Alberta Bone Marrow and Blood Cell Transplant Program:
Standard Practice Manual
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Indications and Conditioning
Acute Myeloid Leukemia (AML)
Presented by: Lynn Savoie

Summary

- Disease risk stratification will be based on the cytogenetic and molecular features of the tumor cells, response to first induction, presence of secondary or therapy related disease and white blood cell (WBC) at diagnosis and measurable residual disease.
- Patients with favourable cytogenetics and no unfavorable molecular changes show good response to chemotherapy 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 a KIT mutation 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 response to consolidation chemotherapy 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 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, 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 extramedullary 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 chemotherapy 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 haematological 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, unfavorable and unknown cytogenetic risk groups

<table>
<thead>
<tr>
<th>Classification</th>
<th>SWOG Criteria</th>
<th>MRC Criteria (as for SWOG, except):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable</strong></td>
<td>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</td>
<td>t(8;21) – with any other abnormality</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>+8, -Y, +6, del(12p) normal karyotype</td>
<td>abnormal 11q23 del(9q),del(7q) – without other abnormalities Complex karyotypes (≥ 3 abnormalities, but &lt;5) All abnormalities of unknown prognostic significance</td>
</tr>
<tr>
<td><strong>Unfavourable</strong></td>
<td>-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)</td>
<td>Complex karyotypes (≥5 abnormalities)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>All other clonal chromosomal aberrations with fewer than 3 abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

Conventional induction chemotherapy for patients with non-promyelocytic AML consists of combination chemotherapy with an anthracycline and Cytarabine. In patients with a FLT3 mutation (see below), a FLT3 inhibitor is added. Patients with acute promyelocytic leukemia are offered induction with Arsenic trioxide and ATRA.
Table 2. Results with conventional chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Favourable Cytogenetics</th>
<th>Intermediate Cytogenetics</th>
<th>Unfavourable Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>80-90%</td>
<td>~70%</td>
<td>30-50%</td>
</tr>
<tr>
<td>DFS</td>
<td>70-85%</td>
<td>40-55%</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

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

Table 3. Relapse rates associated with post-remission therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allogeneic Transplant</th>
<th>Autologous Transplant</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIMEMA 1995</td>
<td>24%</td>
<td>40%</td>
<td>57%</td>
</tr>
<tr>
<td>GOELAM 1997</td>
<td>28%</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>MRC 1998</td>
<td>19%</td>
<td>35%</td>
<td>53%</td>
</tr>
<tr>
<td>ECOG/SWOG 1998</td>
<td>29%</td>
<td>48%</td>
<td>61%</td>
</tr>
</tbody>
</table>

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 CEBPA are associated with significantly better overall survival (OS) compared to patients with the wild-type loci. Mutations to FLT-3 confer inferior OS on patients who harbor these mutations. Similarly, while cytogenetic abnormalities that disrupt Core Binding Factor (t (8;21) and inv(16)) are typically associated with favourable outcomes with conventional therapies, the presence of mutations of c-Kit in these disorders confers a significantly shorter OS and a marked increase in the cumulative incidence of relapse. Patients with these abnormalities should be considered for early allogeneic stem cell transplant. 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.

RUNX1 and ASXL1 mutations, each occurring in 10-15% of AML patients, have each been associated with adverse prognosis, particularly when occurring in intermediate risk disease, and these patients appear to benefit from transplant in CR1. Similarly, TP53 and splicing factor mutations (e.g. SRSF2) have also been associated with independently adverse prognosis. RUNX1, ASXL1 and TP53 mutated disease have been assigned to the adverse risk group in the 2017 ELN classification, except when they occur in otherwise ELN favorable risk disease. Therefore, this
Mutational information can be helpful in risk stratification. With respect to other mutations (e.g. DNMT3A, IDH, TET2) the data regarding prognosis are less clear.

Combined Cytogenetic and Molecular Risk Groups
Table 4 outlines the risk groups according to the European LeukemiaNet (ELN) classification.

Table 4. Risk groups according to the European LeukemiaNet classification

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1&lt;br&gt;inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11&lt;br&gt;Mutated NPM1 without FLT3-ITD (normal karyotype)&lt;br&gt;Mutated CEBPA (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-I*</td>
<td>Mutated NPM1 and FLT3-ITD (normal karyotype)&lt;br&gt;Wild-type NPM1 and FLT3-ITD (normal karyotype)&lt;br&gt;Wild-type NPM1 without FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-II</td>
<td>t(9;11)(p22;q23); MLLT3-MLL&lt;br&gt;Cytogenetic abnormalities not classified as favorable or adverse†</td>
</tr>
<tr>
<td>Adverse</td>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1&lt;br&gt;t(6;9)(p23;q34); DEK-NUP214&lt;br&gt;t(v;11)(v;q23); MLL rearranged&lt;br&gt;-5 or del(5q); -7; abnormal (17p); complex karyotype**</td>
</tr>
</tbody>
</table>

* Includes all AML with normal karyotype except those in the Favourable group.
** Three or more chromosome abnormalities in the absence of a WHO-designated recurring translocation or inversion (t(15;17), t(8;21), inv(16), t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3))

A disadvantage of the ELN classification is that the Intermediate-I risk group has a prognosis with chemotherapy (without HCT) similar to the Adverse risk group. The National Comprehensive Cancer Network (NCCN) classification is more straightforward (Table 5).

Table 5. Risk groups according to the National Comprehensive Cancer Network (NCCN) classification

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Cytogenetics</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable risk</td>
<td>inv(16) / t(16;16)&lt;br&gt;t(8;21)*&lt;br&gt;t(15;17)</td>
<td>Normal cytogenetics plus NPM1 mutation without FLT3 ITD, or isolated CEBPA biallelic mutation</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Normal +8 alone&lt;br&gt;t(9;11)</td>
<td>Non-defined</td>
</tr>
<tr>
<td>Risk Category</td>
<td>Cytogenetics</td>
<td>Molecular</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Poor risk</td>
<td>Complex (≥3 clonal abnormalities)</td>
<td>Normal cytogenetics plus FLT3 ITD, or TP53 mutation</td>
</tr>
<tr>
<td></td>
<td>Monosomal karyotype</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5, 5q-, -7, 7q- 11q23 [non t(9;11)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inv(3), t(3;3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(6;9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(9;22)</td>
<td></td>
</tr>
</tbody>
</table>

* The presence of c-KIT mutation in patients with t(8;21), and to a lesser extent inv(16), probably confers an intermediate risk of relapse.

**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 favorable 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 6 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 6. Cytogenic and molecular risk stratification including minimal residual disease and other

<table>
<thead>
<tr>
<th>AML risk group</th>
<th>AML risk assessment criteria at diagnosis</th>
<th>MRD after cycle 2</th>
<th>Risk of relapse following consolidation approach</th>
<th>Prognostic scores for RM that indicate alloHSCT as preferred consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemotherapy or autoHSCT (%)</td>
<td>AlloHSCT (%)</td>
</tr>
<tr>
<td>Good</td>
<td>-t(8;21) or AML1-ETO, WBC&lt; 20 -inv16/t (16;16) or CBFB-MYH11 -CEBPA-biallelic mutant-positive -t(8;21) or AML1-ETO plus WBC&gt;20 or mutant KIT</td>
<td>Positive or negative</td>
<td>35-40</td>
<td>15-20</td>
</tr>
<tr>
<td>Intermediate</td>
<td>-CN-X-Y, WBC &lt;100, CRe -t(8;21) or AML1-ETO plus WBC &gt;20 or mutant KIT</td>
<td>Negative</td>
<td>50-55</td>
<td>20-25</td>
</tr>
<tr>
<td>Poor</td>
<td>-CN –X-Y, WBC&lt;100, CRe -t(8;21) or AML1-ETO, WBC&gt;20 and/or mutant KIT -CN-X-Y, WBC&lt;100, n CRe -CN-X-Y, WBC&gt;100 -CA, but non-CBF, MK-negative, no abn3q26</td>
<td>Positive</td>
<td>70-80</td>
<td>30-40</td>
</tr>
<tr>
<td>Very Poor</td>
<td>-CN -X –Y, WBC&gt;100 -CA, but non-CBF, MK-negative, no abn3q26, EV1-negative -MK-positive -abn3q26 -Non-CBF, EV11-positive -Non-CBF with mutant p53, or -mutant RUNX1, or mutant ASXL1 -or biallelic FLT3-ITD with FLT3-ITD:FLT3 WT ratio of &gt;0.6</td>
<td>Positive</td>
<td>&gt;90</td>
<td>40-50</td>
</tr>
</tbody>
</table>

From Cornelissen et al: Blood 2016 (ref 58).
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. 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) or inv 16, 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.

- **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 myelablative 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. The patient should proceed to allogeneic stem cell transplantation as soon as a donor is identified.
References


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
  - 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.
- Patients without documented CNS disease should receive at least four doses of intrathecal chemotherapy for CNS prophylaxis.
- 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.
- TKI therapy will be added to chemotherapy as soon as evidence of the Philadelphia chromosome or BCR-ABL transcript has been established and continued until just prior to transplantation. BCR-ABL will be monitored post-transplant and TKI therapy re-instituted upon any evidence of molecular positivity.
- 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.

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. 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. The potential years of life lost due to leukemia in Canada has been reported to be
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%. The long-term prognosis for adults with ALL treated with conventional chemotherapy regimens, however, remain poor, with cure rates of only 30 to 40%. 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. Canadian data has shown that a pediatric approach can safely be extended to adults up to the age of 60 with only minor modifications. 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, Inotuzumab, the addition of Rituximab to chemotherapy and CAR-T cell therapy.

CNS prophylaxis in the form of cranial irradiation, 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 molecularly 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 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.²⁵-²⁹

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%).

