondary prevention as soon as possible after HCT (i.e. ASA, statins, ACE inhibitors)
- For all allo-HCT recipients and selected auto-HCT recipients (those with a history of chest irradiation or cumulative dose of anthracycline ≥ 250 mg/m^2): patients should have a baseline lipid panel and fasting glucose/haemoglobin A1C at 1 year post-HCT and those ≥ 30 years old should have these repeated at 2-3 year intervals with calculation of Framingham risk score. Those who are intermediate or high risk by Framingham or who have LDL >4-5 mmol/L should be initiated on a statin to target lipid values as outlined by the Canadian guidelines (CCS; https://www.ccs.ca/en/guidelines/guidelines-library).
- For all other auto-HCT recipients: screening and management per the general population guidelines.
- Lipid and glucose screening may begin earlier than age 30 for those with one or more risk factors for cardiovascular disease including obesity, smoking, family history of early cardiovascular disease, diabetes, chest radiation or history of GVHD requiring systemic immunosuppression.
- For patients who received HCT in childhood, the CCSS cardiovascular risk calculator (https://ccss.stjude.org/tools-and-documents/calculators-and-other-tools/ccss-cardiovascular-risk-calculator.html) may supplement risk estimates obtained with Framingham-type calculators.
- Those with a history of cumulative dose of anthracycline ≥ 250 mg/m^2 should have yearly history and physical exam for signs/symptoms of CHF and aggressive management of cardiovascular risk factors as outlined above. Echocardiograms at yearly intervals for 5 years post-HCT may be considered for those at highest risk of CHF (i.e. those with one or more risk

factors in addition to anthracycline exposure, including younger age at anthracycline exposure, female sex, chest radiation, hypertension or diabetes).

Bone Health

- All patients should be counselled regarding lifestyle modifications for bone health including calcium intake 1200 mg/day from all sources, vitamin D 1000 IU/day, smoking cessation, limiting alcohol use & regular weight-bearing exercise.
- At 1 year post-HCT or at the onset of cGVHD requiring systemic therapy (whichever occurs earlier), patients should have an assessment of BMD by dual X-ray absorptiometry (DXA) and subsequently a 10 year probability of fracture calculated with the FRAX clinical assessment tool (https://www.sheffield.ac.uk/FRAX/) (except patients with multiple myeloma who are already being treated with bisphosphonates).
- For those who are no longer on immunosuppression at 1 year post-HCT, the Alberta Toward Optimized Practice (TOP) guidelines for osteoporosis (http://www.topalbertadoctors.org/cpgs/?sid=18&cpg_cats=81) should be followed.
- For those who remain on immunosuppression at 1 year post-HCT, therapy should be offered to: 1) those with established osteoporosis (BMD T-score ≤ -2.5) or history of fragility fracture, and 2) those with a moderate to high probability of fracture by FRAX as outlined by the Alberta TOP guidelines (>10% probability).
- In those who remain on chronic glucocorticoid therapy (prednisone equivalent dose >5mg/day) beyond 1 year post-HCT and who do not initiate therapy, annual DXA measurement should be considered.
- For those who initiate therapy, repeat DXA should be obtained at 3-5 years on therapy.
- First line therapy is typically with oral bisphosphonates. If identified, treatment of hypogonadism also could be considered in men and pre-menopausal women (after evaluation and discussion of risks/benefits of hormone replacement). Referral to an endocrinologist may be considered for alternate or second-line therapy options.
- The need for ongoing bisphosphonate therapy should be reassessed at the end of immunosuppressive therapy and/or at 5 years on therapy.
- In those with osteoporosis, a workup for secondary or contributing causes should be undertaken (for example, hypogonadism, hyperthyroidism & hyperparathyroidism).

Subsequent Malignancy Screening

- All patients should be counselled regarding smoking cessation and cutaneous solar protection.
- All patients should have a yearly history and physical exam that includes oral cavity, thyroid, and a complete skin exam.
- All patients should visit their dentist for oral/dental examination and cleaning; at least yearly for most patients and every 6 months for those with oral chronic GVHD.
- Screening for breast (see modifications below for women who have received TBI), cervical, colorectal (see modifications below for those who have received high dose TBI or localized

radiation) and prostate cancer should follow established Albertan/Canadian guidelines (www.screeningforlife.ca & for prostate cancer www.canadiantaskforce.ca).

- For women who have received any dose of TBI: screening mammography starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40.
- For patients who received high dose TBI (≥6 Gy) or abdominal, pelvic, lumbar, sacral, or whole spine irradiation, colorectal cancer screening with colonoscopy should begin at 5 years post-transplant or age 30, whichever occurs later.
- HCT recipients who have received radiation within a particular field, for example chest and those with familial cancer syndromes will require an individualized plan for malignancy screening.
- There are no proven screening measures for t-MN after auto-HCT; yearly CBC with early workup of cytopenias for up to 10 years post-transplant may be considered.

Renal Disease

- All HCT recipients should have at least yearly monitoring of creatinine.
- Allo-HCT recipients should a spot urine albumin/creatinine ratio yearly.
- All patients should have at least yearly blood pressure evaluation and treatment per Canadian (CHEP) guidelines (essentially target BP <140/90 for most patients).
- Basic medical management of CKD includes initiation of an ACE inhibitor or ARB for proteinuria, tight glycemic control for diabetics, aggressive management of cardiovascular risk factors and avoidance of nephrotoxins.
- Referral to a nephrologist should be considered when estimated GFR is <30 mL/min, for management of CKD with proteinuria or for workup of CKD of unknown etiology.

Pulmonary Disease

- The approach to prevention of late pulmonary infections are outlined in the bacterial/pneumocystis prophylaxis, fungal prophylaxis and vaccination chapters of these guidelines.
- For autologous-HCT recipients: PFT at 6 weeks post-HCT for those who received potentially pulmonary toxic conditioning. For all, at least yearly history and physical exam for signs and symptoms of pulmonary disease is recommended.
- For allogeneic-HCT recipients: routine PFTs for all patients every 3 months for the first year post-HCT followed by yearly PFTs until 5 years post-HCT. For those with active cGVHD beyond 1 year post-HCT, continued every 3 month PFTs should be strongly considered. History and physical exam should accompany PFTs.
- Abnormal PFTs or new respiratory symptoms should be worked up promptly with CXR +/- NP swab and sputum culture. For clinical presentations that are not consistent with upper respiratory tract infection or community-acquired pneumonia, CT chest and referral to the BMT pulmonary clinic are suggested.

Endocrine Disease

- Yearly thyroid examination and TSH measurement for all HCT recipients.
- A slow terminal taper of corticosteroids is required for those receiving prolonged courses (>3 weeks) for treatment of GVHD.
- A high index of clinical suspicion for adrenal insufficiency should be maintained when tapering patients from prolonged courses of corticosteroids.
- Management of diabetes and hyperlipidemia within the context of global cardiovascular risk as outlined in the "Cardiovascular disease" section.
- Workup and management of gonadal dysfunction and infertility as published[1,2].

Chronic Pain

- HCT recipients with chronic pain should be managed within a multi-disciplinary team that includes HCT providers, pharmacists and the psychosocial team within the Alberta Blood and Marrow Transplant Program with low threshold for referral to the palliative care team at the Tom Baker Cancer Centre.

Transfusion

- Red cell and platelet transfusion thresholds should be individualized based on clinical circumstances.
- The appropriate blood-group products for transfusion after ABO-incompatible allo-HCT per the "ABO Incompatibility" chapter.
- For allo-HCT recipients: irradiated blood products should be used from start of conditioning until the later of: 1 year post-HCT, end/"burn out" of chronic GVHD or discontinuation of immunosuppression.
- For auto-HCT recipients: irradiated blood products for 7 days prior to stem cell collection and from start of conditioning until 3 months post-HCT, or 6 months post-HCT if TBI was part of conditioning.
- All auto- and allo-HCT recipients should receive standard leukoreduced ("CMV safe") blood products.
- Transitioning from Pediatric to Adult Post-HCT Care
- Survivors of pediatric HCT are typically followed into adulthood and indefinitely in the Alberta Children's Hospital long-term follow-up/survivorship clinic.

Mental Health

- Long-term follow up visits should include screening for mental health concerns. If concerns are identified, patients should be referred to mental health providers and/or community resources as appropriate.

Background

Survival after hematopoietic cell transplant (HCT) has improved[3]. Survivors, however, face significant health challenges that contribute to morbidity and mortality even late after transplant. Among HCT survivors, the 15 year cumulative incidence of a severe or life threatening chronic health condition, such as stroke, myocardial infarction, diabetes and subsequent neoplasm, is approximately 40%: the cumulative incidence does not differ significantly between recipients of autologous (auto) and allogeneic (allo) HCT[4]. As a result, the risk of death after both allogeneic and autologous HCT, remains significantly higher than that of the general population even many years post HCT[5,6]. Therefore, it is imperative to have a structured long-term follow-up plan for survivors of HCT. This document will summarize the current literature with respect to late effects after HCT and will provide guidelines for clinical practice. The following important aspects of post-HCT survivorship care have already been reviewed in detail elsewhere in the ABMTP standard practice manual and can be found in their respective chapters:

- Diagnosis and management of chronic graft-versus-host disease (cGVHD)
- Management of post-HCT relapse
- Reproductive system complications
- Infection prophylaxis and vaccination

Frequency of Follow-up

Due to the potential for onset of cGVHD, the recommended follow-up interval for allo-HCT recipients between day 80 and 1 year post-HCT is every 4-6 weeks. Those suffering from GVHD, infection, relapse or other toxicity may need to be evaluated more frequently. Follow-up of allo-HCT recipients beyond 1 year post-HCT and of auto-HCT recipients may be individualized. However, long-term follow-up visits for allo-HCT recipients should be at least annually.

Transitioning from Pediatric to Adult Post-HCT Care

In Alberta, transition from the pediatric to adult HCT centre for ongoing survivorship/long-term follow-up care occurs when there is agreement between the pediatric survivorship provider, patient and family, and adult survivorship provider. A comprehensive treatment and medical history are forwarded from the pediatric to the adult centre. A shared electronic medical record further enhances continuity of care.

Cardiovascular Disease

Cardiovascular disease is a major cause of late non-relapse mortality in survivors of HCT. Compared to the general population, HCT survivors have a significantly increased cumulative incidence of cardiovascular death (incidence rate difference 3.6 per 1000 person years) and a significantly higher incidence of cardiovascular risk factors, such as diabetes and hypertension, when compared to age and sex matched controls.[7] Cardiovascular disease after HCT can be conceptualized as arterial disease (cerebrovascular, peripheral arterial and coronary artery disease) and cardiac disease

(particularly congestive heart failure but also constrictive pericarditis and valvular disease) with allogeneic HCT survivors being at higher risk of the former and autologous HCT survivors being at higher risk of the latter[8].

The cumulative incidence of arterial events among allo-HCT recipients is in excess of 20% at 20 years and the median age at first myocardial infarction is approximately 53 years, which is at least a decade earlier than that of the general population[8]. In a large single centre study, the cumulative incidence of ≥2 cardiovascular risk factors (of hypertension, dyslipidemia and diabetes) at 10 years after HCT was ~40% for allo-HCT survivors and 26% for auto-HCT survivors[9]. Older age and obesity at HCT, TBI (>2 Gy) and grades 2-4 aGVHD were risk factors for acquisition of cardiovascular risk factors post-HCT. In keeping with these findings, the prevalence of the metabolic syndrome in allo- and auto-HCT recipients is double that of the age-matched general population[10]. Risk factors for occurrence of cardiovascular disease after HCT encompass both traditional risk factors in addition to chest irradiation, GVHD, and exposure to anthracycline chemotherapy[8,9]. Healthy lifestyle choices such as physical activity and fruit/vegetable intake are associated with a lower risk of cardiovascular disease after HCT[11]. Current Canadian guidelines for the general population recommend measurement of a lipid panel and glucose in women and men ≥ age 40 every 5 years[12].

In a large single centre review, the cumulative incidence of late congestive heart failure (CHF) in auto-HCT survivors was approximately 10% at 15 years post-HCT-a 4.5 fold increased risk over that of the general population[13]. Pre-HCT anthracycline exposure, particularly cumulative dose ≥ 250 mg/m^2 is the primary driver of CHF risk, although significant modifiers that increase this risk further include younger age at anthracycline exposure, female sex, chest radiation, hypertension and diabetes[4,8].

Recommendations:

- All patients should be counselled with respect to lifestyle modifications that reduce the risk of cardiac events, such as tobacco avoidance, adequate physical activity, maintaining a healthy weight and a healthy diet.
- All patients should have yearly evaluation of blood pressure with treatment per established Canadian guidelines (CHEP; http://guidelines.hypertension.ca/, essentially target <135/85 for most patients and <130/80 for those with diabetes).
- HCT recipients with established arterial disease should resume secondary prevention as soon as possible after HCT (i.e. ASA, statins, ACE inhibitors)
- For all allo-HCT recipients and selected auto-HCT recipients (those with a history of chest irradiation or cumulative dose of anthracycline ≥ 250 mg/m^2): patients should have a baseline lipid panel and fasting glucose/haemoglobin A1C at 1 year post-HCT and those ≥ 30 years old should have these repeated at 2-3 year intervals with calculation of Framingham risk score. Those who are intermediate or high risk by Framingham or who have LDL >4-5 mmol/L should

be initiated on a statin to target lipid values as outlined by the Canadian guidelines (CCS; https://www.ccs.ca/en/guidelines/guidelines-library).

- For all other auto-HCT recipients: screening and management per the general population guidelines.
- Lipid and glucose screening may begin earlier than age 30 for those with one or more risk factors for cardiovascular disease including obesity, smoking, family history of early cardiovascular disease, diabetes, chest radiation or history of GVHD requiring systemic immunosuppression.
- Those with a history of cumulative dose of anthracycline ≥ 250 mg/m^2 should have yearly history and physical exam for signs/symptoms of CHF and aggressive management of cardiovascular risk factors as outlined above. Echocardiograms at yearly intervals for 5 years post-HCT may be considered for those at highest risk of CHF (i.e. those with one or more risk factors in addition to anthracycline exposure, including younger age at anthracycline exposure, female sex, chest radiation, hypertension or diabetes).

Bone Health

Loss of bone density after HCT is well described and typically occurs in the first 6-12 months post-transplant[12]. Beyond one year post-HCT, recovery of bone mineral density (BMD) to a variable degree may occur if patients do not experience additional risk factors for bone loss. Additional risk factors for osteoporosis include prolonged exposure to corticosteroids and calcineurin inhibitors (i.e. ongoing treatment of cGVHD), major weight loss, malnutrition, older age at HCT and female gender[14,15]. In a recent study, the prevalence of osteoporosis and osteopenia in patients experiencing moderate-severe cGVHD was 17% and 60%, respectively[16]. The estimates in the literature of the incidence of osteoporosis and osteopenia after HCT in those without cGVHD vary widely; however, both auto and allo-HCT recipients, particularly females and older males, have a marked increase in risk of fracture compared to that of the general population[15]. At least two studies have revealed a higher risk of fracture after auto-HCT versus allo-HCT[15,17]. Finally, degree of bone loss after HCT does not seem to directly correlate with risk of fracture,[18] highlighting the potential importance of using clinical assessment tools for fracture risk (such as FRAX) which take into account BMD and clinical factors. The Alberta Toward Optimized Practice (TOP) guidelines for osteoporosis provide recommendations for therapy and follow-up DXA based on the 10 year probability of fracture as calculated by FRAX. While FRAX takes into account corticosteroid exposure in general, it may underestimate the fracture risk for those who are receiving long courses of moderate to high doses of corticosteroids (i.e. cGVHD) and those who have more severe bone loss at the spine versus the hip (as it does not take into account BMD at the lumbar spine). There are, however, no universally agreed upon adjustments to fracture risk estimates for these variables. The recommendations for those with cGVHD below are generally in agreement with the 2017 American College of Rheumatology guidelines for the management of corticosteroid-induced osteoporosis[19].

Recommendations:

- All patients should be counselled regarding lifestyle modifications for bone health including calcium intake 1200 mg/day from all sources, vitamin D 1000 IU/day, smoking cessation, limiting alcohol use & regular weight-bearing exercise.
- At 1 year post-HCT or at the onset of cGVHD requiring systemic therapy (whichever occurs earlier), patients should have an assessment of BMD by dual X-ray absorptiometry (DXA) and subsequently a 10 year probability of fracture calculated with the FRAX clinical assessment tool (https://www.sheffield.ac.uk/FRAX/) (except patients with multiple myeloma who are already being treated with bisphosphonates).
- For those who are no longer on immunosuppression at 1 year post-HCT, the Alberta Toward Optimized Practice (TOP) guidelines for osteoporosis (http://www.topalbertadoctors.org/cpgs/?sid=18&cpg_cats=81) should be followed.
- For those who remain on immunosuppression at 1 year post-HCT, therapy should be offered to:
    - those with established osteoporosis (BMD T-score ≤ -2.5) or history of fragility fracture, and
    - those with a moderate to high probability of fracture by FRAX as outlined by the Alberta TOP guidelines (>10% probability).
- In those who remain on chronic glucocorticoid therapy (prednisone equivalent dose >5mg/day) beyond 1 year post-HCT and who do not initiate therapy, annual DXA measurement should be considered.
- For those who initiate therapy, repeat DXA should be obtained at 3-5 years on therapy.
- First line therapy is typically with oral bisphosphonates. If identified, treatment of hypogonadism also be could be considered in men and pre-menopausal women (after evaluation and discussion of risks/benefits of hormone replacement). Referral to an endocrinologist may be considered for alternate or second-line therapy options.
- The need for ongoing bisphosphonate therapy should be reassessed at the end of immunosuppressive therapy and/or at 5 years on therapy.
- In those with osteoporosis, a workup for secondary or contributing causes should be undertaken (for example, hypogonadism, hyperthyroidism & hyperparathyroidism).

Subsequent Malignancy Screening

Both auto- and allo-HCT recipients are at increased risk of secondary solid tumours. The risk of secondary solid tumours increases over time post-HCT with a cumulative incidence of about 15% at 25 years post-HCT-a two to three fold increased risk versus age and sex matched controls[20,21]. HCT recipients are particularly at risk (standardized incidence ratio >1) of the following malignancies: all skin including melanoma, thyroid, oropharyngeal, esophageal, liver, bone, central nervous system

and connective tissue[22.] Chronic GVHD and duration of immunosuppression > 2 years are major risk factors for skin, oropharyngeal, cervical and esophageal cancers, while conditioning with total body irradiation (TBI), particularly myeloablative TBI, is a risk factor for skin, thyroid, liver and breast cancers[22]. There is little data to guide second malignancy screening practices in HCT survivors: expert recommendations generally suggest screening similar to the general population with some additions as will be described below[22,23]. Those who have received radiation within specific fields, such as chest or cranial, or those with a cancer predisposition syndrome (ex. Fanconi anemia) may require individualized enhanced screening measures.

Survivors of autologous-HCT are at risk of therapy-related myeloid neoplasms (t-MN) (predominantly myelodysplatic syndrome and AML). The cumulative incidence of t-MN is about 7% at 15 years post auto-HCT[20]. Major risk factors for t-MN are alkylator therapy (5-7 year latency from HCT) and topoisomerase II inhibitor therapy (6 month-5 year latency from HCT)[20]. Unfortunately, outcomes of those who develop t-MN is poor[24].

Recommendations:

- All patients should be counselled regarding smoking cessation and cutaneous solar protection.
- All patients should have a yearly history and physical exam that includes oral cavity, thyroid, and a complete skin exam.
- All patients should visit their dentist for oral/dental examination and cleaning; at least yearly for most patients and every 6 months for those with oral chronic GVHD.
- Screening for breast (see modifications below for women who have received TBI), cervical, colorectal (see modifications below for those who have received high dose TBI or localized radiation) and prostate cancer should follow established Albertan/Canadian guidelines (www.screeningforlife.ca & for prostate cancer www.canadiantaskforce.ca).
- For women who have received any dose of TBI: screening mammography starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40.
- For patients who received high dose TBI (≥6 Gy) or abdominal, pelvic, lumbar, sacral, or whole spine irradiation, colorectal cancer screening with colonoscopy should begin at 5 years post-transplant or age 30, whichever occurs later.
- HCT recipients who have received radiation within a particular field, for example chest and those with familial cancer syndromes will require an individualized plan for malignancy screening.
- There are no proven screening measures for t-MN after auto-HCT; yearly CBC with early workup of cytopenias for up to 10 years post-transplant may be considered.

Renal Disease

The definition of chronic kidney disease (CKD) encompasses both decreased kidney function (glomerular filtration rate (GFR) <60 mL/minute) and kidney damage other than decreased GFR (ex.

albuminuria) with duration ≥ 3 months[25]. Estimates of the cumulative incidence of CKD in the months and years after HCT vary widely at 7 to 48%[26]. In one report, 4% of long-term survivors of allo-HCT (19% of the long-term survivors who had developed CKD) developed end-stage renal disease[27]. In both the general population[28] and the post-HCT population[29], CKD is independently associated with increased mortality, particularly cardiovascular mortality. Risk factors for CKD after HCT include history of acute kidney injury (AKI), occurrence of acute & chronic GVHD, age ≥45 at HCT, pre-HCT baseline GFR <90 mL/minute, hypertension and exposure to high dose total body irradiation[26]. While CKD may arise from a number of clinicopathologic entities after HCT; the best described being thrombotic microangiopathy, viral nephropathies and nephrotic syndrome; it is most commonly idiopathic or as a result of incomplete recovery from acute kidney injury early post-HCT[30]. These pathologies have been recently reviewed and are summarized from these sources in Table 1[26,30,31].

Table 1. Etiologies of chronic kidney disease after hematopoietic cell transplant

Clinicopathologic Entity	Incidence	Risk Factors	Clinical Characteristics
Idiopathic	Most patients with CKD post HCT	-AKI after HCT -aGVHD & cGVHD -High dose TBI -Hypertension	-None specific
Thrombotic microangiopathy	2-21%	-TBI -Calcineurin inhibitor use -aGVHD & cGVHD	-Microangiopathic hemolysis -Acute kidney injury, often with incomplete recovery of renal function leading to CKD
Nephrotic Syndrome (66% membranous and 19% minimal change)	1%	-cGVHD	-Associated with cGVHD -Proteinuria >3.5g/24 hours -Hypoalbuminemia -Edema -Hyperlipidemia
BK Nephropathy	Rare	-Immunosuppression	-BK viremia

Proteinuria, even microalbuminuria, particularly after allo-HCT, is increasingly recognized as a prognostic marker. Specifically: 1) those with albuminuria at day 100 post-HCT have a significantly higher risk of non-relapse mortality by one year post-HCT (predominantly due to GVHD and infection), and 2) those with albuminuria at any point between day 100 and one year post-HCT have an increased risk of developing CKD[24,30].

Recommendations:

- All HCT recipients should have at least yearly monitoring of creatinine.
- Allo-HCT recipients should a spot urine albumin/creatinine ratio yearly.

- All patients should have at least yearly blood pressure evaluation and treatment per Canadian (CHEP) guidelines (essentially target BP <140/90 for most patients).
- Basic medical management of CKD includes initiation of an ACE inhibitor or ARB for proteinuria, tight glycemic control for diabetics, aggressive management of cardiovascular risk factors and avoidance of nephrotoxins.
- Referral to a nephrologist should be considered when estimated GFR is <30 mL/min, for management of CKD with proteinuria or for workup of CKD of unknown etiology.

Pulmonary Disease

HCT recipients are at risk of both late infectious and non-infectious pulmonary diseases. Late infectious pulmonary complications include recurrent sinopulmonary infections, Pneumocystis and fungal infections. The approach to late pulmonary infections is addressed elsewhere in these guidelines (bacterial/pneumocystis prophylaxis, fungal prophylaxis and vaccination chapters). Late onset non-infectious pulmonary complications (LONIPCs) mainly affect allo-HCT recipients. LONIPCs are very rare after autologous-HCT-the vast majority of non-infectious pulmonary complications after auto-HCT occur in the peri-engraftment period[33]. The most common LONIPCs are summarized in Table 2 and include bronchiolitis obliterans syndrome (BOS) (a manifestation of cGVHD) and interstitial lung disease (the best defined being organizing pneumonia (OP), but diffuse alveolar damage, non-specific interstitial pneumonia and lymphoid interstitial pneumonia have also been described)[34-36]. Idiopathic pneumonia syndrome, diffuse alveolar haemorrhage and pulmonary veno-occlusive disease most often occur early (day 0-30) post-HCT, but rarely occur as a late toxicity[37]. In a recent prospective study, all LONIPCs were associated with cGVHD and were found to occur predominantly in the first 2 years after allo-HCT with a cumulative incidence of 20% at 3 years[38]. The LONIPCs consisted of BOS (40%), interstitial lung disease (22%), venous thromboembolic disease (16%) and restrictive lung disease with no interstitial lung or pleural disease (including cGVHD with cutaneous sclerosis) (15%). Those who experienced a LONIPC were at increased risk of death (HR 2.2); the main causes of death included relapse followed by respiratory causes and GVHD. Importantly, lower respiratory tract infection in the first 100 days after HCT, pre-HCT chest irradiation and low FEF25-75% at day 100 were risk factors for the development of a LONIPC. Evaluation of risk factors for BOS after allo-HCT have variably found older age, sex-mismatched HCT, history of aGVHD, busulfan-based conditioning, unrelated donor and peripheral blood stem cell graft to be associated with the development of BOS, while T-cell depletion is protective[36.] Finally, it should be noted that several chemotherapeutic agents (such as BCNU, bleomycin, busulfan and methotrexate) may contribute to or cause pulmonary toxicity[22].

Table 2. Late-onset non-infectious pulmonary complications after allogeneic-HCT

Entity	Time of Onset	CT Imaging Features	PFT Features	Clinical Features	Therapy
Bronchiolitis Obliterans	3 months-2 years post-HCT	-Air trapping -Bronchial thickening -Bronchiectasis -Centrilobular nodules	-Obstructive -Diagnosis per NIH criteria[37]	-Extra-pulmonary cGVHD usually present -Asymptomatic early -Cough, dyspnea, wheezing	-Systemic and topical therapy per cGVHD guidelines
Organizing Pneumonia	Median 3 months post-HCT	-Diffuse consolidation or ground glass opacity	-Restrictive > Normal > Obstructive > Mixed	-"Non-resolving infectious pneumonia" -Often in the setting of taper of immunosuppression for acute or chronic GVHD	-1 mg/kg prednisone with slow taper

Because the onset of LONIPCs is often insidious, particularly for BOS, with the potential for significant loss of lung function before symptoms develop, post-HCT screening pulmonary function tests (PFTs) are essential. The approach to abnormal PFTs begins with history and physical exam to elucidate recent or current infections. The investigation is guided by history, physical exam, and pattern of abnormal PFT, but generally begins with chest x-ray (CXR) and non-invasive infectious workup such as nasopharyngeal (NP) swab for respiratory viruses and sputum culture. If no clear etiology is found or empiric therapy fails, the next steps are guided by acuity of the presentation but generally include obtaining a CT chest and referral to the BMT pulmonary clinic with consideration of bronchoscopy with bronchoalveolar lavage +/- lung biopsy.

Recommendations:

- The approach to prevention of late pulmonary infections are outlined in the bacterial/pneumocystis prophylaxis, fungal prophylaxis and vaccination chapters of these guidelines.
- For autologous-HCT recipients: PFT at 6 weeks post-HCT for those who received potentially pulmonary toxic conditioning. For all, at least yearly history and physical exam for signs and symptoms of pulmonary disease is recommended.
- For allogeneic-HCT recipients: routine PFTs for all patients every 3 months for the first year post-HCT followed by yearly PFTs until 5 years post-HCT. For those with active cGVHD beyond 1 year post-HCT, continued every 3 month PFTs should be strongly considered. History and physical exam should accompany PFTs.
- Abnormal PFTs or new respiratory symptoms should be worked up promptly with CXR +/- NP swab and sputum culture. For clinical presentations that are not consistent with upper respiratory tract infection or community-acquired pneumonia, CT chest and referral to the BMT pulmonary clinic are suggested.

Endocrine Disease

Thyroid Function:
Hypothyroidism is relatively common after HCT, occurring in up to 30% of long-term survivors[40]. Risk factors include younger age at HCT, radiation (neck, mediastinal or total body) and exposure to busulfan and cyclophosphamide[20,40]. Symptoms of hypothyroidism are non-specific and include fatigue, cold intolerance, weight gain, constipation and dry skin. Hypothyroidism is also a secondary cause/contributor to hyperlipidemia.