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, which remains the treatment of choice in these patients. 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. BCR/ABL monitoring should be done every 3 months for the first year post transplant then with every visit.
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.
References


Additional References of Interest:

Myelodysplastic Syndromes (MDS)
Presented by: Michelle Geddes

Summary

- All patients should have cytogenetic analysis of bone marrow and calculation of the International Prognostic Scoring System (IPSS) and R-IPSS at diagnosis.
- Sibling typing should be initiated at the earliest opportunity for all transplant-eligible patients.
- Transplant-eligible patients with symptomatic cytopenias or evidence of disease progression who have Intermediate R-IPSS scores can be considered for allogeneic HCT; with consideration of patient values and discussion around risks of transplant compared to the underlying disease.
- Patients with high (>4.5 to 6 points) or very high (>6 points) IPSS-R score should be offered stem cell transplantation if they are transplant-eligible.
- Disease reduction with induction chemotherapy or hypomethylating agents such as azacytidine should be considered for patients with higher risk disease or elevated blast counts at presentation. In untreated patients, a bone marrow biopsy 6 weeks prior to transplant is recommended to allow for treatment planning and risk stratification.
- Efforts should be taken to minimize iron overload pretransplant to minimize the adverse effects of iron overload on treatment-related mortality.
- Our standard conditioning regimen 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).
- In very high risk patients ie complex karyotype and p53 mutations by NGS, 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, demethylating 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)**

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Dysplastic lineages</th>
<th>Cytopenias¹</th>
<th>% BM Ringed sideroblasts</th>
<th>BM and PB blasts</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia</td>
<td>1</td>
<td>1 or 2</td>
<td>&lt;15%/&lt;5%²</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any except del(5q)</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia</td>
<td>2 or 3</td>
<td>1-3</td>
<td>&lt;15%/&lt;5%²</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any except del(5q)</td>
</tr>
<tr>
<td>MDS with ringed sideroblasts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single lineage dysplasia</td>
<td>1</td>
<td>1 or 2</td>
<td>≥15%/&lt;5%²</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any except del(5q)</td>
</tr>
<tr>
<td>Multilineage dysplasia</td>
<td>2 or 3</td>
<td>1-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS with isolated del5q</td>
<td>1-3</td>
<td>1-2</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>del(5q) ±1 additional (not -7or del(7q))</td>
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<tr>
<td>MDS, unclassifiable</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>With 1% PB blasts</td>
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<td>1-3</td>
<td>None or any</td>
<td>BM&lt;5%, PB&lt;1%</td>
<td>Any</td>
</tr>
<tr>
<td>With 1 lineage dysplasia &amp; pancytopenia</td>
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<td>3</td>
<td>None or any</td>
<td>BM&lt;5%, PB&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Defining cytogenetic abnormality</td>
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<td>1-3</td>
<td>&lt;15%</td>
<td>BM&lt;5%, PB&lt;1%</td>
<td>Any</td>
</tr>
</tbody>
</table>

¹: BM=bone marrow, PB=peripheral blood
Table 2. Revised IPSS (R-IPSS) for MDS²

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

*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. Leukemia-free survival based on total score from the R-International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>IPSS-R score</th>
<th>Median overall survival (years)</th>
<th>Median time to 25% AML evolution (years)</th>
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<tbody>
<tr>
<td>Very low</td>
<td>≤1.5</td>
<td>8.8</td>
<td>&gt;14.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5 to 3</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3 to 4.5</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5 to 6</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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

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%).³ The role of treatment intensity was recently 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.⁴ 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 favourably 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. 449 (34%) of patients were >60y of age. Four year OS was 31% and factors associated with higher risk of relapse include use of RIC (HR 1.44, CI, 1.13 to 1.84; P < .01) and advanced disease stage at transplantation (HR, 1.51; 95% CI, 1.18 to 1.93; P < .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 = .01), use of an unrelated donor (P = .03), and RIC (HR, 0.79; 95% CI, 0.65 to 0.97; P = .03). The major factor associated with reduced 4 year survival was disease stage at transplantation (HR, 1.55; 95% CI, 1.32 to 1.83; P < .01) and challenges remain in with both higher relapse rates posttransplant and higher treatment-related mortality with MDS compared to de novo AML.

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. 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 (N=85).

A landmark decision analysis by the IBMTR 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. Low and intermediate-
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.9

The use of azacytidine provides further options for care and potentially for bridge to transplantation and cytoduction. Several case series using azacytidine as bridge to transplantation shows this treatment is feasible; effect on transplant outcomes is being determined.10-12 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.13 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 high risk disease, treatment is recommended as a bridge to curative therapy during transplant workup.
References


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

Second line 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 or ponatinib
- 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
- 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 during the donor search and workup periods

Accelerated Phase
- HLA type patients and siblings and proceed with VUD search if no family match identified
- Use tyrosine kinase inhibitors as a bridge to transplantation in eligible patients (may be sufficient in good prognosis groups such as clonal progression only)
- Allogeneic stem cell transplantation preferred in eligible patients

Blast Phase
- HLA type patients and siblings and proceed with VUD 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 a second generation TKI, preferably one not used pre-transplant if a positive PCR is detected at ≥6 months post-transplant or if the BCR/ABL ratio is rising prior to that
- If no response to TKI a mutation analysis should be sent prior to proceeding to escalating doses of TKI

Accelerated phase relapse:

- Minimize immunosuppression
- Perform mutation analysis
- Initiation of TKI therapy with a second generation TKI preferably one not used pre-transplant
- If no response to TKI proceed to escalating doses of TKI
- Consider TKI in conjunction with DLI
- Consider a second transplant based on GVHD status, age, comorbidities and time from first transplant

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, accelerated 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. In the tyrosine kinase era life expectancy approximates normal.

**Accelerated Phase: World Health Organization (WHO) Classification**

- 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**

- 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 4.5-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, 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. 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. A recent 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 recent report by the Swedish CML registry11 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.

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.12 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

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

<table>
<thead>
<tr>
<th>EBMT Risk Factor Assessment</th>
<th>Points</th>
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<tr>
<td>Risk Factors</td>
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</tr>
<tr>
<td>Age</td>
<td>&lt;20 years</td>
<td>20-40 years</td>
<td>&gt;40 years</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>1st CP</td>
<td>AP</td>
<td>BP or 2nd CP</td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>HLA sib</td>
<td>MUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex Match</td>
<td>All others</td>
<td>Female to Male</td>
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<td></td>
</tr>
<tr>
<td>Time to Therapy</td>
<td>&lt;12 months</td>
<td>&gt;12 months</td>
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<tr>
<td>TRM</td>
<td>20 23 31 46 51 71 73 N/A</td>
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<td></td>
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<tr>
<td>OS</td>
<td>72 70 62 48 40 18 22 N/A</td>
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</tbody>
</table>

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). 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%). 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). In a study of 98 patients, 69 had undetectable, decreasing, or low <50 copies/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). 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. 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 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.

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). 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.

A recent CIBMTR study retrospectively reviewed the outcomes of TKI vs. DLI vs. DLI + TKI in the setting of post-transplant relapse in the TKI era. 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


BCR-ABL-Negative Myeloproliferative Neoplasms
Presented by: Michelle Geddes

Summary

- Transplant eligible patients with myelofibrosis (primary, or post-ET/PV MF) with intermediate-2 or high risk disease according to the Dynamic IPSS-plus criteria should be considered for allogeneic stem cell transplantation. Younger patients with intermediate-1 risk can be considered for transplant and should have a donor search performed.
- 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 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 JAK2 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. Ruxolitinib 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, EZH2, IDH1/2, SFSF2 mutations. 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.

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 3.5-5.5 years. 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:**

The International Prognostic Scoring System (IPSS) can be used at diagnosis and uses five risk factors to estimate survival from time of diagnosis: age >65 years, hemoglobin level <100 g/L, leukocyte count >25 x10^9/L, circulating blasts ≥1%, and presence of constitutional symptoms. The presence of 0, 1, 2, and ≥3 adverse factors define low, intermediate 1, intermediate 2, and high-risk disease, with median survivals of 11.3, 7.9, 4, and 2.3 years, respectively.

This prognostic score was later modified to Dynamic IPSS (DIPSS) for use at any time in the disease course, and most recently DIPSS 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). 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.

**Table 1. Dynamic International Prognostic Scoring System – plus (DIPSS-plus) risk factors used to define low, intermediate 1, intermediate 2 and high risk groups**

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Age &gt; 65</td>
</tr>
<tr>
<td>Hemoglobin &lt; 100 gm/L</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
</tr>
<tr>
<td>Leukocytes &gt; 25 x 10^9 /L</td>
</tr>
<tr>
<td>RBC transfusion requirement</td>
</tr>
<tr>
<td>Platelets &lt; 100 x 10^9 /L</td>
</tr>
<tr>
<td>Unfavourable karyotype (complex or including -5/5q-, -7/7q-, +8, abnormal 11q23, inv(3), 12p-, i(17q))</td>
</tr>
<tr>
<td>Circulating blasts &gt; 1%</td>
</tr>
</tbody>
</table>
Transplantation outcomes in myelofibrosis:

Allogeneic stem cell transplantation 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 JAK1/2 inhibitors found overall survival (OS) at two years was 61%, but 91% for those who experienced clinical improvement pretransplant on JAK inhibitors, and 32% for those with leukemic transformation on JAK1/2 inhibitor therapy. Response to JAK inhibitors (p=0.03), DIPSS score (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.

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. Age and comorbidities affect outcomes and need to be considered as with transplants for other indications.

There are no randomized trials to compare outcomes in patients treated with JAK1/2 inhibitors vs transplantation. However, a retrospective review of 443 patients with primary myelofibrosis under the age of 65 from transplant and nontransplant (censored at time of transplant) regimens showed a survival benefit to transplant in patients under the age of 65 years with int-2 or high risk disease, and this is used by most guidelines as indication for transplant. 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 survival at 5 years between transplant and nontransplant cohorts was 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.

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. 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). 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. 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 (Janus Kinase) ALLO trial 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. For this reason it is recommended to continue JAK1/2 inhibitors until the day before conditioning.11
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.\textsuperscript{18}
References


Additional References


Chronic Lymphocytic Leukemia (CLL)
Presented by: Doug Stewart

Summary

Allogeneic stem cell transplantation may be offered to CLL patients with:
- No del 17p: relapse after 1 prior novel agent including a BTK-inhibitor (eg. Ibrutinib) or PI3kinase inhibitor (eg. Idelalisib) or BCL2 inhibitor (eg. Venetoclax), especially if not responding well to a second novel agent (ie. less than CR)
- del 17p: all patients requiring therapy, especially if no response to induction therapy or relapse after any prior therapy
- Richter’s transformation: complete remission (CR) or partial response (PR) to induction chemotherapy (usually RCHOP)

Autologous stem cell transplantation for CLL:
- Autologous stem cell transplantation is not indicated to treat CLL

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 have median overall survival (OS) rates of approximately 3 years after chemoimmunotherapy. Even novel agents such as Ibrutinib do not control relapsed del(17p) for long durations of time. For example, a recent study by O'Brien and colleagues involving 145 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%.

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 non-myeloablative conditioning.
Allogeneic Stem Cell Transplantation in CLL

In general, series reporting the outcomes of allogeneic SCT in CLL are small (fewer than 50 patients) and the patients reported are highly pre-treated. In addition, the reported results often used a variety of conditioning regimens and stem cell sources. One case series reported by the BC Cancer Agency in conjunction with the Princess Margaret Hospital in Toronto reported the outcome of SCT in 30 patients with CLL. The median time from diagnosis to transplant was 4.8 (0.3-13) years and patients had received a median of 3 prior treatments. In 50% of cases, transplants were done using TBI-based conditioning and 33% were transplanted from HLA (human leukocyte antigen)-matched, unrelated donors. After a median follow-up of 4.3 years, they report cumulative non-relapse mortality of 47% and a relapse rate of 19%. Five-year OS and PFS were both 39%. Similar results (OS 41% and 50%, TRM 22% and 39%) have been reported in other small series.

The CIBMTR and the European Group for Blood and Marrow Transplantation (EBMT) report similarly high treatment related mortality (TRM) for allogeneic SCT in CLL. The EBMT report (n=134, 20% transplanted from unrelated donors) describes TRM 40% and an overall survival of 54% at 3 years, while CIBMTR reported on 242 patients (12% matched unrelated donor (MUD)) with TRM 46%, and an overall survival of 45%. The outcome of allogeneic SCT from matched unrelated donors has also been reported by the CIBMTR in a separate report by Pavletic and colleagues. They report on 38 patients with a median age of 45 years undergoing MUD alloSCT, a median of 51 months after diagnosis. Again, patients were highly pre-treated (median prior regimens = 3) and most (55%) were chemo-refractory. TBI was used in the majority of cases (92%) and standard GVHD prophylaxis was given. The 5-year overall survival rate was 33%, with disease progression (32%) and TRM (38%) as competing causes of treatment failure.

The EBMT recently analyzed 368 chronic lymphocytic leukemia patients who underwent allogeneic hematopoietic stem cell transplantation between 1995 and 2007. 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. Retrospective comparisons of reduced-intensity conditioning (RIC) and myeloablative transplant for CLL have shown decreased TRM but increased relapse using the less intensive conditioning. As a result, there is no difference in overall or event-free survival between the two transplant types. RIC is often chosen for patients with significant co-morbidities (eg. liver disease) or prior high dose therapy
from previous autologous or allogeneic SCT. The following tables show outcomes of RIC alloSCT for CLL.\textsuperscript{11}

**Table 1.** Summary of transplant characteristics and survival in the largest reported prospective studies of RIC HSCT in CLL

<table>
<thead>
<tr>
<th></th>
<th>Fred Hutchinson Cancer Center\textsuperscript{8}</th>
<th>German CLL Study Group\textsuperscript{10,48}</th>
<th>MD Anderson Cancer Center\textsuperscript{9}</th>
<th>Dana-Farber Cancer Institute\textsuperscript{11}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>82</td>
<td>90</td>
<td>86</td>
<td>76</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>Flu/low-dose TBI</td>
<td>Flu/Cy ± ATG</td>
<td>Flu/Cy ± R</td>
<td>Flu/Bu</td>
</tr>
<tr>
<td>Donors, % sibling/% MUR</td>
<td>63/37</td>
<td>41/59</td>
<td>50/50</td>
<td>37/63</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>60</td>
<td>72</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>Median PFS, %</td>
<td>39 (at 5 y)</td>
<td>38 (at 6 y)</td>
<td>36 (at 6 y)</td>
<td>43 (at 6 y)</td>
</tr>
<tr>
<td>Median OS, %</td>
<td>50 (at 5 y)</td>
<td>58 (at 6 y)</td>
<td>51 (at 6 y)</td>
<td>63 (at 6 y)</td>
</tr>
</tbody>
</table>

**Table 2.** Summary of key adverse events reported in the largest prospective studies of RIC HSCT in CLL

<table>
<thead>
<tr>
<th></th>
<th>Fred Hutchinson Cancer Center\textsuperscript{8}</th>
<th>German CLL Study Group\textsuperscript{10,48}</th>
<th>MD Anderson Cancer Center\textsuperscript{9}</th>
<th>Dana-Farber Cancer Institute\textsuperscript{11}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early mortality, % (&lt;100 d)</td>
<td>&lt;10</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>NRM, %</td>
<td>23</td>
<td>23</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Acute grade ¾ GvHD, %</td>
<td>20</td>
<td>14</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Severe chronic GvHD, %</td>
<td>53</td>
<td>55</td>
<td>56</td>
<td>48</td>
</tr>
</tbody>
</table>

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).\textsuperscript{6} 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
Although prior guidelines suggested that HSCT should be considered in fit CLL patients with del(17p) or who had <2-3 year response to previous immunochemotherapy, the availability of very effective new agents has decreased enthusiasm for allogeneic transplantation in CLL patients who have not yet received one of these agents. These agents primarily consist of inhibitors of B-cell receptor (BCR) signaling such as Ibrutinib (BTK-I) and Idelalisib (PI3k-I), as well as BCL-2 inhibitors (Venetoclax). In the absence of del(17p), the majority of patients with relapsed CLL who receive one of these agents remain progression-free for more than 3 years. Relapsed after one of these novel agents, however, is associated with a very poor prognosis, including rapidly progressive CLL and Richter’s transformation to DLBCL (diffuse large B-cell lymphoma). Therefore, referral for discussion of allogeneic stem cell transplant and HLA typing is not unreasonable even for patients who are responding to a novel agent, so that an allogeneic transplant can be expedited at the time of relapse. This is especially true for young, healthy patients with a well matched sibling donor.

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 progressed after prior chemoimmunotherapy and prior BTK-inhibitor (eg. Ibrutinib) or PI3kinase inhibitor (eg. Idelalisib) or BCL2 inhibitor (eg. Venetoclax), or those whose CLL possess del(17p) and require treatment. Allogeneic stem cell transplantation may be delayed in relapsed patients without del 17p CLL who respond to a novel agent; however HLA typing should be considered to identify a possible transplant donor. High risk features that should prompt earlier consideration of HSCT include patients who have had ≥ 3 prior lines of therapy and those with complex karyotypes by conventional cytogenetics. In the M14-032 trial (Jones JA, et al. Lancet Oncol. 2018 ;19(1):65-75) of venetoclax in 91 patients who progressed after prior Ibrutinib (47% del17p, 75% IGHV unmutated), ~2/3 responded, and the 1 yr PFS for these 57 responding patients was 100% in the 24 (42%) who achieved MRD negative responses, but approximately 75% for the 33 (58%) with MRD positive response (estimated 2yr PFS of ~50%). The overall 1yr EFS was ~55% for the 91 pts.

**Richter's Transformation:**
Small series of patients who have undergone stem cell transplantation for Richter’s transformation have reported a probable benefit over chemotherapy alone. For example, Tsimberidou and colleagues reported improved outcomes of 20 patients who underwent SCT (17 allogeneic SCT and 3 autologous SCT) compared to 128 patients who did not. Among those who underwent SCT, the estimated cumulative 3-year survival probability was 75% for those who were transplanted in CR or PR, compared to 21% for patients who underwent SCT as salvage therapy for relapsed/refractory RS. The estimated 3-year survival probability was 27% for those patients who responded to initial chemotherapy for RS, but did not undergo subsequent SCT. The European Group for Blood and Marrow Transplantation retrospectively reported 59 patients who underwent SCT (34 autologous SCT and 25 allogeneic SCT),
with an estimated 3-year survival of 36% for allogeneic SCT compared with 59% for autologous SCT.\textsuperscript{13} In a multivariate analysis of relapse-free survival among allogeneic SCT recipients, age <60 years, reduced intensity conditioning, and CR/PR at the time of transplantation were associated with superior relapse-free survival. Although there was no clear plateau in OS or relapse-free survival among the 34 patients who underwent autologous SCT, only 11 of 17 relapses were related to RS (the remainder were due to CLL), suggesting autologous SCT may eradicate the RS component in many patients even though the underlying CLL may persist.
Figure 1. Percent survival (A) and percent progression-free survival (B, C) in patients receiving allogeneic stem cell transplants for chronic lymphocyte leukemia in Calgary between 2000 and 2015.