Hyperlipidemia and Diabetes:
As discussed in the cardiovascular disease section above, both autologous and allogeneic HCT recipients acquire cardiovascular risk factors such as hyperlipidemia and diabetes faster and more frequently than the general population. While GVHD & immunosuppressive therapy are well known risk factors for hyperglycemia and hyperlipidemia[41], it should be noted that HCT survivors at least five years post-transplant without active GVHD and not on immunosuppressive therapy had double the risk of developing metabolic syndrome versus the age-matched population and this risk was independent of allo- versus auto-HCT[10]. As discussed in the cardiovascular disease section above, management of diabetes should follow standard practice for that of the general population and management of hyperlipidemia should be guided by global cardiovascular risk.

Adrenal Insufficiency:
A single centre study found that the cumulative incidence of adrenal insufficiency after allo-HCT was 13%, while it was 1% after auto-HCT[42]. Those who are treated with long courses of corticosteroids for GVHD are particularly at risk. An ACTH stimulation test may be used to confirm the diagnosis of adrenal insufficiency. Management of adrenal insufficiency includes initiation of physiologic corticosteroid dosing followed by a very slow taper. Weak data and expert opinion suggest that an alternate day tapering regimen may reduce the risk of adrenal insufficiency[40]. Additionally, a medical alert bracelet or information card should be worn or carried and patients should be alerted to seek immediate medical attention if they develop signs or symptoms of adrenal insufficiency (ex. nausea/vomiting/abdominal pain/postural hypotension).

Gonadal Dysfunction and Fertility:
Gonadal dysfunction and infertility are reviewed elsewhere[1,2].

Recommendations:
- Yearly thyroid examination and TSH measurement for all HCT recipients.
- A slow terminal taper of corticosteroids is required for those receiving prolonged courses (>3 weeks) for treatment of GVHD.
- A high index of clinical suspicion for adrenal insufficiency should be maintained when tapering patients from prolonged courses of corticosteroids.

- Management of diabetes and hyperlipidemia within the context of global cardiovascular risk as outlined in the “Cardiovascular disease” section.
- Workup and management of gonadal dysfunction and infertility as published[1,2].

Management of Chronic Pain

Survivors of HCT may experience chronic pain related to a number of treatment-related complications such as GVHD, peripheral neuropathy and non-specific cramping/muscle spasm among others. Management of chronic pain requires a multi-disciplinary approach that includes HCT providers, palliative care providers, pharmacists, and psychosocial providers.

Recommendations:

- HCT recipients with chronic pain should be managed within a multi-disciplinary team that includes HCT providers, pharmacists and the psychosocial team within the Alberta Blood and Marrow Transplant Program with low threshold for referral to the palliative care team at the Tom Baker Cancer Centre.

Transfusion

In general, most HCT recipients do not require transfusion in the post-engraftment period. However, if transfusion is required, thresholds for transfusion of red cells and platelets should be individualized based on the specific clinical circumstances (ex. symptoms, co-morbidities, underlying disease etc.). Product attributes for transfusion as recommended below (i.e. irradiation and CMV status) are in agreement with established Canadian guidelines[43,44]. Appropriate blood-group products for ABO-incompatible allo-HCT are reviewed in the “ABO Incompatibility” chapter of these guidelines.

Recommendations:

- Red cell and platelet transfusion thresholds should be individualized based on clinical circumstances.
- The appropriate blood-group products for transfusion after ABO-incompatible allo-HCT per the “ABO incompatibility” chapter.
- For allo-HCT recipients: irradiated blood products should be used from start of conditioning until the later of: 1 year post-HCT, end/“burn out” of chronic GVHD or discontinuation of immunosuppression.
- For auto-HCT recipients: irradiated blood products for 7 days prior to stem cell collection and from start of conditioning until 3 months post-HCT, or 6 months post-HCT if TBI was part of conditioning.
- All auto- and allo-HCT recipients should receive standard leukoreduced (“CMV safe”) blood products.

Mental Health

A significant minority of HCT survivors will experience persistent anxiety, depression and/or post-traumatic stress disorder in the years after transplant[45].

Recommendations:

- Long-term follow up visits should include screening for mental health concerns. If concerns are identified, patients should be referred to mental health providers and/or community resources as appropriate.

Acknowledgements

Dr. Emma Billington critically reviewed the bone health section & Dr. Brian Clarke critically reviewed the cardiovascular disease section.

References

1. Bhatia S. Caring for the long-term survivor after allogeneic stem cell transplantation. Hematology Am Soc Hematol Educ Program 2014;(1): 495-503
2. Brennan A, Hickey M. Gynaecological care after stem cell transplant: An overview. Maturitas 2017; 105:30-32.
3. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 2010;363:2091-101.
4. Sun CL, Kersey JH, Francisco L, et al. Burden of morbidity in 10+ year survivors of hematopoietic cell transplantation: report from the bone marrow transplantation survivor study. Biol Blood Marrow Transplant 2013;19:1073-80.
5. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood 2007;110:3784-92.
6. Myers RM, Hill BT, Shaw BE, et al. Long-term outcomes among 2-year survivors of autologous hematopoietic cell transplantation for Hodgkin and diffuse large b-cell lymphoma. Cancer 2018;124:816-25.
7. Chow EJ, Mueller BA, Baker KS, et al. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. Ann Intern Med 2011;155:21-32.
8. Armenian SH, Chow EJ. Cardiovascular disease in survivors of hematopoietic cell transplantation. Cancer 2014;120:469-79.
9. Armenian SH, Sun CL, Vase T, et al. Cardiovascular risk factors in hematopoietic cell transplantation survivors: role in development of subsequent cardiovascular disease. Blood 2012;120:4505-12.
10. Annaloro C, Usardi P, Airaghi L, et al. Prevalence of metabolic syndrome in long-term survivors of hematopoietic stem cell transplantation. Bone Marrow Transplant 2008;41:797-804.
11. Leger KJ, Baker KS, Cushing-Haugen KL, et al. Lifestyle factors and subsequent ischemic heart disease risk after hematopoietic cell transplantation. Cancer 2018;124:1507-15.
12. Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2016;32:1263-82.
13. Armenian SH, Sun CL, Shannon T, et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. Blood 2011;118:6023-9.
14. McClune BL, Majhail NS. Osteoporosis after stem cell transplantation. Curr Osteoporos Rep 2013;11:305-10.
15. Pundole XN, Barbo AG, Lin H, Champlin RE, Lu H. Increased incidence of fractures in recipients of hematopoietic stem-cell transplantation. J Clin Oncol 2015;33:1364-70.
16. Pirsl F, Curtis LM, Steinberg SM, et al. Characterization and Risk Factor Analysis of Osteoporosis in a Large Cohort of Patients with Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant 2016;22:1517-24.
17. Lin JN, Chen HJ, Yang CH, et al. Risk of osteoporosis and pathologic fractures in cancer patients who underwent hematopoietic stem cell transplantation: a nationwide retrospective cohort study. Oncotarget 2017;8:34811-9.
18. Savani BN, Donohue T, Kozanas E, et al. Increased risk of bone loss without fracture risk in long-term survivors after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2007;13:517-20.
19. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Rheumatol 2017;69:1521-37.
20. Bhatia S, Armenian SH, Landier W. How I monitor long-term and late effects after blood or marrow transplantation. Blood 2017;130:1302-14.
21. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood 2009;113:1175-83.
22. Inamoto Y, Shah NN, Savani BN, et al. Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant 2015;50:1013-23.
23. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Bone Marrow Transplant 2012;47:337-41.
24. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood 2000;95:3273-9.
25. Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011) 2013;3:19-62.
26. Hingorani S. Renal Complications of Hematopoietic-Cell Transplantation. N Engl J Med 2016;374:2256-67.
27. Ando M, Ohashi K, Akiyama H, et al. Chronic kidney disease in long-term survivors of myeloablative allogeneic haematopoietic cell transplantation: prevalence and risk factors. Nephrol Dial Transplant 2010;25:278-82.

28. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073-81.
29. Jo T, Arai Y, Kondo T, et al. Chronic Kidney Disease in Long-Term Survivors after Allogeneic Hematopoietic Stem Cell Transplantation: Retrospective Analysis at a Single Institute. Biol Blood Marrow Transplant 2017;23:2159-65.
30. Abboud I, Peraldi MN, Hingorani S. Chronic kidney diseases in long-term survivors after allogeneic hematopoietic stem cell transplantation: monitoring and management guidelines. Semin Hematol 2012;49:73-82.
31. Beyar-Katz O, Davila EK, Zuckerman T, et al. Adult Nephrotic Syndrome after Hematopoietic Stem Cell Transplantation: Renal Pathology is the Best Predictor of Response to Therapy. Biol Blood Marrow Transplant 2016;22:975-81.
32. Momoki K, Yamaguchi T, Ohashi K, Ando M, Nitta K. Emergence of Dipstick Proteinuria Predicts Overt Nephropathy in Patients Following Stem Cell Transplantation. Nephron 2017;135:31-8.
33. Afessa B, Abdulai RM, Kremers WK, Hogan WJ, Litzow MR, Peters SG. Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. Chest 2012;141:442-50.
34. Schlemmer F, Chevret S, Lorillon G, et al. Late-onset noninfectious interstitial lung disease after allogeneic hematopoietic stem cell transplantation. Respir Med 2014;108:1525-33.
35. Yoshihara S, Yanik G, Cooke KR, Mineishi S. Bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans organizing pneumonia (BOOP), and other late-onset noninfectious pulmonary complications following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2007;13:749-59.
36. Bergeron A. Late-Onset Noninfectious Pulmonary Complications After Allogeneic Hematopoietic Stem Cell Transplantation. Clin Chest Med 2017;38:249-62.
37. Soubani AO, Pandya CM. The spectrum of noninfectious pulmonary complications following hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther 2010;3:143-57.
38. Bergeron A, Chevret S, Peffault de Latour R, et al. Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. Eur Respir J 2018;51.
39. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389-401 e1.
40. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. Haematologica 2017;102:614-25.
41. Marini BL, Choi SW, Byersdorfer CA, Cronin S, Frame DG. Treatment of dyslipidemia in allogeneic hematopoietic stem cell transplant patients. Biol Blood Marrow Transplant 2015;21:809-20.
42. Khera N, Storer B, Flowers ME, et al. Nonmalignant late effects and compromised functional status in survivors of hematopoietic cell transplantation. J Clin Oncol 2012;30:71-7.
43. Recommendations for use of irradiated blood components in Canada. National Advisory Committee on Blood and Blood Products 2017.
44. Prokopchuk-Gauk O, Solh Z. Chapter 15. CMV Seronegative, Irradiated and Washed Blood Components. Canadian Blood Services Clinical Guide to Transfusion 2017.
43. Mosher, CE, Redd WH, Rini CM, et al. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. Psycho-Oncology 2009;18:113-127.

Nutrition Support in Hematopoietic Cell Transplant

Presented by: Esther Lac RD, Edward Walker RD

Summary

- Hematopoietic cell transplant patients are at risk of malnutrition before, during, and after transplant.
- Malnutrition risk may be mitigated through initiation of nutrition support, preferably through the use of enteral nutrition (tube feeding).
- Nutrition support should be initiated for hematopoietic cell transplant patients if: inadequate intake (less than 60% of requirements) for 5 days or likely to remain inadequate for >5 days, or weight loss in a euvolemic patient of >5% in one month or >2% in one month if BMI <20kg/m^2, except for those patients meeting these criteria during the expected period of mucositis and for 7-10 days after resolution of mucositis.

Background

Patients undergoing hematopoietic cell transplant (HCT) are at risk of malnutrition due to the gastrointestinal (GI) side effects of the treatment which impede oral intake, including, but not limited to, mucositis, anorexia, dysgeusia, nausea, vomiting, and diarrhea[1,2]. As a result, patients often are unable to consume enough food to adequately meet their nutritional needs during transplant, with some consuming less than 60% of their estimated requirements for one to two weeks[3-5], which is the defined criteria in the literature for inadequate oral intake among cancer patients. HCT patients are often strongly advised to gain weight prior to their transplant as pre-transplant weight loss is related to increased relapse risk and shorter disease-free survival post-transplant and non-relapse mortality[6,45]. Body mass index (BMI) less than 18.5kg/m^2, underweight[7] and weight loss were historically used to identify malnutrition, but are no longer considered effective markers on their own[5]. Assessment and diagnosis of malnutrition is not always straightforward and requires dietitian involvement early and throughout the transplant process[43-45]. Malnutrition assessments that account for sarcopenia–defined as low muscle mass and poor muscle strength–categorize patients into mild, moderate and severe malnutrition[45,50]. Individuals who have more than two of the following are considered severely malnourished: obvious muscle wasting, loss of subcutaneous fat, decreased functional status, weight loss of > 2% in 1 week, 5% in 1 month, or 7.5% in 3 months[8] or consume less than 60% of recommended nutritional intake for 2 weeks or more[3-5]. Muscle loss comprises a large proportion of short-term weight loss, wherein immobile or bedridden hospitalized patients can lose up to 0.5% of total body muscle mass per day[9], with considerable muscle loss occurring during a prolonged hospital stay[10]. Malnutrition is associated with lower health-related quality of life[11,12], impaired functional ability[12,13], higher rates of infection[14], impaired wound healing[15], longer hospital length of stay[16,17], increased health care costs[16], and higher mortality[18,19].

Both enteral and parenteral nutrition can be utilized to provide nutrition support to HCT patients who are at risk of malnutrition and whose oral intake is impeded by the gastrointestinal side effects of treatment. Standard of clinical practice regarding use of enteral and/or parenteral nutrition varies significantly among institutions due to differences in country of practice and knowledge, availability of nutrition experts, and clinician perception of invasiveness and poor tolerance though there is consensus that nutrition support during HCT is required[47,48].

Enteral nutrition can be delivered via nasogastric or nasoduodenal/nasojejunal tubes (short term, ideally less than 4 weeks) or via endoscopically, surgically or radiologically placed percutaneous gastric/jejunal tubes (long term)[24]. Naso-enteric feeding tubes can contribute to both physical and psychological discomfort for the patient, or possibly more serious complications of nasopharyngeal lesions, sinusitis or reflux esophagitis, tube dislocation and/or movement within the nares and throat, and the tube presence being a reminder of illness[25]. Clinicians may be concerned about risk of bleeding during naso-enteric feeding tube insertion. Prophylactic platelet infusion (i.e. transfuse if platelet count $<30x10^9$) pre-insertion may help to mitigate this risk, with one study demonstrating no association between thrombocytopenia and increased risk of bleeding after feeding tube insertion among critically ill oncology patients[26].