(A) AlloSCT for CLL in Calgary 2000-2015 (n=49)

- 5yr TTP: 70.6%
- 5yr OS: 63.4%
- 5yr PFS: 52.7%

(B) AlloSCT for CLL in Calgary 2000-2015 (n=49)

- 17p- (n=12)
- No 17p- (n=37)

- logrank p=0.37

(C) AlloSCT for CLL in Calgary 2000-2015 (n=47)

- MUD (n=26)
- MRD (n=21)

- logrank p=0.18
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. 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.
References


Hodgkin and Non-Hodgkin Lymphoma: Indications for Transplantation
Presented by: Doug Stewart

Summary

Patient Eligibility:
• Age ≤ 75 years, ECOG 0-2, adequate organ function, no active infections, if HIV+ then CD4>100
• Lymphoma (chemo-sensitive):
  o partial response (PR) or better to last chemotherapy

High-Dose Chemotherapy (HDCT) Regimens:
• Preparative regimens for autologous and allogeneic HCT in lymphoma are outlined in the Pretransplant Conditioning chapter later in this Standard Practice Manual

Indications for HDCT and Autologous SCT:
1. Indolent non-Hodgkin lymphoma:
  o Follicular, marginal zone, small lymphocytic, lymphoplasmacytic lymphoma:
    ▪ Chemosensitive first or second treatment failure (relapse, progression or no response) after chemoimmunotherapy
  o Mantle cell lymphoma (especially low or intermediate risk MIPI score):
    ▪ First remission (CR or PR)
2. Aggressive non-Hodgkin lymphoma:
  o Chemosensitive first relapse or first remission-induction failure
  o Part of initial therapy (eg.RCHOPx4 +/- HDMTX then RDICEP or RDHAP then HDCT/ASCT) for poor prognosis disease such as:
    ▪ double hit lymphoma with MYC/BCL2 rearrangements by FISH and IPI=2-5
    ▪ DLBCL with IPI=4-5, especially for those who also have:
      1) MYC and BCL2 protein expression by IHC; or
      2) PET+ after 4-6 cycles RCHOP (particularly as determined by change in SUVmax <66% from baseline)
3. Hodgkin lymphoma:
  o First chemotherapy failure (relapse or 1\textsuperscript{0} refractory)

Indications for HDCT and Allogeneic SCT:
1. Indolent non-Hodgkin lymphoma:
  o Follicular, marginal zone, small lymphocytic/CLL, lymphoplasmacytic lymphoma:
    ▪ Chemosensitive second to fourth treatment failure (relapse, progression or no response) after chemoimmunotherapy (last time to progression < 2 years)
  o Mantle cell lymphoma
- First remission for high risk MIPI score, blastoid variant, or heavy blood/marrow involvement
- Chemosensitive first chemotherapy failure (relapse, progression or no response)

2. **Aggressive non-Hodgkin lymphoma:**
   - Diffuse large B-cell or peripheral T-cell lymphomas
     - Chemosensitive relapse following HDCT/ASCT if time to relapse >1yr and IPI=0-2
   - Lymphoblastic lymphoma (see ALL guidelines): first remission high risk disease or chemo-sensitive first relapse

3. **Hodgkin lymphoma:**
   - Chemosensitive relapse following HDCT/ASCT if time to relapse >1 year

4. **Any lymphoma patient with indication for HDCT/ASCT but unable to collect adequate autograft**
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Diagnosis and Pathologic Classification

An excisional lymph node biopsy of the largest regionally involved lymph node is the optimal specimen for initial diagnostic assessment. Similarly, a sizable biopsy from the organ of origin in extranodal lymphomas is also suitable. Occasionally, needle core biopsies may be adequate but this needs to be assessed on a case-by-case basis. Whenever possible, a reference lymphoma pathologist should confirm the diagnosis. The following histological sub classification of the malignant lymphomas is an adaptation of the World Health Organization (WHO) classification and is based on the light microscopic interpretation complemented by special stains, immunophenotyping, cytogenetics and other information as available. The specific lymphomas are divided into three major groups for treatment planning. All B-Cell lymphomas should be immunophenotyped to determine if they are positive for CD20.

Table 1. Lymphoma classification

<table>
<thead>
<tr>
<th>Indolent</th>
<th>T-cell</th>
</tr>
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<tbody>
<tr>
<td>Follicular, grades 1-2, 3a</td>
<td>Mycosis fungoides /Sezary syndrome</td>
</tr>
<tr>
<td>Small lymphocytic Lymphoma/Chronic Lymphocytic Leukemia</td>
<td>Primary cutaneous, CD30+</td>
</tr>
<tr>
<td>Marginal zone, extranodal (MALT)</td>
<td>Primary cutaneous perioheral T-cell lymphoma</td>
</tr>
<tr>
<td>Splenic marginal zone</td>
<td>PTCL, CD30-</td>
</tr>
<tr>
<td>Marginal zone, nodal (monocytoid B-cell)</td>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>Lymphoplasmacytic (Waldenström’s macroglobulinemia)</td>
<td></td>
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<tr>
<td>Primary cutaneous, follicle centre</td>
<td></td>
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<tr>
<td>Hairy cell leukemia</td>
<td></td>
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<tr>
<td>Nodular lymphocyte predominant Hodgkin Lymphoma</td>
<td></td>
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<tr>
<td>Mantle cell (can be aggressive)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Aggressive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell</td>
<td>Peripheral T-cell, unspecified</td>
</tr>
<tr>
<td>o T-cell/histocyte-rich DLBCL</td>
<td>Angioimmunoblastic (AITL. formerly AILD)</td>
</tr>
<tr>
<td>o Primary DLBCL of the CNS</td>
<td>Enteropathy associated T-cell</td>
</tr>
<tr>
<td>o Primary cutaneous DLBCL, leg-type</td>
<td>Hepatosplenic T-cell</td>
</tr>
<tr>
<td>o EBV-positive DLBCL of the elderly</td>
<td>Subcutaneous panniculitis-like</td>
</tr>
<tr>
<td>DLBCL associated with chronic inflammation</td>
<td>Anaplastic large cell (CD30+) ALK+</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>Anaplastic large cell (CD30+) ALK-</td>
</tr>
<tr>
<td>Primary mediastinal large B-cell</td>
<td>Extranodal NK/T-cell, nasal type</td>
</tr>
<tr>
<td>Intravascular large B-cell</td>
<td></td>
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<tr>
<td>ALK positive large B-cell</td>
<td></td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td></td>
</tr>
<tr>
<td>LBCl in HHV8-associated Castleman disease</td>
<td></td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td></td>
</tr>
<tr>
<td>Follicular grade 3b (large cell)</td>
<td></td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>⇒ Nodular sclerosis</td>
<td></td>
</tr>
<tr>
<td>⇒ Mixed cellularity</td>
<td></td>
</tr>
<tr>
<td>⇒ Lymphocyte rich</td>
<td></td>
</tr>
<tr>
<td>⇒ Lymphocyte depleted</td>
<td></td>
</tr>
</tbody>
</table>
Burkitt lymphoma
Intermediate between DLBCL and BL
Intermediate between DLBCL and Hodgkin lymphoma
B lymphoblastic leukemia/lymphoma
B prolymphocytic leukemia
Lymphomas associated with HIV infection
Lymphomas associated with primary immune disorders
Post-transplant lymphoproliferative disorders (PTLD)
Other iatrogenic immunodeficiency-associated lymphomas

T lymphoblastic leukemia/lymphoma
Adult T-cell leukemia/lymphoma (ATLL)
T prolymphocytic leukemia

**Mandatory Staging Procedures**

- Hematopathology review (essential for core needle biopsies)
- Complete history and physical examination with ECOG Performance Score
- CBC & differential
- Serum creatinine, electrolytes, Alk P, ALT, LDH, bilirubin, total protein, albumin, calcium
- Beta-2-microglobulin
- Bone marrow aspiration and biopsy (2cm core preferable) with flow cytometry on the marrow aspirate
- Chest X-ray (PA, lateral) and CT scan chest/abdomen/pelvis +/- neck
- PET/ Diagnostic CT scanning: After (re-)induction chemotherapy, prior to HDCT/ASCT
- LP for CSF cytology for BL and LBL or if DLBCL and aaniPI=2-3, or brain or sinus disease.
- Slit lamp exam of eye if brain lymphoma

Abbreviations: aaniPI = age-adjusted international prognostic index; Alk P = alkaline phosphatase; ALT = alanine aminotransferase; ASCT = autologous stem cell transplant; BL = Burkitt lymphoma; CBC = complete blood count; CSF = cerebrospinal fluid; CT = computerized tomography; DLBCL = diffuse large B cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HDCT = high-dose chemotherapy; LBL = lymphoblastic lymphoma; LDH = lactate dehydrogenase; LP = lumbar puncture; PA = posterior-anterior; PET = positron-emission tomography.
Staging System

**Table 2. Lymphoma staging system**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Single lymph node region (I) or one extralymphatic organ (IE)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Two or more lymph node regions, same side of the diaphragm (II), or local extralymphatic extension plus lymph nodes, same side of the diaphragm (IIE)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Lymph node regions on both sides of the diaphragm or with spleen involvement, either alone (III) or with local extralymphatic extension (IIIE)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diffuse involvement of one extralymphatic organs with associated nodal involvement beyond the regional site, or involvement of more than one extralymphatic organs or sites.</td>
</tr>
</tbody>
</table>

B symptoms

- One of:
  - unexplained weight loss >10% baseline during 6 months prior to staging
  - unexplained fever >38°C
  - night sweats

Bulk

- Any tumour diameter > 10cm

Re-Staging Tests

**PET/ diagnostic CT scanning:** After re-induction chemotherapy, prior to HDCT/ASCT

**Diagnostic CT scanning:**

- 6-8 weeks post-SCT. If a residual mass is seen on the CT after completion of SCT, then consider PET/CT if involved-field radiotherapy an option, or repeat CT scan 6 months post-SCT
- Also, as indicated to investigate clinical signs or symptoms, or abnormal laboratory tests

**Bone marrow aspirate and biopsy if results would change management (with sample sent for flow cytometry if indolent NHL):**

- Prior to stem cell mobilization
- If positive, repeat 8 weeks post-SCT

**Table 3. European Cooperative Oncology Group (ECOG) Performance Status**

<table>
<thead>
<tr>
<th>ECOG Performance Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (i.e. light housework, office work)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Salvage Age Adjusted International Prognostic Index (sAAIPI) Factors for Lymphoma

- ECOG 2-4    Score 0: Low Risk
- Stage III/IV Score 1: Intermediate Risk
- ↑ serum LDH above normal Score 2-3: High Risk

Table 4. Salvage Age Adjusted International Prognostic Index (sAAIPI) factors for lymphoma

<table>
<thead>
<tr>
<th>sAAIPI</th>
<th>PFS</th>
<th>Overall Survival</th>
<th>Round to Remember for HDCT/ASCT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>Chemosensitive</td>
<td>ITT</td>
<td>Chemosensitive</td>
</tr>
<tr>
<td>0 factors</td>
<td>70%</td>
<td>74%</td>
<td>83%</td>
</tr>
<tr>
<td>1 factor</td>
<td>39%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>2-3 factors</td>
<td>16%</td>
<td>18%</td>
<td>26%</td>
</tr>
<tr>
<td>3 factors</td>
<td>16%</td>
<td>18%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Abbreviations: ITT = intent-to-treat; PFS = progression-free survival.