Nasogastric tubes may be advantageous over nasoduodenal/nasojejunal tubes due to: (1) decreased cost, as they can be inserted at the bedside by a nurse, rather than by a physician in fluoroscopy, (2) ability to infuse either intermittent (bolus) or continuous tube feeds and (3) more physiological for motility and hormones[27] and medication administration[28]. Nasoduodenal/nasojejunal feeds require a pump for continuous infusion and may be preferred over nasogastric tubes in settings of intractable vomiting and to reduce risk of aspiration, although this risk is not entirely eliminated[27]. However, a continuous tube feed may impact patient quality of life as it can limit activity when a patient is connected to the pump all day[28]. Bolus feeding (gastric feeds only) may contribute to increased risk of aspiration and to increased incidence of diarrhea, depending on rate of formula infusion[28].

Parenteral nutrition may be indicated when a patient has a non-functional gastrointestinal tract (i.e. bowel obstruction or paralytic ileus) or in the presence of high gastrointestinal losses (diarrhea, vomiting, short bowel syndrome)[20]. Total parenteral nutrition (TPN) requires central venous access such as a percutaneous non-tunneled central catheter, a tunneled cuffed catheter, a peripherally inserted central catheter (PICC) or an implanted port prior to initiation[21]. Peripheral parenteral nutrition (PPN) may be used when enteral nutrition is contraindicated and the patient has a peripheral access but no central venous access, usually as a short-term bridge to total parenteral nutrition or enteral nutrition. Complications of parenteral nutrition may include refeeding syndrome, infection, thromboembolic events, hyperglycemia, cholestasis, hypertriglyceridemia, metabolic bone disease[21,22,46] and acalculous cholecystitis[23]. Although parenteral nutrition may be delivered more consistently than enteral nutrition due to interruptions related to gastrointestinal intolerance of the enteral formula, enteral nutrition is advantageous for a number of reasons including maintenance of the gut function, integrity, and barrier which protects against bacterial translocation, fewer infections, decreased length of stay and decreased financial cost[27,29,30,46]. Enteral nutrition may be discontinued

for a number of reasons including nausea, vomiting, diarrhea, psychological intolerance, tube blockage or displacement[32].

Both the American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.) and the European Society for Clinical Nutrition and Metabolism (E.S.P.E.N.) recommend enteral nutrition over parenteral nutrition for nutrition support among HCT patients[33,34]. A.S.P.E.N. recommends enteral nutrition in HCT patients with a functioning gastrointestinal tract, and nutrition support in malnourished patients anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time[33]. E.S.P.E.N. recommends initiation of enteral nutrition except in situations of severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic gastrointestinal graft versus host disease (GVHD), when parenteral nutrition could be provided instead[34].

Tolerance to enteral nutrition in allogeneic HCT patients was demonstrated in a large RCT by Andersen *et al.* who found that over a median of 8 days, patients received a median of 73% of goal calories and protein through enteral nutrition. The authors suggested that enteral nutrition use over parenteral use could decrease costs and minimize parenteral nutrition-related complications[32]. A variety of retrospective and prospective studies found that enteral nutrition in HCT was associated with reduced non-relapse mortality, lower incidence of acute GVHD of the GI tract, decreased risk of infection, improved neutrophil and platelet engraftment, and improved overall survival[32,35-37]. In contrast, parenteral nutrition was associated with increased early mortality and delayed platelet engraftment[37]. Several studies and systematic reviews concluded that enteral nutrition, in conjunction with medications to improve tolerance (antiemetics, antidiarrheals, analgesia), may be associated with a decreased risk of infectious complications and prevention of GVHD compared to parenteral nutrition[36-41].

Studies and reviews that have emerged since 2022 examine the benefits of enteral nutrition over parenteral nutrition on the modulation of the gut microbiota and suggest that maintaining gut stimulation has a role in retention of muscle mass, lower rates of acute GVHD, and lower risk of bloodstream infections. As chemotherapy, radiation therapy, and antibiotic treatments disrupt the mucosal barrier and cause microbiota dysbiosis (defined as decrease microbiota diversity, loss of commensal bacteria, expansion of pathogenic bacteria), nutrition being a main driver of species diversity and function in the gut microbiome can be a primary defense[44,46,48]. Oral or enteral nutrition stimulates metabolite production such as short-chain fatty acids that have a role in anabolism and muscle energy expenditure, and may prevent intestinal domination by a single bacterium (a single bacterial taxon comprising of > 30% of the gut microbiome)[44,48]. Stein-Thoeringer *et al.* found *Enterococcus spp.* domination in up to 65% of patients after an allogeneic transplant, and this was associated with reduced overall survival and increased risk of acute GVHD[49,49]. Conversely, parenteral nutrition cannot counter the gut atrophy that occurs inevitably in intestinal fasting if it is the sole source of nutrition[46]. Literature suggests that the longer patients fast after completing

conditioning chemotherapy, the higher the risk of GVHD, as well as a reduction in gut microbiota diversity[46,48].

2021-2024 Data on Use of Enteral Nutrition at the Foothills Medical Centre

The nutrition support algorithm (Figure 1) was implemented in 2021 and from August that year to September 2024, data was collected on the use of enteral and parenteral nutrition in the HCT population at the Foothills Medical Centre. During this period, approximately 22% of the 612 patients admitted for HCT were screened out and offered early enteral nutrition (36% of all allogeneic HCTs and 8% of all autologous HCTs). Of those offered enteral nutrition, 56% of allogeneic HCT patients (60 patients) and 50% of autologous HCT patients (13 patients) accepted and started enteral nutrition during their transplant admission. Several patients who started enteral nutrition on a readmission are not reflected in this data, as the focus of this standard practice was on initiation of early enteral nutrition during the transplant admission.

Reasons patients do not start enteral nutrition despite being screened for it include: patient perception of invasiveness and fear of discomfort, fear of worsening GI symptoms like nausea or diarrhea, fear of epistaxis, and underestimating the barrier that mucositis will pose on oral intake as the admission progresses. Despite these barriers, patients have been increasingly more accepting of supplemental enteral nutrition as part of their HCT treatment process due to earlier introduction to the option of enteral nutrition from the physician in pre-transplant assessments and from the dietitians and nurses throughout the patient's admission as they reinforce the benefits of EN or answer questions patients may have.

Collected data shows the tolerance of enteral nutrition is high, with allogeneic HCTs tolerating 100% median or 83% average, and autologous HCT tolerating 80% median or 69% average of their total prescribed calories and protein. The currently preferred enteral feeding route for allogeneic HCTs is with a nasoduodenal or nasojejunal feeding tube, a calorically dense (2.0kcal/mL) formula, and feeding during the daytime only, all with the goal of lowering aspiration risk. The most important consideration to lower aspiration risk regardless of enteral tube type is maintaining a head of bed of at least 30 degrees. Use of hypercaloric formulas may improve patients' tolerance by reducing volume administered[46].

Instances of complications with enteral feeding were tracked in allogeneic HCT patients: 18% (11 patients) had nausea and vomiting induced tube dislodgement, 0% had tube related aspiration events, 3% (2 patients) had tube clogging, and 2% (1 patient) had worsened epistaxis. After enteral nutrition was attempted, 15% of allogeneic HCT (9 patients) required a transition to parenteral nutrition without supplemental enteral nutrition, either due to loss of feeding tube and inability or refusal to reinsert, or due to gut-related complications that required gut rest. Patients are often transitioned back to oral nutrition prior to discharge and very rarely are discharged home on the

Home Enteral Nutrition Program. More commonly, patients may be readmitted with failure to thrive and prolonged poor intake post-transplant requiring supplemental enteral nutrition and discharge with the Home Enteral Nutrition Program.

Allogeneic HCT patients who received early enteral nutrition had a median weight loss of 6.1% (4kg) compared to 7.8% (6.2kg) for screened patients who did not start enteral nutrition. This difference was statistically significant (p=0.00988) however this median difference of 2kg may not be clinically significant. Fluid retention, edema, pre-transplant weight or BMI, and length of stay are all confounding variables. Though data was collected to compare length of stay, it was observed that patients with more complications resulting in longer lengths of stay may eventually require enteral nutrition despite initially refusing. Therefore, the longer average length of stay for HCT patients who received enteral nutrition is likely affected by other confounding factors.

Though data on incidences of GVH, infection, and 100-day survival were not explicitly collected for patients screened for enteral nutrition, literature explores and proposes mechanistic explanations for the benefits of enteral nutrition on these outcome measures.

Standard Practice in Alberta for Adults

The standard of practice in Alberta currently is for practitioners, primarily Registered Dietitians who are consulted for every HCT patient admitted, to use the Nutrition Support Algorithm (Figure 1) to recommend initiation of enteral nutrition when appropriate. As literature varies in recommendation and use of feeding route, duration, and formula type, the Registered Dietitian should make a clinical decision alongside the medical team with close monitoring for tolerance and adjusting as indicated. If enteral nutrition is tried and unsuccessful, parenteral nutrition should be considered after an assessment of benefits against risk with the medical team. Regardless of use of enteral or parenteral nutrition, maintenance of oral nutrition even in small amounts should be recommended as tolerated to support the gut barrier and prevent gut atrophy among various other benefits.

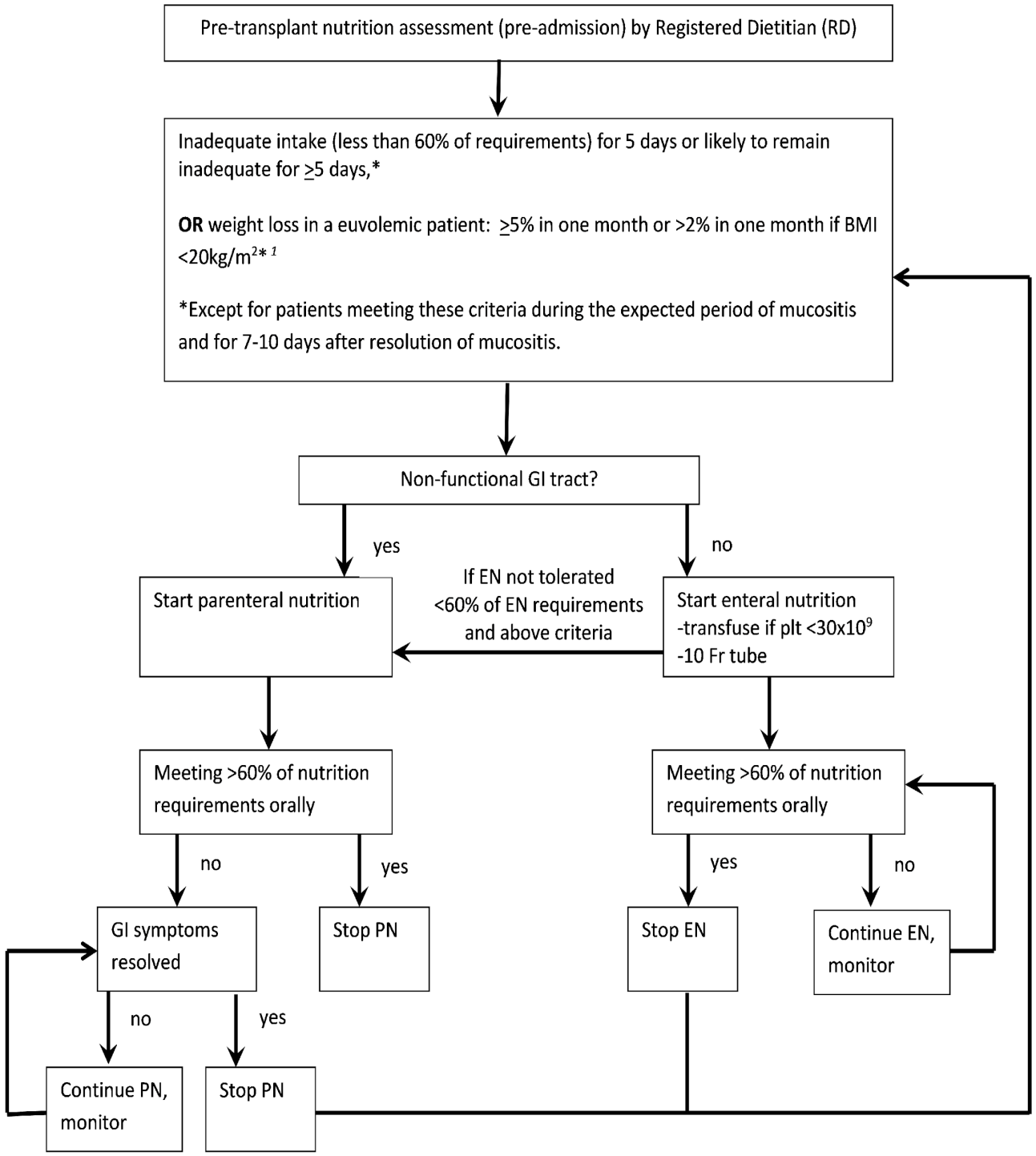


Figure 1. Nutrition support algorithm for hematopoietic cell transplant (HCT) patients in Calgary, AB. Adapted from *Beckerson et. al.*[35] and *Andersen et al.*[42]
plt = platelets

References

1. Tuncer HH, Rana N, Milani C, Darko A, Al-Homsi SA. Gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *World J Gastroenterol.* 2012;18(16):1851-1860.
2. Iestra JA, Fibbe WE, Zwinderman AH, van Staveren WA, Kromhout D. Body weight recovery, eating difficulties and compliance with dietary advice in the first year after stem cell transplantation: a prospective study. *Bone Marrow Transplant.* 2002;29(5):417-424.
3. Walrath M, Bacon C, Foley S, Fung HC. Gastrointestinal side effects and adequacy of enteral intake in hematopoietic stem cell transplant patients. *Nutr Clin Pract.* 2015;30(2):305-310.
4. Arends J, Bodoky G, Bozzetti F, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clin Nutr.* 2006;25(2):245-259.
5. Arends J, Baracos V, Bertz H, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr.* 2017;36(5):1187-1196.
6. Fuji S, Mori T, Khattry N, et al. Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased risk of subsequent non-relapse mortality. *Bone Marrow Transplant.* 2015;50(1):100-105.
7. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. . 2000;894:i-253.
8. Phillips W. Coding for Malnutrition in the Adult Patient: What the Physician Needs to Know. *Pract Gastroenterol.* 2014(133):56-64.
9. Wall BT, van Loon LJ. Nutritional strategies to attenuate muscle disuse atrophy. *Nutr Rev.* 2013;71(4):195-208.
10. Wall BT, Dirks ML, Snijders T, Senden JM, Dolmans J, van Loon LJ. Substantial skeletal muscle loss occurs during only 5 days of disuse. *Acta Physiol (Oxf).* 2014;210(3):600-611.
11. Vero LM, Byham-Gray L, Parrott JS, Steiber AL. Use of the subjective global assessment to predict health-related quality of life in chronic kidney disease stage 5 patients on maintenance hemodialysis. *J Ren Nutr.* 2013;23(2):141-147.
12. Felder S, Lechtenboehmer C, Bally M, et al. Association of nutritional risk and adverse medical outcomes across different medical inpatient populations. *Nutrition.* 2015;31(11-12):1385-1393.
13. Vivanti A, Ward N, Haines T. Nutritional status and associations with falls, balance, mobility and functionality during hospital admission. *J Nutr Health Aging.* 2011;15(5):388-391.
14. Schaible UE, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. *PLoS Med.* 2007;4(5):e115.
15. Stechmiller JK. Understanding the role of nutrition and wound healing. *Nutr Clin Pract.* 2010;25(1):61-68.
16. Curtis LJ, Bernier P, Jeejeebhoy K, et al. Costs of hospital malnutrition. *Clin Nutr.* 2017;36(5):1391-1396.
17. Horsley P, Bauer J, Gallagher B. Poor nutritional status prior to peripheral blood stem cell transplantation is associated with increased length of hospital stay. *Bone Marrow Transplant.* 2005;35(11):1113-1116.
18. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. *Clin Nutr.* 2012;31(3):345-350.
19. Agarwal E, Ferguson M, Banks M, et al. Malnutrition and poor food intake are associated with prolonged hospital stay, frequent readmissions, and greater in-hospital mortality: results from the Nutrition Care Day Survey 2010. *Clin Nutr.* 2013;32(5):737-745.
20. Madsen H, Frankel E. The Hitchhiker's Guide to Parenteral Nutrition Management for Adult Patients. *Pract Gastroenterol.* 2006(40):46-68.
21. Derenski K, Catlin J, Allen L. Parenteral Nutrition Basics for the Clinician Caring for the Adult Patient. *Nutr Clin Pract.* 2016;31(5):578-595.
22. Lappas BM, Patel D, Kumpf V, Adams DW, Seidner DL. Parenteral Nutrition: Indications, Access, and Complications. *Gastroenterol Clin North Am.* 2018;47(1):39-59.
23. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. *Clin Gastroenterol Hepatol.* 2010;8(1):15-22.
24. Bankhead R, Boullata J, Brantley S, et al. Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr.* 2009;33(2):122-167.
25. Blumenstein I, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. *World J Gastroenterol.* 2014;20(26):8505-8524.
26. Patel RP, Canada TW, Nates JL. Bleeding Associated With Feeding Tube Placement in Critically Ill Oncology Patients With Thrombocytopenia. *Nutr Clin Pract.* 2016;31(1):111-115.
27. Niv E, Fireman Z, Vaisman N. Post-pyloric feeding. *World J Gastroenterol.* 2009;15(11):1281-1288.

28. Ichimaru S. Methods of Enteral Nutrition Administration in Critically Ill Patients: Continuous, Cyclic, Intermittent, and Bolus Feeding. *Nutr Clin Pract.* 2018;33(6):790-795.
29. Seres DS, Valcarcel M, Guillaume A. Advantages of enteral nutrition over parenteral nutrition. *Therap Adv Gastroenterol.* 2013;6(2):157-167.
30. Reddy P, Malone M. Cost and outcome analysis of home parenteral and enteral nutrition. *JPEN J Parenter Enteral Nutr.* 1998;22(5):302-310.
31. Wang J, Liu M, Liu C, Ye Y, Huang G. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for patients with head and neck cancer: a systematic review. *J Radiat Res.* 2014;55(3):559-567.
32. Andersen S, Weber N, Kennedy G, Brown T, Banks M, Bauer J. Tolerability of proactive enteral nutrition post allogeneic haematopoietic progenitor cell transplant: A randomised comparison to standard care. *Clin Nutr.* 2019.
33. August DA, Huhmann MB. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enteral Nutr.* 2009;33(5):472-500.
34. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr.* 2017;36(1):11-48.
35. Beckerson J, Szydlo RM, Hickson M, et al. Impact of route and adequacy of nutritional intake on outcomes of allogeneic haematopoietic cell transplantation for haematologic malignancies. *Clin Nutr.* 2019;38(2):738-744.
36. Guieze R, Lemal R, Cabrespine A, et al. Enteral versus parenteral nutritional support in allogeneic haematopoietic stem-cell transplantation. *Clin Nutr.* 2014;33(3):533-538.
37. Seguy D, Duhamel A, Rejeb MB, et al. Better outcome of patients undergoing enteral tube feeding after myeloablative conditioning for allogeneic stem cell transplantation. *Transplantation.* 2012;94(3):287-294.
38. Baumgartner A, Bargetzi A, Zueger N, et al. Revisiting nutritional support for allogeneic hematologic stem cell transplantation-a systematic review. *Bone Marrow Transplant.* 2017;52(4):506-513.
39. Reese MK, Hewlings S. Enteral Versus Parenteral Nutrition: Use in Adult Patients Undergoing Hematopoietic Stem Cell Transplantation. *Clin J Oncol Nurs.* 2019;23(2):173-179.
40. Seguy D, Berthon C, Micol JB, et al. Enteral feeding and early outcomes of patients undergoing allogeneic stem cell transplantation following myeloablative conditioning. *Transplantation.* 2006;82(6):835-839.
41. Andersen S, Kennedy G, Banks M. A randomised controlled comparison of enteral versus parenteral nutritional support post allogeneic haematopoietic cell transplantation. *Clin Nutr ESPEN.* 2015;10(3):e102-e106.
42. Andersen S, Brown T, Kennedy G, Banks M. Implementation of an evidenced based nutrition support pathway for haematopoietic progenitor cell transplant patients. *Clin Nutr.* 2015;34(3):536-540.
43. Szovati S, Morrison C, Couch S. Nutritional Status of Allogeneic Hematopoietic Stem Cell Transplant Recipients and Post-transplant Outcomes. *Nutrition and Cancer.* 2023;75(4):1200-1210.
44. Limpert R, Pan P, Wang L, Chen X. From support to therapy: rethinking the role of nutrition in acute graft-versus-host disease. *Front. Immunol.* 2023;14:1192084.
45. Price S, Kim Y. Body Composition Impacts Hematopoietic Stem Cell Transplant Outcomes in Both Autologous and Allogeneic Transplants: A Systematic Review. *Nutrition and Cancer.* 2022;74(8):2731-2747.
46. Seguy D, Hueso T. Nutritional interventions in patients with graft versus host disease. *Curr Opin Clin Nutr Metab Care.* 2023;26(5):455-462.
47. Madsen K, Lee K, Chen S, et al. Weight loss post-allogeneic stem cell transplant is associated with increased transplant-related mortality. *Supportive Care in Cancer.* 2023;31:564.
48. Muratore E, Leardini D, Baccelli F, et al. Nutritional modulation of the gut microbiome in allogeneic hematopoietic stem cell transplantation recipients. *Front. Nutr.* 2022;9:993668.
49. Stein-Thoeringer C, Nichols K, Lazrak A, et al. Lactose drivers Enterococcus expansion to promote graft-versus host disease. *Science.* 2019;366:1143-9
50. Aoyama T, Notsu A, Ichimaru K, et al. Impact of Body Mass Index on 5-Year Survival Rates in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. *Nutrition and Metabolic Insight*s. 2022;15:1-8.

Microbially Contaminated or Non-Conforming Cellular Therapy Products

Presented by: Andrew Daly

Summary

Upon notification of a potentially or confirmed microbially-contaminated or otherwise non-conforming cellular therapy product the *recipient's transplant physician* will:

- Notify the recipient of the non-conformance and ensure the recipient receives follow up care/treatment to reduce risks associated with the non-conforming product. This will be documented in the recipient's medical record.
- Notify the donor transplant physician.
- Notify the Program Quality Manager.
- Notify Cellular Therapy Lab (if not yet notified). CTL will initiate non-conforming product investigation according to applicable SOP's.
- In the case that the donor is an unrelated donor the physician will contact the Canadian Blood Services Stem Cell Registry Case Manager on call at (613) 260-6800. Registry personnel must notify the transplant centre of the non-conformance.

Upon notification of a potentially or confirmed microbially-contaminated or otherwise non-conforming cellular therapy product the *donor's transplant physician* will:

- Notify the donor of the positive microbial result. Ensure the donor receives follow up care if applicable. This discussion shall be documented in the donor's medical record and the donor's regular physician should be advised.

Background

Despite rigorous quality control and adherence to good manufacturing practices, cellular therapy products (CTPs) may occasionally fail to meet the high standards set for cellular therapy. These products may still be suitable for use, and in most cases are the most appropriate products for the patient. The purpose of these guidelines is to ensure notification and appropriate follow-up of the donor and recipient of these products, notification of the donor and recipient physicians and to ensure notification of regulatory agencies. These guidelines are also intended to standardize the management of patients receiving non-conforming products, in accordance with the foundation for accreditation of cellular therapy (FACT) standards.

Non-conforming products include but are not limited to products with the following types of deficiencies:

1. Those with potential or proven microbial contamination
    - Positive microbial testing
    - Cracked or damaged storage bag
    - Improper transport or storage
    - CTP variance at time of infusion

2. Those with increased potential for infusion-related adverse events
    - Failed release criteria (clots, clumps, abnormal colour)
    - Deficiencies or errors in processing

3. Those that increase risk of engraftment failure
    - Low cell dose
    - Improper storage or handling

The identification of any of the above situations will require the following protocol(s) to be followed:

1. *For cellular therapy products with potential or proven microbial contamination:*
    a. A non-conforming product investigation will be initiated by the Cellular Therapy Laboratory.
    b. The recipient and donor transplant physicians shall be informed of the positive culture result or a potentially contaminated product, and this discussion shall be documented in the medical record.
    c. In the case of allogeneic cellular therapy products with positive microbial cultures, the donor physician shall be advised of the positive result in order that he or she can arrange appropriate follow-up of the donor.
    d. All products will have aerobic, anaerobic and fungal cultures drawn and kept in culture for 5-14 days to allow isolation of fastidious organisms. This should be indicated on the requisition.
    e. Patients should receive a dose of Vancomycin before infusion of the product, with further doses based upon results of repeat cultures, likelihood of falsely positive cultures and the patient's clinical status.
    f. Daily blood cultures will be drawn from the patient for a minimum of 3 days after infusion of the cellular therapy product.
    g. Fevers should be managed according to appropriate guidelines, with repeat blood cultures drawn according to guidelines for management of febrile neutropenia or based on advice of the infectious disease consultant.

h. The potential for infusion of a microbially- or endotoxin-contaminated cellular therapy product should be considered in patients with flushing, high fever (> 2 degree C rise from baseline), rigors, confusion or circulatory collapse shortly after infusion and appropriate management instituted. Appropriate antibiotic treatment should be initiated and an infectious disease consult called as needed.
i. Canadian Blood Services Stem Cell Registry must be informed immediately of positive microbial test results on products collected for distribution outside the ABMTP. They can be reached by calling the Registry On Call Case Manager at (613) 260-6800.

2. *For cellular therapy products with increased potential for infusion-related adverse events:*
   a. A non-conforming product investigation should be initiated by CTL for products that fail to meet release criteria or when a deficiency or error occurs during processing.
   b. The patient should be advised of the product variance and of any action to mitigate risk (such as increased premedication or monitoring post-infusion). This should be documented in the patient's medical record.

3. *For cellular therapy products with higher risk of engraftment failure:*
   a. Inform the Cellular Therapy Laboratory and Workup Nurse of the deficiency.
   b. Inform the patient and the transplant physician of the risk of engraftment failure and any action that may be taken to decrease the risk (such as early infusion of a new cellular therapy product or enhanced monitoring for engraftment failure). Document this discussion in the patient's medical record.

Appendices

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Autologous Transplant

TEST	2 wk	4 wk	6 wk	8 wk	11 wk	12 wk
Standard post auto SCT blood work: CBC & Diff, EP, Creatinine, ALT, Alk Phos, LDH, Bili, Mg	Frequency to be done in accordance with physician clinic assessment					
SPEP and serum Immunofixation (MM pt.'s only)					X	
Quantitative Immunoglobulins (IgG, IgA,IgM)						X
PFT *Do at 6 weeks post-SCT if patient has received BCNU			X	Physician directed		
Bone Marrow Asp/Bx **as ordered by physician.** Myeloma: Restage between Day + 80-90 (11 wk)					X	
IRS Study (Storek Lab) Autoimmune patients only Notify BMT Clinical Research RN if pt. relapses	See Connect Care story board for "Research Participant" banner. If banner noted, see "SnapShot" found under "Chart Review" for research time points and specific dates of blood draws.					
Myeloma only: 24-hr urine testing for: creat clearance, T. protein, UPEP, Immunofixation **as ordered by physician.** Myeloma: Restage between Day + 80-90 (11 wk). Do not repeat at 12 wk.					X	
Myeloma only: Free Light Chain (Serum) If non secretory myeloma or light chain disease only					X	
Skeletal Survey: Myeloma Only **as ordered by physician.**					X	
AFP, Beta HCG (Testicular) Germ Cell Tumors					X	
Amyloid • Serum testing for: Troponin T, FLC, alk phos, albumin • 24hr urine testing for: UPEP, SPEP, creat clearance • Other: echocardiogram, Bone Marrow Asp/Bx At 1y, 2y, 3y, 5y, and then every 5 years post transplant (10y, 15y, etc).					X	
VRE/MRSA surveillance swabs	Frequency of swabs directed as per Infection Prevention and Control however ordered under the BMT Attending physician					

TEST	2 wk	3 wk	4 wk	5 wk	6 wk	7 wk	8 wk	9 wk	10 wk	11 wk	12 wk	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
CD4, TSH, lipid panel, A1C **Females:** FSH, LH, estradiol **Males**: testosterone																				x
Autoimmune Only (i.e. Multiple Sclerosis, Scleroderma, Myasthenia Gravis)																				
CMV PCR (Prov lab)	x	x	x	x	x	x	x	x	x	x	x									
EBV PCR (Prov lab)	x	x	x	x	x	x	x	x	x	x	x									
CBC & Diff, EP, Creatinine, ALT, Alk Phos, LDH, Bili	x	x	x	x	x	x	x	x	x	x	x									

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Autologous Transplant

TEST	Monthly	6 mo	12 mo	Every 3 mo	Every 6 mo	Yearly	24 mo	3 Years	q5 Years
CBC & Diff, EP Weekly during RT.		X	X		X				
Creatinine, ALT, Alk Phos, LDH, Bili		X	X						
Quantitative Immunoglobulins (IgG, IgA,IgM)		X	X	X					
SPEP *Patients with M-protein detected in past, SPEP and CBC & Diff should be done every 3 months		X	X		X				
Myeloma Only: SPEP, UPEP, Serum Free Light Chains, Calcium				X					
Bone Density Six to twelve months post ASCT. Start bisphosphonate therapy if significant bone loss			X						
CT (Lymphoma) <u>as ordered by physician.</u>		X							
Non-live vaccinations and COVID-19 and influenza vaccinations due (Alberta Health Wellness Guidelines) - Send referral to Population and Public Health - Provide approval letter to patient and instruct them to book appointment.		X							
Live vaccine clearance due (Alberta Health Wellness Guidelines) - Provide approval letter to patient and instruct them to book appointment.							X		
Other Immunization Serology (Prov Lab) - Anti-tetanus, measles (ALL pts) -,Rubella (only in women in childbearing potential years) -Anti-HBs (only if pt. is a health care worker or has lifestyle risks) Monitor immunization serology for booster requirements and obtain order from primary physician. Provide patient with *Booster Dose(s) Required letter*								X X	
IRS Study (Storek Lab) - Autoimmune patients only Notify BMT Clinical Research RN if pt. relapses		See EMR for "Research Participant" banner. If banner noted, see "SnapShot" found under "Chart Review" for research time points and specific dates of blood draws.							