References:
Hematopoietic Stem Cell Transplantation Eligibility Criteria

Criteria to determine eligibility of lymphoma patients for hematopoietic stem cell transplantation (SCT) are not based upon high levels of evidence, and therefore, vary somewhat between transplant centres. In general, the following factors are taken into account when considering eligibility for SCT:1

1. age ≤ 75 years
2. KPS 60-100% (ECOG 0-2)
3. Chemosensitive lymphoma without active secondary spread to the CNS (parenchymal brain, leptomeninges)
4. Adequate major organ function: LVEF ≥50%, PFTs [FVC, FEV1, DLCO] > 60% predicted, creatinine < 150 μmol/L, ALT <2 xULN, Bilirubin <2 x ULN, no evidence of cirrhosis
5. Ability to give informed consent
6. No serious active infections (HIV, TB, HBeAg, active bacterial/fungal disease)
7. Able to collect adequate stem cell graft (for autologous SCT >2 x10^6 CD34+ cells/kg free of tumour contamination, usually possible only with baseline blood platelet count >100 and WBC >3.0, and prior radiotherapy <30% marrow)

Abbreviations: CNS = central nervous system; DLCO = diffusing capacity of lung for carbon monoxide; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HBeAg = hepatitis B viral protein; HIV = human immunodeficiency virus; KPS = Karnofsky Performance Scale; LVEF = left ventricular ejection fraction; PFT = pulmonary function test; TB = tuberculosis; ULN = upper limit of normal; WBC = white blood cell.

Absence of any one of these factors does not constitute an absolute contraindication to HDCT/ASCT, and successful outcomes have been reported in a variety of poor prognosis settings, even HIV infection.2,3 It is widely accepted, however, as the number of unmet eligibility criteria increases, the likelihood of a poor outcome from SCT also increases. For example, the Center for International Blood and Marrow Transplant Research (CIBMTR) compared the clinical outcomes of 805 older (age ≥55 years) patients with non-Hodgkin’s lymphoma (NHL) to 1949 younger patients (<55 years) with NHL receiving ASCT during 1990-2000. The study concluded that ASCT in older NHL patients is feasible, but most disease-related outcomes are statistically inferior to younger patients.4,5 For example, in multivariate analysis, while adjusting for patient-, disease-, and treatment-related variables, older patients with aggressive histologies were 1.86 times (95% CI 1.43-2.43, P < .001) more likely than younger patients to experience treatment-related mortality (TRM).5

Autologous Stem Cell Transplantation Eligibility Criteria

A. Diffuse Large B-cell Lymphoma (DLBCL)

Indications and Outcomes:
Diffuse Large B-cell Lymphoma (DLBCL) accounts for approximately 1/3 of all lymphomas, and represents the majority of patients treated in SCT studies for aggressive lymphoma.6 HDCT/ASCT has been standard therapy for chemo-sensitive relapsed/refractory DLBCL ever since the results of
the PARMA study were published more than a decade ago. The PARMA study is the only randomized controlled trial (RCT) of high dose versus conventional dose salvage chemotherapy for relapsed, chemosensitive NHL, and demonstrated a significant failure-free (51% vs. 12%) and overall survival (OS) (53% vs. 32%) advantage for high dose BEAC (BCNU, etoposide, Ara-C, cyclophosphamide) and ASCT over standard-dose DHAP (dexamethasone, Ara-C, cisplatin). This was found despite the fact that not all patients allocated to the HDCT arm of the trial actually received HDCT, and many patients in the control arm eventually underwent HDCT/ASCT at the time of second disease progression.

The major prognostic factors for outcome of relapsed DLBCL include the time to relapse, IPI (international prognostic index) risk factors, and chemosensitivity. In the PARMA study, time to relapse <1 year was associated with a 40% response to DHAP, and only 13% 8 year OS. Costa and colleagues reported mean OS of only 5 months for patients with both a time to relapse <18 months as well as IPI=3-5, suggesting that these poor prognosis patients should not be subjected to ASCT. Hamlin and colleagues reported that the salvage aaIPI predicts outcome of relapsed DLBCL with PFS rates of approximately 69%, 46%, 25% for chemosensitive relapsed DLBCL patients with aaIPI scores of 0, 1, and 2-3, respectively. More recently, in the first interim analysis of 200 patients treated in the CORAL study (R-ICE Versus R-DHAP in relapsed DLBCL patients, followed by ASCT +/- maintenance rituximab) reported by Gisselbrecht and colleagues, factors associated with response to salvage therapy were refractory or relapse <12 months (52% vs. 88%), sIPI (second-line International Prognostic Index) 2-3 (54% vs. 77%), and relapse after prior rituximab (54% vs. 82%). (Note: R-ICE = rituximab + ifosfamide + carboplatin + etoposide; R-DHAP = rituximab + dexamethasone + ara-C + cisplatin). For the 107 (53%) patients who underwent ASCT, factors associated with 2-year event-free survival (EFS) were: prior rituximab, 34% vs. 66% (p=.0001); refractory/early relapse 36% vs. 68% (p <0.0001); and secondary IPI 2-3: 39% vs. 0-1: 56% (p=0.03). DLBCL subtypes and extranodal presentations seem to be of less importance for those patients who prove chemosensitivity and undergo ASCT. For example, Kuruvilla and colleagues compared outcomes of 37 relapsed/refractory primary mediastinal DLBCL (PMLCL) patients with those of 143 other DLBCL patients. The overall response rate to salvage chemotherapy (25% vs. 48%, p = 0.01) and 2-year OS after diagnosis of relapse/refractory disease (15% vs. 34%, p = 0.018) was inferior in PMLCL patients, but the 2-year post-ASCT OS (67% PMLCL vs. 53%, p = 0.78) and PFS (57% PMLCL vs. 36%, p = 0.64) were similar. Finally, the combination of IPI and PET/CT assessment of chemosensitivity may provide even greater predictive ability. Schot and colleagues reported the use of fludeoxyglucose (FDG)-PET after 2 cycles salvage DHAP-VIM chemotherapy in 101 patients (78 aggressive NHL [53 DLBCL], 23 HL), of whom 80 were chemosensitive and 77 eventually had ASCT. For NHL, the 2-year FFS was 67%, 56%, 26%, and 12% for aaIPI 0, 1, 2, 3, respectively. The 2-year failure-free survival (FFS) by PET response to salvage DHAP-VIM was 72% for complete response (CR), 38% for partial response (PR) and 10% for no response (NR). The two factors were combined by assigning 0 points for CR, 1 point for PR, and 2 points for NR on PET imaging. The 2-year FFS rates were 82%, 58%, 24% and 5% for patients with a combined risk score of 0-1, 2, 3, and 4-5.
points, respectively.\textsuperscript{13} Using evidence from the above studies, it is therefore probable that relapsed DLBCL patients can be appropriately excluded from ASCT if they have three, and possibly even two of the following adverse prognostic factors:

- time to relapse of $<12$ months
- relapse aAIPI scores of 2-3
- chemoresistance as defined as lack of at least a PR to salvage chemotherapy

No RCT has been conducted to evaluate potential benefit of HDCT/ASCT for patients with chemoresistant relapsed/refractory large cell lymphoma (i.e. patients who do not respond to second-line chemotherapy) or for patients who have experienced failure of more than one prior chemotherapy regimen. Retrospective reports, however, suggest only low rates of long-term progression-free survival (PFS) following HDCT for these poor prognosis patients. As such, in many transplant centres, ASCT is not offered in these settings.

Conflicting results have been reported from RCTs evaluating first remission-consolidation with HDCT/ASCT for aggressive NHL.\textsuperscript{14} Many studies were negative, while a few have shown significant PFS benefits from HDCT. Criticisms of these studies, however, are numerous. Many studies had inadequate statistical power, most did not use the aAIPI as an eligibility or stratification criterion, and overall they were extremely heterogeneous with respect to histological subtypes, choice of standard and HDCT regimens, and timing of HDCT relative to number of induction chemotherapy cycles. Some studies used a non-conventional, intensive chemotherapy “control arm”. These studies reported that up to 40% of patients in the HDCT arm never received the assigned HDCT, often due to an inadequate response to abbreviated induction chemotherapy prior to planned HDCT/ASCT. The use of abbreviated induction therapy followed by a single HDCT/ASCT is not considered a viable strategy for future trials. Greb and colleagues performed a systematic meta-analysis searching the Cochrane Library, MEDLINE and other databases (1990 to 2005) for studies that evaluated the efficacy of front-line HDCT relative to conventional chemotherapy in aggressive NHL.\textsuperscript{15} Fifteen RCTs including 2728 patients were identified. The results of this meta-analysis demonstrated that HDCT does not improve OS (hazard ratio (HR) 1.05, 95% CI 0.92-1.19) or EFS (HR 0.92, 95% CI 0.80-1.05) compared with conventional chemotherapy for all patients included in these studies, if one does not consider IPI risk score, or type of “conventional” chemotherapy. However, subgroup analysis for OS indicated different effects (p=0.032) for good (HR 1.46, 95% CI 1.02-2.09) and poor risk (HR 0.95, 95% CI 0.81-1.11) patients. Funnel plot heterogeneity excluded the Groupe d’Etude des Lymphomes de l’Adulte LNH 93-3 study wherein the dose-intensity of the control arm exceeded that of the HDCT arm.\textsuperscript{16} Excluding the LNH 93-3 study, the meta-analysis demonstrated a significant benefit for HDCT over SDCT in terms of EFS (HR 0.78, 95%CI 0.65-0.94) and OS (HR 0.81, 95%CI 0.67-0.97) for patients with high intermediate or high risk IPI scores.

Despite this meta-analysis, upfront HDCT is still considered investigational. Recently, PFS and OS rates for DLBCL following standard dose therapy have improved by approximately 15% with the addition of rituximab to the CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone).
regimen. Of interest, however, RCHOP (rituximab and CHOP) has never been compared to CHOP in a RCT for poor prognosis DLBCL patients who were the target of prior HDCT RCTs; those who are under 60 years of age with 2-3 aaIPI risk factors. Potentially, a more definitive HDCT study has recently been completed by the American Intergroup and NCIC-CTG (LY.11), which enrolled 370 eligible aggressive histology NHL patients who had 2-3 aaIPI risk factors. In this study, 253 patients who responded to 5 cycles of RCHOP chemotherapy were then randomized to one more RCHOP followed by HDCT/ASCT (n=125) or to 3 more cycles of RCHOP (n=128). The first analysis of this study reported at the 2011 ASCO meeting demonstrated improved 2 year PFS (69% vs. 56%, p=0.005) for late first remission consolidation with HDCT/ASCT but no difference in 2 year OS (74% vs. 71%, p=0.32). There was, however, improved OS in the subgroup of aaIPI=3 patients (82% vs. 64%).

Other approaches still worthy of study involve multiple cycles of high dose sequential induction chemotherapy as pioneered by groups in Italy, or early identification of patients who are unlikely to be cured by standard induction therapy through the use of interim response PET/CT imaging after 2-4 cycles of chemotherapy, and then treating unfavorable responders with immediate salvage HDCT/ASCT.

**HDCT/ASCT as Part of Initial Therapy for DLBCL:**

Randomized phase 3 trials have not proven an OS benefit for first remission consolidation with ASCT compared to RCHOP alone for aaIPI=2-3 DLBCL patients. Most recently, Chiapella et al. (2017) evaluated Rituximab-dose-dense chemotherapy with or without HDCT/ASCT in 412 patients with aaIPI=2-3 DLBCL (DLCL04), and reported improved PFS but not OS with ASCT consolidation. This is similar to the US intergroup/NCIC study reported by Stiff PJ et al. (2013)54, however, in the latter study, patients who had aaIPI=3 experienced statistically significant improvements in 2yr PFS (75% vs 43%) as well as OS (82% vs 64%) with ASCT compared to RCHOP alone, respectively. aaIPI does not adequately identify poor prognosis DLBCL in young patients, as evidenced by the OS of 75-80% for aaIPI=2 patients in the RCHOP-only arms of the US intergroup trial and the Italian DLCL04 trial. This is supported by unpublished retrospective Alberta population data from a 2013 analysis, wherein 112 HIV-, CNS- patients 18-65yo with IPI=3-5 DLBCL experienced 5yr OS of 68% with ASCT (n=37) vs 56% without ASCT (n=75), however, including 166 IPI=2-5 patients, the OS difference was not significantly different with (n=46) or without (n=120) ASCT (72% vs 64%). Newer methods of identifying poor prognosis DLBCL patients include the use of interim or final PET+ response to RCHOP, as well as cell of origin (COO) GCB vs non-GCB, and MYC/BCL2 expression. Ennishi et al. (2017) reported very poor outcomes (5yr TTP <30%) for GCB DLBCL patients associated with high IPI scores and BCL2 translocations, as well as ABC DLBCL associated with high IPI scores and BCL2 gain/expression. In addition, several investigators have reported very low salvage rates for the use of ASCT for relapsed/refractory MYC/BCL2 dual protein expression DLBCL. However, determining COO by IHC algorithms is unreliable, and COO by nanostring Lymph2Cx GEP is not currently funded. Unpublished data for 237 patients aged 18-65 years with IPI=3-5 DLBCL treated in Alberta from 2006-2017 found a 5 year overall survival rate of 81% for 100 IPI=3 patients but
only 63% for 137 IPI=4-5 patients. Only a minority had first remission ASCT consolidation therapy. This local real world experience suggests that 40% of IPI=4-5 DLBCL patients are not cured by induction RCHOP or subsequent salvage therapy with ASCT for relapsed/refractory disease. The Positron Emission Tomography–Guided Therapy of Aggressive NonHodgkin Lymphomas (PETAL) study [Ulrich D’uhrs, J Clin Oncol 36:2024-2034. 2018] reported 5yr eventfree survival from the day of negative vs positive interim PET scanning (change SUVmax 66%) as follows: 80% vs 40% for IPI=0-1, 60% vs 40% for IPI=2, 60% vs 30% for IPI=3, and 40% vs 10% for IPI=4-5. In conclusion, patients who present with DLBCL and IPI=4-5 are reasonably treated with ASCT as first remission consolidation after 4-6 cycles RCHOP induction therapy, especially those who also have: 1) MYC and BCL2 protein expression by IHC; or 2) PET+ after 4-6 cycles RCHOP (particularly as determined by change in SUVmax <66% from baseline).

**Secondary CNS Lymphoma:**23-26

Selected patients with CNS relapse/progression may be candidates for aggressive therapy. One of 3 induction regimens is recommended for transplant-eligible patients and one of two options for transplant in-eligible patients, based on presentation:

1) Isolated CNS lymphoma: HDMTX-based induction then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT for transplant eligible or HDMTX/AraC then ifosfamide for transplant ineliglible.

2) Early Systemic and CNS lymphoma (prior to completing RCHOP x6): RCHOP and HDMTX x4 cycles then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT for transplant eligible or RCHOP/MTX followed by AraC then ifosfamide in transplant ineliglible.

3) Late relapse (prior RCHOP x6) with systemic and CNS lymphoma: HDMTX-ifosfamide-etoposide x2 then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT for transplant eligible or palliation for transplant ineliglible.

Unfortunately, most patients with secondary CNS lymphoma experience poor response to salvage therapy, including high dose methotrexate/cytarabine-based regimens. These patients who are unfit to receive or do not respond to high dose methotrexate/cytarabine-based therapy are best managed with palliative intent, including possible use of intrathecal chemotherapy or palliative cranial radiotherapy.

**Treatment of Special DLBCL Entities:**

**Double hit lymphoma with MYC and BCL2 mutations/rearrangements by FISH:**

The largest multicentre retrospective analysis of 311 double hit lymphoma patients reported an OS rate of <50% if IPI=2-5 vs 65% for IPI=0-1, and >80% if IPI=0.27 In addition, the OS rate was approximately 90% for 39 patients who achieve CR following induction chemotherapy and then underwent SCT compared to 60% for 112 patients who achieved CR but did not receive SCT. Although this numerical difference was not statistically significant (p=0.1), it was very clinically significant, indicating that the study was underpowered to draw any meaningful conclusions regarding the role of ASCT consolidation. More recently, reported outcomes of 159 patients with double-hit lymphoma who achieve CR following induction therapy.28 This study demonstrated that PFS and OS were superior with an intensive regimen
relative to RCHOP, and that ASCT only improve outcomes for patients who initially received RCHOP, but not an intensive regimen. These studies suggest that DHL patients treated with RCHOP should be considered for ASCT consolidation, especially those with IPI=2-5 at diagnosis, however other patients who achieve CR after an intensive induction regimen (such as DA-EPOCH-R or R-CODOXM/IVAC) probably should not receive ASCT consolidation. Due to the lack of prospective randomized controlled studies, however, it is impossible to determine if the optimal approach involves RCHOP induction followed by ASCT or an intensive induction chemotherapy regimen.

Alberta recommendations for special DLBCL entities:

1. **DLBCL with MYC mutation by FISH:**
   - MYC mutated DLBCL (or intermediate between DLBCL and Burkitt Lymphoma) but no translocation of BCL2 or BCL6: R-CHOP x 6 cycles for most patients. However, for the poor prognosis situation of MYC mutated and age <70 years and IPI 3-5: R-CHOP x4 then RDHAP or RDICEP x1, then HDCT/ASCT. Alternatively R-CODOX-M/IVAC should be considered.
   - MYC mutated and BCL2 or BCL6 mutated (DOUBLE HIT) or BCL2 and BCL6 mutated (TRIPLE HIT):
     - Options for IPI=0-1:
       - R-CHOP or RCHEPx6 with HDMTX after cycles 2,4,6
       - DA-EPOCH-R
     - Options for IPI=2-5:
       - R-CHOP or RCHEPx2-4 with HDMTX after cycles 2 (+4) then RDICEP x1 then HDCT/ASCT using CNS penetrating regimen with either R-BuMel/ASCT or R-MelTBI/ASCT (not BEAM)
       - Note: it is difficult to mobilize autologous blood stem cells after multiple cycles of intensive chemotherapy + G-CSF (eg. RCHEP or RCODOXM/IVAC), particularly for older patients. Therefore, if the goal is to proceed to transplant, then R-CHOPx4 + HDMTXx2 is generally preferred for patients >60 years, or those who received prior chemotherapy for indolent lymphoma in the past and now have transformed disease.
     - DA-EPOCH-R or R-CODOX-M/IVAC

2. **Intermediate between DLBCL and Hodgkin Lymphoma:**
   - R-CHOP x 6 cycles for most patients
   - Consider R-CHOEPx6 or RCHOP followed by ASCT if high risk factors are present (IPI=3-5)

B. **Primary CNS Lymphoma**

Conventional therapy for primary central nervous system lymphoma (PCNSL) involves high dose methotrexate-based induction, potentially followed by cranial radiation, although long term outcomes are poor, especially for patients over age 50 years or with poor performance status at
diagnosis.\textsuperscript{29,30} In addition, high dose methotrexate followed by cranial radiation is associated with a high risk of dementia and neurotoxic death in patients over age 50-60 years.\textsuperscript{31} If patients refuse radiotherapy because of the concern regarding radiation-induced dementia, and fulfill standard eligibility for ASCT, they should be considered for high dose thiotepa, busulfan-based chemotherapy and autologous stem cell transplantation as part of their initial treatment, or at the time of first relapse following initial therapy since reports suggest long term progression free survival rates of 40-50\% with this approach.\textsuperscript{32,33}

**Choice of Re-induction Therapy Prior to HDCT/SCT:**

Several salvage chemotherapy regimens exist for relapsed DLBCL, but RCTs have not been performed to determine whether one regimen is superior to another.\textsuperscript{34} Most regimens involve prolonged intravenous administration and therefore, require hospitalization. The GDP regimen (gemcitabine 1g/m\(^2\) IV days 1 and 8, dexamethasone 40mg p.o. days 1-4, cisplatin 75mg/m\(^2\) IV day 1) can easily be administered on an outpatient basis, and has been reported by the NCIC CTG to give 49\% response rate in 51 patients with the relapsed/refractory NHL.\textsuperscript{35} This is similar to other salvage chemotherapy options such as ICE or DHAP. The NCIC CTG LY12 trial is currently evaluating RDHAP versus RGDP for relapsed/refractory aggressive NHL, with responding patients proceeding to HDCT/ASCT and then to a second randomization between observation and rituximab consolidation therapy every 2 months for one year. The other RCT examining salvage regimens for relapsed DLBCL, the CORAL study, thus far shows similar response rates and PFS rates for the RICE and RDHAP treatment arms.\textsuperscript{11} There is some suggestion from phase II studies that intensive salvage therapy prior to HDCT/ASCT may improve OS rates, but this needs to be proven in well conducted RCT before wide adoption.\textsuperscript{36,37} Finally, rituximab combined with salvage chemotherapy has been shown in a RCT and several historically controlled studies to improve post-ASCT outcomes relative to salvage chemotherapy alone.\textsuperscript{38-40} The majority of this data involves patients who did not receive rituximab with their primary CHOP-like initial induction therapy prior to relapse. Nevertheless, rituximab is now commonly added to salvage therapy regimens, at least for patients who relapsed more than 6-12 months after completing initial RCHOP, or who never received rituximab with primary chemotherapy.