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Allogeneic Transplant

TEST	WEEK									MONTHLY								YEARLY				
	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12	24	q1y	q3y	q5y
CBC, Differential Note: Retics (physician directed)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
If pt on CSA (Levels to be stopped once taper has begun). Begin taper @ Day +56 - off by Day +84, except for Aplastic Anemia. (Physician directed)	x	x	x	x	x	**As directed by physician**																
If pt on Tacrolimus (Levels to be stopped once taper has begun).). Begin taper @ Day +56 - off by Day +84, except for Aplastic Anemia. (Physician directed)	x	x	x	x	x	**As directed by physician**																
EP, Creat, Liver panel 1, Mg, Random Glucose (if on steroids)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
CMV PCR (Prov Lab)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
EBV PCR (Prov Lab)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Ferritin, Transferrin saturation,									x									x				
IgG, IgM, IgA									x			x						x	x		x	
Hemoglobin A1C and lipid profile																		x				
TSH																		x	x	x		

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Allogeneic Transplant

TEST	WEEK									MONTHLY								YEARLY				
	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12	24	q1y	q3y	q5y
Non-live vaccinations and COVID-19 and influenza vaccinations due (Alberta Health Wellness Guidelines) -Send referral to Population and Public Health - Provide approval letter to patient and instruct them to book appointment.												x										
Live vaccine clearance due (Alberta Health Wellness Guidelines) -Provide approval letter to patient and instruct them to book appointment																			x			
Immunization serology (Prov Lab) Order the following blood work: -Anti-tetanus, measles (all pts.) - Rubella (only women in child bearing potential years) - Anti-HBs (only if pt. is a health care worker or has lifestyle risks) Monitor immunization serology for booster requirements, if required obtain order from primary physician and provide patient with *Booster Dose(s) Required letter*																					x x	
Hormones testing Males : Free Testosterone (sex hormone binding globulin. To be done between 7 and 10am.) Females: FSH/LH/estradiol																		x				

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Allogeneic Transplant

TEST	WEEK									MONTHLY								YEARLY				
	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12	24	q1y	q3y	q5y
Pharmacist –post-transplant medication review									x									x				
Cardiovascular Risk Assessment																		x				
IRS and Predictors of Relapse (Storek Lab)	See EMR for Research Participant banner. If patient flagged as “Research participant”, see “SnapShot” found under “Chart Review” for research time points and specific dates of blood draws.																					

Notify BMT Clinical Research RN if:
- pt. has relapsed *sample to be collected at time of relapse
- pt. has graft failure
- pt. has PTLD (only if requires an admission)
- pt. has secondary malignancy

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Allogeneic Transplant

TEST	WEEK									MONTHLY								YEARLY				
	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12	24	q1y	q3y	q5y
Bone Density (Spine and Hip) *Physician directed, consider if patient has been on steroids																		x *				
Ophthalmology Follow-up *Calgary pts: RN to instruct pt. to arrange									x													
Schirmer's Testing									x			x			x			x				
Gynecology Follow-up *Calgary pts. :RN to instruct pt. to arrange												x										
Dental *Dental: TBB @3mths for Calgary pts., TBB@4mths for Edmonton pts. *Calgary pts.: RN to instruct pt. to arrange									x *	x *												
Bone Marrow Aspirate +/- Biopsy Order as directed by physician Do NOT order chimerism on marrow (routine chimerism is performed on blood, not marrow).									x													

Alberta Health Services

Alberta Blood and Marrow Transplant Program
Follow-up Guidelines: Post-Allogeneic Transplant

TEST	WEEK									MONTHLY								YEARLY				
	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12	24	q1y	q3y	q5y
Blood for Molecular Studies Order as directed by physician Example: bcr/abl, PML/RAR, FLT3, and *Suggested interval for testing however frequency may be physician directed								x*			x*				x*		x*		x*	Then yearly		
Blood for Chimerism (CD3 cells, and malignancy lineage/phenotype cells)									x													
CT chest/abdomen/pelvis – only lymphoma or CLL *if no prior CR confirmed									X*									x				
CXR (if abnormal PFT)										x												
PFT *ONLY required if history of acute or chronic GVHD* *Edmonton patients booked @ CCI on return visit (unless delayed return)									x*			x			x			x	Yearly for the first 5 years			
VRE/MRSA surveillance swabs	Frequency of swabs directed as per Infection Prevention and Control however ordered under the BMT Attending physician																					
Multiple Myeloma: Calcium, SPEP, UPEP, Free Light Chain			x					x			x			x			x		x			
Multiple Myeloma: Skeletal survey								x									x			x		

TEST / ASSESSMENT / PROCEDURE	3 wk	4 wk
Standard post CAR T-cell blood work: CBC and differential, electrolyte panel, calcium, magnesium, creatinine, ALT, alkaline phosphate, albumin, LDH, total bilirubin, uric acid, c-reactive protein, ferritin	Frequency done in accordance with physician clinic assessment	

Weekly assessment by ABMTP physician
• History and physical
• Labs (as above)
• Cytokine Release Syndrome (CRS) and Neurotoxicity Assessment **(BOTH NURSING AND PHYSICIAN SECTIONS)**
  ○ CRS/Neurotoxicity Assessment Flowsheet
  ○ Neurotoxicity Monitoring BMTF70007
	To be completed at minimum weekly.	

Additional non-MD nursing visits (1-2x/week at ABMTP physician discretion)
• Labs (as above)
• Cytokine Release Syndrome (CRS) and Neurotoxicity assessment **(NURSING SECTION ONLY)**
  ○ Cytokine Release Syndrome (CRS) and Neurotoxicity Monitoring Flowsheet
  ○ Neurotoxicity Monitoring BMTF70007
	Physician directed	

Antimicrobial prophylaxis - Septra & Valtrex	As per Standard Practice Manual for Hematopoietic Cell Therapy (HCT)	
Growth factor support	Physician directed	
Bone marrow aspirate & biopsy (morphology, flow cytometry and cytogenetics) Leukemia disease Surveillance *(can be done day 28-32)*		X
Computerized Tomography (CT) Scan Lymphoma disease surveillance *(can be done day 28-32)*		X
MRSA surveillance swabs	Frequency of swabs directed as per Infection Prevention and Control (IPC), however ordered under the ABMTP physician	

TEST / ASSESSMENT / PROCEDURE	2 mo	3 mos	Q 1-3 mo	12 mo
Labs: CBC and differential, electrolyte panel, calcium, magnesium, creatinine, ALT, alkaline phosphate, albumin, LDH, total bilirubin, uric acid, Immunoglobulins (IgG, IgA, and IgM),	X	X	X	X
CD4, TSH, lipid panel, A1C Females: FSH, LH, estradiol Males: testosterone				X
B-cell aplasia bloodwork ***Leukemia disease ONLY*** • Flow cytometry (peripheral blood) - Immunodeficiency screening panel		X	Mos 6 & 9	X
Physician clinic assessment – minimum recommendation as per schedule • History and physical • Labs (as above)	X	X	X	X

Cytokine Release Syndrome (CRS) and neurotoxicity assessment
• To be done in accordance with physician clinic assessment
• The following methods are appropriate options for CRS/Neurotoxicity assessment as per physician direction.
  ○ Connect Care Cytokine Release Syndrome (CRS) and Neurotoxicity Monitoring Flowsheet
  ○ Neurotoxicity Monitoring – Handwriting monitoring (see appendix for example)
  ○ American Society for Transplantation and Cellular Therapy (ASTCT) Practice Guidelines App
	Physician directed
	No longer recommended after 8 weeks			

Growth factor support	Physician directed			
Antimicrobial prophylaxis - Septra & Valtrex	As per Standard Practice Manual for HCT			
Intravenous immunoglobulin (IVIg) replacement	Physician directed			
Positron emission tomography/ computerized tomography (PET/CT) scan: disease status assessment lymphoma – to be ordered by ABMTP physician		X		
Bone marrow aspirate & biopsy (morphology, flow cytometry and cytogenetics): Disease status assessment Leukemia - (ONLY required if abnormal at 4 week period)		X		
COVID-19 and Influenza vaccination Due (Alberta Health Wellness Guidelines) - Provide approval letter to patient and instruct them to book appointment		X		

TEST / ASSESSMENT / PROCEDURE	6 mo	Yearly	24 mo	3 Years	Years 2-15
Assessment as directed by physician (minimum 1/year)		X			
Antimicrobial prophylaxis • Septra & Valtrex	As per Standard Practice Manual for HCT				
Immunization Serology in All Patients (Prov Lab) - Anti-tetanus - Measles - Rubella - Anti-HBs	X		X		
Non-live vaccinations due (Alberta Health Wellness Guidelines) - Send referral to Population and Public Health - Provide approval letter to patient and instruct them to book appointment.	X				
Live vaccine clearance due (Alberta Health Wellness Guidelines) - Provide approval letter to patient and instruct them to book appointment.			X		
Diseases Surveillance - Discretion of Physician					X

Appendix

Patient Label

Alberta Blood and Marrow Transplant Program
Neurotoxicity Monitoring – Handwriting Assessment

Instructions:
Handwriting assessment for neurotoxicity shall be completed as part of the **Neurotoxicity 10 Point Assessment (ICE)** within the CRS/Neurotoxicity Assessment flowsheet within the patient's Electronic Medical Record (EMR).

An alternate sentence may be used with patients when English is not their first language or utilize Neurotoxicity Monitoring – Modified Handwriting Assessment BMTF70033 for persons with literacy issues.