In Calgary, we have analyzed 115 patients with refractory or relapsed NHL (DLBC or large T-cell) who received DICEP salvage therapy (dexamethasone, cyclophosphamide, etoposide, cisplatin, mesna, Septra) from 1995 to 2009. Of these patients, 104 (90\%) proceeded to HDCT/ASCT. Initial time to relapse under 1 year, elevated LDH, ECOG 2-4, and aaIPI=3 were all more common in the 11 patients who did not proceed to ASCT. For example, of the 25 patients with aaIPI=3, only 17 (68\%) proceeded to ASCT compared to 87 of 90 patients (97\%) with aaIPI=0-2. We also compared the results of the 104 patients who received DICEP then HDCT/ASCT with the other 44 Calgary patients who received HDCT/ASCT during the same time period (1995-2009) but did not receive DICEP. Clinical factors more common in DICEP than no DICEP groups included:

- age <60 years: 86\% vs. 59\% (p=0.0002)
- TTP<1 year: 72.1\% vs. 47.7\% (p=0.004)
- refractory: 29.8\% vs. 6.8\% (p=0.002)
• bulk >10cm: 24.3% vs. 9.1% (p=0.042)

Despite generally worse prognostic factors in the DICEP group, PFS rates were not significantly different between the groups (logrank p=0.11).

**High Dose Therapy Regimen:**
The most common HDCT regimens used for lymphoma include: cyclophosphamide, etoposide, carmustine (CEB or CBV), carmustine, etoposide, cytarabine, melphalan (BEAM), fractionated total-body irradiation (fTBI) with cyclophosphamide (Cy) and possibly etoposide (VP-16) (CyTBI or VPCyTBI) and, melphalan, etoposide with or without TBI (MeVPTBI). RCTs comparing these regimens for lymphoma have not been conducted. Non-randomized retrospective studies suggest somewhat better efficacy and tolerability for BEAM over CBV or the TBI-containing regimens in the setting of aggressive lymphoma.41-44 For example, Salar and colleagues investigated the impact of the preparative regimens on the outcome of 395 patients with diffuse large cell lymphoma, consecutively reported to the registry of the Spanish GEL/TAMO.45 Conditioning consisted of chemotherapy-only in 348 patients (BEAM, n=164; BEAC, n=145; and CBV, n=39) and CyTBI in 47 patients. Median times to engraftment and discharge were significantly shorter in the chemotherapy-only group, and early TRM was significantly higher with CyTBI. Survival rates of patients conditioned with BEAM or BEAC (58%, 95% CI 50-66) was more favourable than with CBV (40%, 95% CI 24-56), and significantly better than with CY-TBI (31%, 95% CI 18-44), a finding that persisted in multivariate analysis. Other studies suggest that high TBI doses (>12Gy) or combinations of TBI and etoposide may increase the risk of secondary myelodysplasia/AML, and are to be discouraged.46,47 Perhaps the use of targeted TBI though radioimmunoconjugates will improve the efficacy while reducing toxicity of TBI, however, this has yet to be proven in randomized studies.48 Primary CNS Lymphoma requires chemotherapy agents that cross well through the blood brain barrier such as busulfan and thiotepa (eg. thiotepa 600mg/m², busulfan 9.6 mg/kg) rather than agents that penetrate poorly such as melphalan and etoposide.32

**Post-ASCT Therapy:**
G-CSF 5µg/kg/day is generally given to all ASCT patients starting day +7 post-SCT until ANC >1.5 x 10^9/L. This is based on RCTs showing improved neutrophil engraftment and shortened length of hospital stay compared to no G-CSF, as well as trials showing no significant benefit of using higher doses of G-CSF or starting G-CSF earlier post-SCT.49-52

**C. Mantle Cell Lymphoma**
Mantle-cell lymphoma (MCL) is characterized by poor prognosis with a median survival of only 3 to 5 years following conventional therapy, and little improvement in outcome when rituximab is added to conventional CHOP.53,54 In 1996, the European MCL Network initiated a randomized trial comparing consolidation with CyTBI/ASCT (TBI 12 Gy, cyclophosphamide 120 mg/kg) to a conventional α-interferon maintenance (6x10^6 IE IFN-α 3x weekly) for patients under 65 years of age who were in first remission after a CHOP-like induction regimen.55 A total of 232 previously untreated patients with advanced stage MCL were randomized upfront. Only 173 (76%) of 228 evaluable patients responded to initial induction chemotherapy, and 151 of these (87%)
proceeded to the assigned consolidation therapy. Baseline characteristics were comparable in the per-protocol and intent-to-treat cohorts. By intent-to-treat, and after a median follow-up of 6.1 years, patients in the ASCT study arm experienced a significantly longer median time to treatment failure of 2.6 versus 1.4 years (p=0.0001) as well as longer median OS of 7.5 versus 5.3 years (p = 0.031). Accordingly, first-remission HDCT/ASCT represents the current therapeutic standard in younger MCL patients. The second Nordic MCL phase II trial in 160 patients suggests that HDCT/ASCT outcomes can possibly be improved upon by the addition of high dose Ara-C and rituximab, with projected 6-year overall, event-free, and progression-free survival rates of 70, 56 and 66%, respectively, with no relapses occurring after 5 years. Other single centre reports suggest R-HyperCVAD induction followed by HDCT/ASCT may also a reasonable strategy, but confirmatory RCTs are lacking. Because virtually all MCL patients eventually relapse following autologous SCT, and relapse rates are known to be lower following allogeneic SCT, allogeneic SCT may be the preferred strategy for eligible patients in poor prognosis situations including first partial remission with several IPI risk factors or peripheral blood involvement at diagnosis, or patients in first relapse.

Robinson and colleagues recently reported a large retrospective EBMT study of reduced intensity SCT (RIST) in MCL. Between 1998 and 2006 279 patients with MCL received RIST with 210 procedures performed after the year 2001. Patients had received a median of 3 lines (range 1-9) of prior therapy and 119 (43%) had undergone a previous autologous SCT. The median time from diagnosis to transplant was 30 months (range 3-161). Conditioning for RIST was achieved with fludarabine plus an alkylating agent in 66%, fludarabine plus TBI in 13%, and a variety of other reduced intensity regimens in 20%. The 100 day, 1 year and 3 year non-relapse mortality rates were 13, 32 and 41% respectively. The Kaplan-Meier estimate of the PFS at 1 and 3 years was 49% and 29% respectively. PFS was significantly worse for patients with refractory disease (response rate (RR)=2.2, p<0.001), poor PS (RR=2.6, p=0.005) or those transplanted prior to 2002 (RR=1.5, p=0.03).

D. Peripheral T-Cell Lymphoma
In North America, peripheral T-cell lymphomas (PTCL) represent 5-10% of all lymphomas. In terms of frequency, 75% of PTCL in North America are represented by PCTL-NOS (34%), CD30+ anaplastic large cell lymphoma (24%, ALK+ 16%, ALK- 8%), and angioimmunoblastic T-cell lymphoma (AITL) (16%). With the exception of CD30+ anaplastic large cell lymphoma (ALCL), PTCLs are associated with only 10-20% chance of long-term progression-free survival following conventional chemotherapy. Some small single-centre reports of HDCT/ASCT for relapsed/refractory PTCL suggest poor PFS rates of only 10-20%, while other reports, including larger transplant registry series, suggest outcomes similar to those for relapsed DLBCL, with uniformly superior outcomes for ALCLs compared to other PTCLs.

Nickelsen and colleagues reported a retrospective analysis on 424 patients with mature T-cell lymphoma who received HDCT/ASCT in EBMT centres between 2000 and 2005. Histological subtypes were ALCL=98, PTCLu=176, AITL=120, unknown=30. Median time from diagnosis to ASCT was 9 months (range=4-99), and median follow up for surviving patients was 36 months.
Disease status was CR1 (1st complete remission) in 35%, chemo-sensitive disease worse than CR1 in 52%, and refractory disease 13%. Only 9% received TBI. At 3 years after ASCT, the non-relapse mortality was 7.4%, the relapse rate was 43.1%, PFS was 49.5% and OS was 62.3%. In multivariate analysis for PFS, refractory disease and chemo-sensitive disease worse than CR1 were significant adverse factors compared to CR1 (RR=3.2 and 1.7, respectively, p<0.001 each) as was refractory disease compared to chemo-sensitive disease (including CR1; RR=1.9, p=0.004). Other significant adverse factors were age at SCT >60 years (RR=1.4, p=0.04), poor performance status at ASCT (RR=2.1, p=0.046) and PTCLu versus other subgroups (RR=1.4, p=0.02).