Monitoring Frequency: As per physician orders

Write the following sentence: **The leaf on the Canadian flag is red.**

Date	Time		RN Initials
	Time		RN Initials
	PRN		RN Initials

Date	Time		RN Initials
	Time		RN Initials
	PRN		RN Initials

Date	Time		RN Initials
	Time		RN Initials
	PRN		RN Initials

Date	Time		RN Initials
	Time		RN Initials
	PRN		RN Initials

Date	Time		RN Initials
	Time		RN Initials
	PRN		RN Initials

Abbreviations

2-CDA, 2-chlorodeoxyadeno-sine; AAIPI, age-adjusted international prognostic index; ABG, arterial blood gas; ABMTP, Alberta Bone Marrow Transplant Program; ABMTR, Alberta Bone Marrow Transplant Registry; ABVD, adriamycin + bleomycin + vinblastine + dacarbazine; ABW, actual body weight; ACA, additional cytogenetic abnormalities OR anti-centromere antibody (depending on section); ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; ADL, activities of daily living; aGVHD, acute graft-versus-host-disease; AIBW, adjusted ideal body weight; AILD, angioimmunoblastic lymphadenopathy with dysproteinemia; AITL, angioimmunoblastic T-cell lymphoma; AL, amyloid light-chain; ALCL, anaplastic large cell lymphoma; Alem, alemtuzamab; Alk p, alkaline phosphatase; ALL, acute lymphoblastic leukemia; alloSCT, allogenic stem cell transplant; ALT, alanine transaminase / alanine aminotransferase; ALT, adult T-cell lymphoma; AMBd, amphotericin B deoxycholate; AML, acute myeloid leukemia; ANA, antinuclear antibody; ANC, absolute neutrophil count; AP, accelerated phase; APC, antigen presenting cells; aPML, acute promyelocytic leukemia; ARR, annual relapse rate; ARS, antigen recognition site; ASBMT, American Society for Blood and Marrow Transplantation; ASCO, American Society of Clinical Oncology; ASCT, allogeneic stem cell transplantation OR autologous stem cell transplantation (dependent upon section); AST, aspartate aminotransferase OR alanine aminotransferase (dependent upon section); ATG, antithymocyte globulin; AUC, area under the curve; autoSCT, autologous stem cell transplant; BAL, bronchoalveolar lavage; BAT, best-available therapy; BC, blast crisis; BCLL, B-cell chronic lymphocytic leukemia; BCR, B-cell receptor; BCT, blood cell transplantation; BEAC, BCNU + etoposide + Ara-C + cyclophosphamide; BEAM, BCNU + etoposide + AraC + melphalan; BEAU, BCNU + etoposide + Ara-C + cyclophosphamide; BL, Burkitt lymphoma; BM, busulfan + melphalan; BMA, bone marrow aspirate; BMD, bone mineral density; BMT, bone marrow transplantation; BOOP, bronchiolitis obliterans organizing pneumonia; BP, blast phase; BSA, body surface area; Bu, busulfan; BuCy, busulfan + cyclophosphamide; CA, cytogenetic abnormalities; CAP, cyclophosphamide + doxorubicin + prednisone; CAR-T, chimeric antigen receptor T-cells; CBC, complete blood count; CBF, core binding factor; CCR or CCyR or CCgR, complete cytogenetic response; CDC, Centers for Disease Control and Prevention; CEB or CBV, cyclophosphamide + etoposide + carmustine; cGVHD, chronic graft-versus-host-disease; CHF, congestive heart failure; CHF, congestive heart failure; CHOP, cyclophosphamide + adriamycin + vincristine + prednisone; CHR, complete hematologic response; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CK, creatine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CMR, complete molecular response; CMV, cytomegalovirus; CN, cytogenetically normal; CNI, calcineurin inhibitor; CNS, central nervous system; CP, chronic phase; CR, complete remission/response; CR1, 1st complete remission; CR2, second complete response; CRBSI, catheter-related bloodstream infection; CRe, early complete remission; CRel, correctly released; CREST, calcinosis of skin, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, teleangiectasia; CRS, cytokine release syndrome; Csa, cyclosporine; CSF, cerebrospinal fluid; CT, computerized tomography; CVAMP, cyclophosphamide + vincristine + doxorubicin + methylprednisolone; CVC, central venous catheter; Cy, cyclophosphamide; CyA-Mtx, cyclosporine + methotrexate; Cy-ATG, cyclosporine + antithymocyte globulin; CyR, cytogenetic response; CyTBI or VPCyTBI, cyclophosphamide and possible etoposide (VP-16); DEXA scan, dual energy X-ray absorptiometry; DFS, disease-free survival; DHAP, dexamethasone + Ara-C (cytarabine) + cisplatin; DICEP, dose-intensified cyclophosphamide 5.25 g/m2, etoposide 1.05g/m2, and cisplatin 105 mg/m2; DIPSS, Dynamic International Prognostic Scoring System; DLBCL, diffuse large B-cell lymphoma; DLCO, diffusing capacity of lung for carbon monoxide; DLI, donor lymphocytic infusion; DMT, disease modifying therapy; DSA, donor specific antibodies; DVT, deep vein thrombosis; EBER, EBV-encoded RNA; EBMT, European Group for Blood and Marrow Transplantation; EBMTR, European Bone Marrow Transplant Registry; EBV, Epstein-Barr virus; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ECP, extracorporeal photopheresis; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; ED, erectile dysfunction; EDSS, expanded disability status scale; EFS, event-free survival; EGD, upper endoscopy; ELN, European LeukemiaNet; ENT, ear, nose, and throat; ESR, erythrocyte sedimentation rate; ET, essential thrombocythemia; EVIL, European Conference on Infections in Leukemia; FAB, French-American-British; FCA, fludarabine + Cy-ATG; FCR, fludarabine + cyclophosphamide + rituximab; FEV1, forced expiratory volume in one second; FFS, freedom from second failure OR failure-free survival (depending on chapter); FHF, fulminant hepatic failure; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; FLU, fludarabine; FLUBU, fludarabine + busulfan; FND, fludarabine + mitoxantrone + dexamethasone; FSH, follicle stimulating hormone; FSS, functional system scores; FTBI, fractionated total body irradiation; FVC, forced vital capacity; GB, gallbladder; GCSF, granulocyte colony stimulating factor; GD, gadolinium; GDP, gemcitabine + dexamethasone + cisplatin; GI, gastrointestinal; GM-CSF, granulocyte-macrophage colony-stimulating factor; GnRH, gonadotropin-releasing hormone; GVH or GVHD, graft-versus-host or graft-versus-host disease; GVL, graft-versus-leukemia; HAMA, human anti-mouse antibodies; HAP, hospital acquired pneumonia; hATG, horse ATG; Hb, hemoglobin; Hb S, sickled hemoglobin; HBeAg, hepatitis B viral protein; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCT/HSCT, hematopoietic stem cell transplantation; HCT-CI, Hematopoietic cell transplantation comorbidity index; HCV, hepatitis C virus; HDCT/HDT, high-dose chemotherapy; HHV6, human herpes virus 6; HiDAC, high dose Ara-c; HLA, human leukocyte antigens; HLA-DSA, donor-specific HLA antibodies; HMPV, human metapneumovirus; HR, hazard ratio; HRT, hormone replacement therapy; HSV, herpes simplex virus; HTLV-1, Human T-cell lymphoma virus type 1; IBMTR, International Bone Marrow Transplant Registry; IBW, ideal body weight; ICE, ifosfamide + carboplatin + etoposide; ICSI, intracytoplasmic sperm injection; ICU, intensive care unit;

IFI, invasive fungal infection; IL-2, interleukin-2; INR, international normalized ratio; IPI, international prognostic index; IPS, idiopathic pneumonia syndrome; IPSS, International Prognostic Scoring System; IRAEs, infusion-related adverse events; IST, immunosuppressive therapy; ITD, internal tandem duplication; ITT, intent-to-treat; IV, intravenous; IVIMG or IVIG, intravenous immunoglobulin; JAK, Janus Kinase; KGF, keratinocyte growth factor; KIR, killer-cell immunoglobulin like receptor; KPS, Karnofsky Performance Scale; KSAV, Kaposi's sarcoma-associated virus; L ampho B, liposomal amphotericin B; LBCL, large B-cell lymphoma; LBL, lymphoblastic lymphoma; LDH, lactate dehydrogenase test; LDHD, lymphocyte depletion Hodgkin disease; LES, lower esophageal sphincter; LFS, leukemia-free survival OR lung function score (dependent upon section); LH, luteinizing hormone; LMWH, low molecular weight heparin; LP, lumbar puncture; LPHD, lymphocyte predominant Hodgkin disease; LPL, lymphoplasmacytic lymphoma; LPS, Lansky Performance Status; LRCHD, lymphocyte-rich classical Hodgkin disease; LVEF, left ventricular ejection fraction; MALT, mucosa-associated lymphoid tissue; MBL, metallo-betalactamase; MCHD, mixed cellularity Hodgkin disease; MCL, mantle cell leukemia/lymphoma; MCR or MCyR, major cytogenetic response; MDS, Myelodysplasia / myelodysplastic syndrome; MEL, melphalan; MeVPTBI, melphalan + etoposide with or without TBI; MHC, major histocompatibility complex; miHAs, minor histocompatibility antigens; MK, monosomal karyotype; MM, mismatched; MMF, mycophenolate mofetil; MMR, major molecular response; MMRD, mismatched related donor; MP, melphalan + prednisone; MPD, methylprednisolone; MPT, melphalan + prednisone + thalidomide; MRC, Medical Research Council; MRD, minimal residual disease; MRel, mistakenly released; MRI, magnetic resonance imaging; MRSA, methicillin-resistant Staphylococcus aureus; mRSS, modified Rodnan skin score; MS, Multiple Sclerosis; MSD, matched sibling donor; MSKCC, Memorial Sloan-Kettering Cancer Center; mTOR, mammalian target of rapamycin; MTX, methotrexate; MUD, matched unrelated donor; MUGA, multiple gated acquisition scan; MZL, marginal zone lymphoma; NBTE, nonbacterial thrombotic endocarditis; NCCN, National Comprehensive Cancer Network; NHL, non-Hodgkin lymphoma; NK, natural killer cells; NMDP, National Marrow Donor Program; NOS, not otherwise specified; NR, no response; NRM, non-relapse mortality; NSAID, nonsteroidal anti-inflammatory drugs; NSHD, nodular sclerosis Hodgkin disease; NST, non-myeloablative conditioning; NT-proBNP, N-terminal propeptide brain-type natriuretic peptide; OR, odds ratio; ORR, overall response rate; OS, overall survival; PA, posterior-anterior; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PBPC, peripheral blood progenitor cells; PBSC, peripheral blood stem cells; PCNSL, primary central nervous system lymphoma; PCP, Pneumocystis jirovecii pneumonia; PCR, Polymerase chain reaction; PDGFR, platelet-derived growth factor receptor gene; PE, pulmonary embolism; PET, positron-emission tomography; PFS, progression-free survival; PFT, pulmonary function test; PHN, post-herpatic neuralgia; PICC, peripherally inserted central catheter; PK, Pharmacokinetics; PMF, primary myelofibrosis; PML, progressive multifocal leukoencephalopathy; PMLCL, primary mediastinal large B-cell lymphoma; PNH, paroxysmal nocturnal hemoglobinuria; PPI, proton pump inhibitor; PR, partial response/remission; Pred, Prednisone; PT, prothrombin time; PTCL, peripheral T-cell lymphoma; PTCy, post-trasnplantation cyclophosphamide; PTLD, Post-transplant lymphoproliferative disorder; PTT, partial thromboplastin time; PUD, peptic ulcer disease; PV, polycythemia vera; QID PO, four times a day per os (orally); QOL, quality of life; Q-PCR, quantitative polymerase chain reaction; R, rituximab; rATG, rabbit ATG; R-CHOP, rituximab + cyclophosphamide + Adriamycin + vincristine + prednisone; RCT, randomized controlled trial; RCVP, rituximab + cyclophosphamide + vincristine + prednisone; R-DHAP, rituximab + dexamethasone + Ara-C (cytarabine) + cisplatin; RFCM, rituximab + fludarabine + cyclophosphamide + mitoxantrone; RFND, rituximab + fludarabine + mitoxantrone + dexamethasone; RFS, relapse-free survival; RI, reduction of immunosuppression; RIC, reduced intensity conditioning; R-ICE, rituximab + ifosfamide + carboplatin + etoposide; RIST, Reduced intensity SCT; RIT, radioimmunoconjugate therapy; RPLS, reversible posterior leukoencephalopathy syndrome; RR, response rate; RRMS, relapsing-remitting multiple sclerosis; RSV, respiratory syncytial virus; SAA, severe aplastic anemia; SAAIPI, Salvage Age Adjusted International Prognostic Index; SCA, sickle cell anemia; SCD, sickle cell disease; SCID, severe combined immunodeficiency; SCT, stem cell transplant; SDCT, standard-dose chemotherapy; SDH, subdural hematoma; sIPI, second-line International Prognostic Index; SIRS, systemic inflammatory response syndrome; SLL, small lymphocytic leukemia; SOS, sinusoidal obstruction syndrome; SSc, systemic sclerosis; STPR, skin thickness progression rate; STR, short tandem repeat; SWOG, Southwest Oncology Group; T2/FLAIR, T2-weighted-fluid-attenuated inversion recovery; Tac, tacrolimus; t-AML, therapy-related AML; TBC, thiotepa + busulfan + cyclophosphamide; TBI, total body irradiation; TEE, transesophageal echocardiography; TGF-β, transforming growth factor beta; TIPS, transjugular intrahepatic portosystemic shunt; TKI, tyrosine kinase inhibitor; TMA, thrombotic microangiopathy; TMP-SMX, co-trimoxazole (Septra ®, Bactrim ®); TNC, Total nucleated cell; TRM, transplant-related mortality or treatment-related mortality; Trv, tricuspid regurgitant velocity; TSH, thyroid stimulating hormone; TTA, time to antibiotic; TTP, time to positivity; UCBT, umbilical cord blood transplantation; UGI, upper gastrointestinal series (test); ULN, upper limit of normal; URTI, upper respiratory tract infection; UV, ultraviolet; VAD, vincristine + adriamycin + dexamethasone; VGPR, very good partial response; VOD, veno-occlusive disease; VP-16, etoposide; VRE, vancomycin-resistant Enterococcus; VRSA, vancomycin-resistant Staphylococcus aureus; VUD, volunteer unrelated donor; VZV, varicella zoster virus; WBC, white blood cell; WBRT, whole-brain radiotherapy; WHO, World Health Organization; WMUD, 'well matched' unrelated donor; WPSS, World Health Organization Prognostic Scoring System; -X or –Y, deleted X or Y chromosome.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Bone Marrow and Blood Cell Transplant Program and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Copyright © (2024) Alberta Health Services

This copyright work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivative 4.0 International license. You are free to copy and distribute the work including in other media and formats for non-commercial purposes, as long as you attribute the work to Alberta Health Services, do not adapt the work, and abide by the other license terms. To view a copy of this license, see https://creativecommons.org/licenses/by-nc-nd/4.0/.

The license does not apply to AHS trademarks, logos or content for which Alberta Health Services is not the copyright owner.

Funding Source

Financial support for the development of CancerControl Alberta's evidence-based clinical practice guidelines and supporting materials comes from the CancerControl Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Generated using the standard COI form.

Dr. Nizar Bahlis

Dr. Sara Beattie has nothing to disclose.

Dr. Ahsan Chaudhry has nothing to disclose.

Dr. Andrew Daly has nothing to disclose.

Dr. Peter Duggan has nothing to disclose.

Dr. Michelle Geddes reports personal fees from Celgene, personal fees from Jazz, personal fees from novartis, outside the submitted work.

Rebecca Holmes has nothing to disclose

Dr. Kareem Jamani has nothing to disclose.

Dr. Catherine Leyshon has nothing to disclose.

Dr. Nicole Prokopishyn has nothing to disclose.

Dr. Lynn Savoie reports other from Abbvie, Amgen, Pfizer, Novartis, Jazz, Astellas, Paladin, outside the submitted work.

Dr. Mona Shafey has nothing to disclose.

Dr. Russell Sterrett reports honoraria from Abbvie for presentations outside the submitted work

Dr. Doug Stewart reports honoraria from Janssen, AstraZeneca, Gilead, Novartis, Roche, Sandoz, Seattle Genetics, Amgen, Apobiologix, Abbvie, and leadership on the Lymphoma Canada Scientific Advisory Board outside the submitted work.

Dr. Jan Storek has nothing to disclose.

Dr. Jason Tay has nothing to disclose.

Edward Walker has nothing to disclose

Caitlin Wallis has nothing to disclose

Revision History

Date	Topic Title	Action
July 6, 2011	Severe Aplastic Anemia: Indications for Stem Cell Transplantation	Updated
Sept 12, 2011	Management of Relapse after Stem Cell Transplantation	Updated
Sept 14, 2011	BCR-ABL1-Negative Myeloproliferative Neoplasms	New
Oct 4, 2011	Transplantation for CLL	Updated
Oct 5, 2011	Management of Chronic Graft Versus Host Disease	New
Oct 25, 2011	Chimerism and Its Uses	New
Dec 13, 2011	MDS and Secondary AML: Indications for Transplantation	Updated
Dec 13, 2011	Acute GVHD: Prevention and Treatment	Updated
Dec 13, 2011	Catheter-Related Complications	Updated
Dec 13, 2011	Head and Neck Complications, Including Mucositis	Updated
Dec 13, 2011	Donor Management, Including Mobilization	New
Jan 26, 2012	Fungal Infections Before, During and After Transplant	Updated
Jan 26, 2012	CMV and other Herpes Viruses	New
Mar 16, 2012	Acute GVHD: Prevention and Treatment	Updated
Mar 16, 2012	Workup and Treatment of Fever Post-Transplant	Updated
Mar 16, 2012	Cardiac Complications of Transplant	Updated
Mar 16, 2012	Umbilical Cord Blood Transplantation	New
July 27, 2012	CMV and other Herpes Viruses	Updated
Oct 17, 2012	Criteria for Donor Selection	Updated
Oct 17, 2012	GI Complications of Transplant	Updated
Oct 17, 2012	Urinary and Renal Complications	New
Oct 17, 2012	Epstein Barr Virus/Posttransplant Lymphoproliferative Disorder	New
Oct 17, 2012	Poor Graft Function and Engraftment Failure	New
Oct 17, 2012	Vaccination	New
Oct 17, 2012	Hepatic Complications and Viral Hepatitis	Updated
Oct 17, 2012	Therapeutic Drug Monitoring	New
Nov 12, 2012	Management of the ABO-Incompatible Graft and Recipient	New
Feb 5, 2013	CMV and other Herpes Viruses	Updated
Feb 5, 2013	Management of Chronic GVHD	Updated
Feb 5, 2013	Pneumocystis & Bacterial Prophylaxis	New
May 28, 2013	Donor Management, Including Mobilization	Updated
June 20, 2013	Vaccination	Updated
Aug 21, 2013	Catheter-Related Complications	Updated
Mar 13, 2014	Criteria for Donor Selection	Updated
Mar 14, 2014	Cord blood transplants	Updated
Mar 14, 2014	Acute GVHD, Prevention and Treatment	Updated
Mar 14, 2014	Criteria for Donor Selection	Updated
May 28, 2014	CMV, VZV, HSV, HHV6 (formerly CMV and other Herpes viruses)	Updated
Jul 22, 2014	Management of Chronic Graft Versus Host Disease	Updated
Oct 17, 2014	Distribution of Microbially-Contaminated or Non-Conforming Cellular Therapy Products	New

Oct 17, 2014	Pretransplant Conditioning	New
Nov 10, 2014	Autologous Hematopoietic SCT for Active Multiple Sclerosis	New
Nov 10, 2014	Transplantation for Acute Lymphoblastic Leukemia	Updated
Feb 18, 2015	Pneumocystis and Bacterial Prophylaxis	Updated
Feb 26, 2015	Pretransplant Conditioning	Updated
Feb 26, 2015	BCR-ABL1 Negative Myeloproliferative Neoplasms	Updated
Feb 26, 2015	Acute Myeloid Leukemia: Indications for Stem Cell Transplant	Updated
Feb 26, 2015	Hodgkin and Non-Hodgkin Lymphoma: Indications for Transplantation	Updated
Mar 17, 2015	Transplantation for Germ Cell Tumours	Updated
April 28, 2015	Hepatic Complications and Viral Hepatitis	Updated
Sep 8, 2015	CMV, VZV, HSV, HHV6	Updated
Sep 15, 2015	Epstein-Barr Virus/Posttransplant Lymphoproliferative Disorder	Updated
Nov 24, 2015	Pretransplant Conditioning	Updated
May 17, 2016	Transplantation for Scleroderma/Systemic Sclerosis	New
June 20, 2016	Epstein-Barr Virus / Posttransplant Lymphoproliferative Disorder	Updated
Nov 25, 2016	Hemoglobinopathies	New
Dec 9, 2016	Autologous Hematopoietic SCT for Active Multiple Sclerosis	Updated
Jan 3, 2017	Hematopoietic Cell Transplantation for Severe Aplastic Anemia	Updated
Jan 16, 2017	Acute GVHD: Prevention and Treatment	Updated
Jan 16, 2017	Acute Myeloid Leukemia	Updated
Jan 24, 2017	Chronic Lymphocytic Leukemia	Updated
Feb 8, 2017	Vaccination	Updated
Feb 8, 2017	Chronic GVHD	Updated
Feb 8, 2017	Pneumocystis & Bacterial Prophylaxis	Updated
Feb 9, 2017	CMV, VZV, HSV, HHV6	Updated
Aug 2, 2017	Epstein Barr Virus / Posttransplant Lymphoproliferative Disorder	Updated
Aug 2, 2017	Fungal Prophylaxis	Updated
Aug 2, 2017	Criteria for Donor Selection	Updated
Aug 2, 2017	Neutropenic Fever	Updated
Aug 2, 2017	Multiple Sclerosis	Updated
Sept 21, 2017	Patient Eligibility	New
Oct 2, 2017	Conditioning	Updated
Oct 10, 2017	EBV/PTLD	Updated
Jan 23, 2018	Chimerism	Updated
Feb 6, 2018	Therapeutic Drug Monitoring	Updated
Feb 27, 2018	Hodgkin and Non-Hodgkin Lymphoma: Indications for Transplantation	Updated
May 8, 2018	Relapse of Leukemia after Transplant	Updated
May 8, 2018	Acute Lymphoblastic Leukemia	Updated
May 8, 2018	Graft Failure and Poor Graft Function	Updated
May 8, 2018	ABO Incompatible Graft and Recipient	Updated
May 8, 2018	Chronic Graft Versus Host Disease	Updated
May 8, 2018	Myelodysplastic Syndromes	Updated
May 8, 2018	Reproductive System Complications Post-transplant	Updated

May 8, 2018	Hepatic Complications and Viral Hepatitis	Updated
May 8, 2018	BCR-ABL1-Negative Myeloproliferative Neoplasms	Updated
June 22, 2018	Transplantation for Chronic Myelogenous Leukemia	Updated
June 22, 2018	Scleroderma / Systemic Sclerosis	Updated
June 22, 2018	Transplantation for Germ Cell Tumours	Updated
June 22, 2018	Pretransplant Conditioning	Updated
June 22, 2018	Central Venous Catheter (CVC)-Related Complications	Updated
June 22, 2018	Vaccination	Updated
June 22, 2018	Umbilical Cord Blood Transplantation	Updated
June 22, 2018	Long-Term Follow-Up	New
Sep 28, 2018	Acute GVHD: Prevention and Treatment	Updated
Oct 15, 2018	Pneumocystis & Bacterial Prophylaxis	Updated
Jan 15, 2019	CAR T Cell Toxicity	New
Jan. 24, 2019	Vaccination	Edited
April 18, 2019	Stem Cell Mobilization (formerly Donor Management)	Updated
April 18, 2019	Multiple Sclerosis	Updated
April 18, 2019	CLL	Updated
April 18, 2019	Hemoglobinopathies	Updated
July 10, 2019	Transplant AML	Updated
July 10, 2019	Patient Eligibility	Updated
July 10, 2019	Fungal Prophylaxis	Updated
July 10, 2019	Infusion of Microbially-Contaminated or Non-Confirming Products	Updated
July 26, 2019	Infusion of Microbially-Contaminated or Non-Confirming Products	Updated
July 31, 2019	Hemoglobinopathies	Updated
July 31, 2019	CMV, VZV, HSV, HHV6	Updated
July 31, 2019	Hematopoietic Cell Transplantation for Severe Aplastic Anemia	Updated
July 31, 2019	Pretransplant Conditioning	Updated
Aug. 1, 2019	Scleroderma / Systemic Sclerosis	Edited
Aug. 1, 2019	Hepatic Complications and Viral Hepatitis	Updated
Aug. 7, 2019	CAR T Cell Toxicity	Updated
Oct. 7, 2019	Chronic GVHD	Updated
Oct. 24, 2019	Pretransplant Conditioning	Updated
Dec, 16, 2019	Donor Selection	Updated
Jan. 9, 2020	Systemic Sclerosis	Updated
Jan. 23, 2020	Nutritional Support	New
Jan. 23, 2020	Lymphoma	Updated
July 30, 2020	CML	Updated
July 30, 2020	Acute GVHD	Updated
July 30, 2020	Transfusions and Management of Cytopenias Early Post-HSCT	New
Sept. 23, 2020	Vaccination	Updated
Sept. 29, 2020	ALL	Updated
Oct. 20, 2020	Transfusions and Management of Cytopenias Early Post-HSCT	Updated
Dec. 2, 2020	Symptomatic Myeloma and AL Amyloidosis, formerly Plasma Cell Disorders	Updated
Dec. 2, 2020	Pneumocystis and Bacterial Prophylaxis	Updated

Dec. 2, 2020	Acute GVHD	Updated
Jan. 8, 2021	EBV/PTLD	Updated
Jan. 8, 2021	CAR T Cell Toxicity	Updated
Jan. 12, 2021	Umbilical Cord Blood Transplant	Updated
Jan. 18, 2021	Scleroderma/ Systemic Sclerosis (SSc)	Updated
Jan. 19, 2021	Multiple Sclerosis	Updated
Feb. 3, 2021	CLL	Updated
Mar. 16, 2021	DLI/2nd HCT Relapse, formerly Relapse	Updated
Mar. 23, 2021	Donor Selection	Updated
Mar. 30, 2021	Lymphoma	Updated
Apr. 12, 2021	Stem Cell Mobilization	Updated
Apr. 13, 2021	CVAD Complications, formerly CVC-Related Complications	Updated
April 21, 2021	ALL	Updated
May 27, 2021	Vaccination	Updated
May 27, 2021	Fungal Prophylaxis	Updated
May 27, 2021	Hepatic Complications and Viral Hepatitis	Updated
May 27, 2021	Hemoglobinopathies	Updated
May 27, 2021	Chimerism	Updated
June 8, 2021	CMV, VZV, HHV6	Updated
June 15, 2021	AML	Updated
July 5, 2021	Reproductive System Complications	Removed
July 7, 2021	Stem Cell Mobilization	Edited
July 7, 2021	Umbilical Cord Blood Transplant	Edited
July 12, 2021	Myelodysplastic Syndromes (MDS)	Updated
July 13, 2021	BCR-ABK-Negative Myeloproliferative Neoplasms	Updated
Aug 10, 2021	Distribution of Microbially-Contaminated or Non-Conforming Cellular Therapy Products	Updated
Aug 24, 2021	Transplantation Eligibility Assessment: Patient Factors	Updated
Sept 14, 2021	Long-Term Follow up	Updated
Oct 12, 2021	Graft vs Host Disease	New
Nov 2, 2021	Conditioning (formally Pretransplant Conditioning)	Updated
Nov 4, 2021	Acute GVHD	Removed
Nov 4, 2021	Chronic GVHD	Removed
Nov 4, 2021	Therapeutic Drug Monitoring	Removed
Dec. 8, 2021	Germ Cell Tumours	Updated
Dec. 14, 2021	Fever	Updated
Dec. 17, 2021	Vaccination	Edited
Feb. 8, 2022	Donor Selection	Updated
Mar. 2 2022	Vaccination	Edited
Apr. 26, 2022	Scleroderma/ Systemic Sclerosis (SSc)	Updated
Apr. 26, 2022	Vaccination	Updated
May 3, 2022	CML	Updated
May 25, 2022	Scleroderma/ Systemic Sclerosis (SSc)	Edited
May 25, 2022	Donor Selection	Edited
July 26, 2022	Fungal Prophylaxis	Updated

Sept. 13, 2022	Nutritional Support	Updated
Oct. 4, 2022	Pneumocystis and Bacterial Prophylaxis	Updated
Oct. 11, 2022	ALL	Updated
Oct. 25, 2022	Symptomatic Myeloma and AL Amyloidosis	Updated
Dec. 6, 2022	GVHD	Updated
Dec. 12, 2022	Scleroderma/ Systemic Sclerosis (SSc)	Edited
Jan. 24, 2023	CAR T Cell Toxicity	Updated
Jan. 31, 2023	Scleroderma/ Systemic Sclerosis (SSc)	Edited
Jan. 31, 2023	Conditioning	Updated
Feb. 1, 2023	CLL	Updated
Mar. 21, 2023	Aplastic Anemia	Updated
May 16, 2023	GVHD	Updated
May 23, 2023	ABO Incompatible Graft and Recipient	Updated
June 27, 2023	Transfusions and Management of Cytopenias Early Post-HSCT	Updated
Aug 3, 2023	Management of Transfusion and Cytopenias Post-HSCT	Edited
Aug 22, 2023	Transplantation Eligibility Assessment: Patient Factors	Updated
Sept. 26, 2023	DLI/2nd HCT	Updated
Oct. 3, 2023	Hemoglobinopathies	Updated
Oct. 19, 2023	Stem cell Mobilization	Updated
Nov. 7, 2023	Germ Cell Tumours	Updated
Nov. 21, 2023	Microbially-Contaminated or Non-Conforming Cellular Therapy Products	Updated
Nov. 22, 2023	Conditioning	Edited
Dec. 5, 2023	Hepatic Complications and Viral Hepatitis	Updated
Jan. 9, 2024	CMV, VZV, HHV6	Updated
Jan. 30, 2024	Transplantation Eligibility Assessment: Patient Factors	Updated
Feb. 6, 2024	Multiple Sclerosis	Updated
Feb. 13, 2024	AML	Updated
Mar. 5, 2024	Vaccination	Updated
Mar. 5, 2024	Long-Term Follow Up	Updated
Apr. 2, 2024	EBV/PTLD	Updated
May 7, 2024	CVAD Complications	Updated
May 28, 2024	Lymphoma	Updated
June 18, 2024	Graft Failure and Poor Graft Function	Removed
June 18, 2024	Chimerism	Removed
June 18, 2024	Graft Failure, Poor Graph Function, Chimerism	New
June 25, 2024	Hemoglobinopathies	Updated
July 15, 2024	Scleroderma/ Systemic Sclerosis (SSc)	Edited
July 23, 2024	Multiple Sclerosis	Updated
Aug. 6, 2024	Scleroderma/ Systemic Sclerosis (SSc)	Edited
Sept. 3, 2024	CML	Updated
Sept. 17, 2024	Symptomatic Myeloma and AL Amyloidosis	Updated
Sept. 24, 2024	Symptomatic Myeloma and AL Amyloidosis	Edited
Oct. 1, 2024	Donor Selection	Updated
Oct. 1, 2024	Umbilical Cord Blood Transplantation	Updated

Oct. 15, 2024	Nutrition Support	Updated
Nov. 5, 2024	Pneumocystis and Bacterial Prophylaxis	Updated
Nov. 12, 2024	Fever	Updated
Dec. 13, 2024	Stem Cell Mobilization	Edited
Jan. 21, 2025	Autologous Hematopoietic Cell Transplant in Systemic Sclerosis(SSc)	Updated
Feb. 26, 2025	Germ Cell Tumours	Edited