In view of poor outcomes following conventional CHOP-like chemotherapy, many studies have investigated first-remission HDCT/ASCT for PTCL. Jantunen and colleagues reported a survey of 37 adult PTCL patients transplanted in Finland during 1990-2001 (PTCL-NOS=14, ALCL=14, other=9).69 Disease status at the time of ASCT was CR/PR1 in 18 patients, CR/PR2 in 14 patients, and other in 5 patients. HDT consisted of either BEAC (N=22) or BEAM (N=15). The estimated 5-year OS was 54%. Patients with ALCL had superior OS when compared with other subtypes (85 vs. 35%, p=0.007). OS at 5 years was 63% in patients transplanted in CR/PR1 vs. 45% in those transplanted in other disease status (p not significant). In contrast to these encouraging results, Reimer and colleagues reported a prospective multicentre study of 4-6 cycles of CHOP followed in responding patients by CyTBI/ASCT.70 From June 2000 to April 2006, 83 patients were enrolled and 55 (66%) patients received ASCT. In an intent-to-treat analysis, the 3-year PFS rate was only 36%. Mercadal and colleagues reported results of a phase II study involving 41 patients with PTCL who received 6 cycles of intensive chemotherapy followed in responding patients by HDCT/ASCT.71 Only 17 patients ultimately underwent ASCT, with 17 patients not achieving PR/CR, and 7 failing to mobilize stem cells. Overall, the 4-year PFS was 30%, with similar outcome whether or not ASCT was performed. Rodriguez and colleagues reported 74 patients transplanted in first CR from the Spanish Lymphoma and Autologous Transplantation Group cooperative group.72 Eighty-eight percent presented advanced (III-IV) Ann Arbor stage; and 52% had high lactate dehydrogenase; 65% had 2 or 3 risk factors of the aaIPI. The 5-year OS was 68% and PFS reached 63%. Kyriakou and colleagues from the EBMT reported a retrospective, multicentre study of 146 patients with AITL who received ASCT.73 The actuarial OS was 67% at 2 years and 59% at 4 years and the cumulative incidence of relapse was estimated at 40% and 51% at 2 and 4 years, respectively. The estimated 2 and 4 year PFS rates for patients who received their transplants in CR were 70% and 56%, compared to 42% and 30% for patients with chemotherapy-sensitive relapsed disease, and 23% at both time points for patients with chemotherapy-refractory disease. Available retrospective and phase II evidence, therefore, suggests that PTCL patients can benefit from HDCT/ASCT when used in the settings of chemosensitive relapse, or first remission consolidation.74 RCTs evaluating treatments for these uncommon lymphomas are lacking, however.
E. Lymphoblastic Lymphoma

Lymphoblastic lymphoma (LBL) is a rare, clinically aggressive neoplasm of the young that frequently involves the bone marrow and/or central nervous system. These patients require aggressive combination chemotherapy (similar to acute lymphoblastic leukemia therapy) with induction, consolidation, prophylactic intrathecal chemotherapy and either maintenance therapy or first remission autologous stem cell transplantation. Sweetenham and colleagues reported a prospective RCT comparing a first remission HDCT/ASCT to conventional-dose consolidation and postremission maintenance chemotherapy in adults with lymphoblastic lymphoma. In total, 119 patients entered the study from 37 centers. Of the 98 patients eligible for randomization, only 65 were randomized: 31 to ASCT and 34 to conventional therapy. Although the actuarial 3-year RFS rate was 24% versus 55% in favour of ASCT (HR= 0.55; 95%CI 0.29-1.04, p=0.065), the sample size was too small to demonstrate any effect on OS (45% vs. 56%, p=0.71). It can be concluded from low level evidence in this rare disease, that either induction therapy followed by first remission HDCT/ASCT or conventional ALL-type intensive induction/consolidation/maintenance chemotherapy with salvage SCT at relapse are reasonable approaches for LBL. Conditioning regimens typically include TBI based upon low level evidence from ALL studies suggesting TBI improves outcomes compared to busulfan regimens. For example, Bunin and colleagues evaluated children less than 21 years with ALL undergoing allogeneic SCT with either busulfan or TBI, with etoposide 40 mg/kg and cyclophosphamide 120 mg/kg. Randomization was stratified based upon duration of remission, remission status, and prior cranial irradiation. A total of only 43 patients were enrolled. At a median follow-up of 43 months, event-free survival was 29% in the busulfan arm and 58% in the TBI arm (p=0.03).

Because LBL is similar to ALL, some centers prefer allogeneic hematopoietic SCT to autologous SCT. The IBMTR and ABMTR databases were retrospectively analyzed for outcomes of LBL patients who underwent autologous (auto, n=128) or HLA-identical sibling (allo, n=76) SCTs from 1989 to 1998. Allogeneic SCT (alloSCT) recipients had higher TRM at 6 months (18% versus 3%, p=0.002), and this disadvantage persisted at 1 and 5 years. Significantly lower relapse rates were observed in alloSCT recipients at 1 and 5 years (32% versus 46%, p=0.05; and 34% versus 56%, p=0.004, respectively), but no differences were noted in 5 year lymphoma-free survival rates (36% versus 39%, p=0.82) or 5 year OS (44% versus 39%, p=0.47) between alloSCT and autoSCT. Multivariate analyses to account for confounding factors confirmed these results. In summary, alloSCT for LBL is associated with fewer relapses compared to autoSCT, but higher TRM offsets any potential survival benefit. Independent of SCT type, bone marrow involvement at the time of transplantation and disease status more advanced than first complete remission were associated with inferior outcomes. In addition to this retrospective study, the EORTC ALL-3 trial evaluated the efficacy of alloSCT compared with that of autologous marrow transplantation and maintenance chemotherapy in 220 acute lymphoblastic leukemia and non-Hodgkin lymphoma patients younger than or equal to age 50 who reached CR. Among these patients, 184 patients started consolidation and were HLA typed; 68 had a donor and 116 had no sibling donor. The median follow-up was 9.5 years. AlloSCT was performed in 47 (68%) patients with a donor while autoSCT or maintenance chemotherapy was given to 84 (72%) patients without a sibling donor.
The 6-year disease-free survival rate was similar in the groups with and without donor [38.2% (SE=5.9%) vs. 36.8% (SE=4.6%), HR=1.01; 95% CI 0.67-1.53]. Comparing the donor group with the no donor group, the former had a lower relapse incidence (38.2% vs. 56.3%, p=0.001), but a higher cumulative incidence of death in CR (23.5% vs. 6.9%, p=0.0004). The 6-year survival rates were similar [41.2% (SE=6.0%) vs. 38.8% (SE=4.6%)]. AlloSCT is, therefore, generally reserved for second-line therapy of relapsed/refractory LBL, whereas ASCT is considered a treatment option for first-remission consolidation in lieu of prolonged consolidation/maintenance therapy with complex conventional chemotherapy regimens.

F. Burkitt Lymphoma
True Burkitt lymphoma is rare, representing <1% of all lymphomas. Conventional primary induction therapy consists of intensive chemotherapy with CNS prophylaxis using regimens such as CODOX-M/IVAC. SCT is generally reserved for recurrent disease or chemo-sensitive primary induction failures. There is very little data on SCT for Burkitt lymphoma, and no evidence that allogeneic SCT is superior to autologous SCT for this disease. Therefore, patients with relapsed/refractory Burkitt lymphoma who fulfill standard eligibility criteria for autologous SCT indicated above, are usually treated with this approach. The largest series of Burkitt lymphoma patients undergoing SCT was reported by the EBMT in 1996 by Sweetenham and colleagues. This study of 117 patients included Burkitt and Burkitt-like lymphomas in first remission (n=70) or relapse/refractory states (n=47). The 3 year OS rate following SCT was 72% for patients in first remission, 37% in chemo-sensitive relapse, and 7% for chemo-resistant patients.

References:


radiation-based and chemotherapy-only preparative regimens. Bone Marrow Transplantation 2001 Sep;28(5):455-61.
Allogeneic Hematopoietic Stem Cell Transplantation for Aggressive Lymphomas

Full Intensity (Myeloablative) Conditioning
As opposed to autologous SCT, randomized controlled trials have never been performed to evaluate the role of allogeneic SCT for aggressive lymphoma. Available retrospective data is very difficult to interpret due to alterations in lymphoma classification over the past 20 years and newly identified entities like mantle cell lymphoma were previously grouped with other NHL subtypes. In addition, most series have relatively low numbers of patients, who were very heterogeneous in terms of remission status, disease burden, amount and type of prior therapy. Finally, these patients have received a variety of conditioning and graft-versus-host-disease (GVHD) prophylactic regimens.

Retrospective studies that attempt to compare results of autologous and allogeneic SCT for lymphoma have identified that patients treated with allogeneic SCT tend to have more advanced, heavily pre-treated disease, and more marrow involvement. Despite this selection bias, allogeneic SCT seems to result in lower relapse rates than autologous SCT for lymphoma. This may be due to infusion of a tumour-free graft, induction of a graft versus tumour effect, the use of different types of high dose conditioning, or to subtle differences in patient selection that may result in slower progressive types of disease. For example, it is uncommon that aggressive lymphoma patients in second or third relapse would be considered candidates for an allogeneic SCT, therefore, those patients who actually receive this form of late salvage therapy must maintain excellent performance status, and generally maintain chemosensitive, low tumour burden disease. Large transplant registry data demonstrate that high 20-40% TRM from allogeneic SCT, unfortunately offsets the lower relapse rate, and 5 year overall survival rates of 35-40% are not superior to those of autologous SCT for aggressive lymphoma. These results seem to be fairly similar regardless of lymphoma subtype, with a little less than one third of patients dying from non-relapse mortality and similar proportion experiencing disease relapse, and a little more than one third of patients achieving long-term disease-free survival. Somewhat better results have occasionally been reported by single centres, studying small numbers of patients, but of course these reports are far less reliable. Results of allogeneic SCT for aggressive lymphoma after failure of prior autologous SCT are particularly poor; 5 year PFS rates of <10% have been reported.

Reduced Intensity (Non-Myeloablative) Conditioning
Reduced intensity conditioning (RIC) allogeneic SCT is associated with approximately 10-15% lower TRM, but higher relapse rates compared to traditional full myeloablative allogeneic SCT. Since the beneficial treatment outcome of RIC allogeneic SCT relies upon an immunological graft versus tumour effect, this strategy is questionable for aggressive NHL, particularly for bulky, rapidly progressive disease situations. When these aggressive tumours are treated with RIC allogeneic SCT, the disease often progresses prior to the potential onset of GVDH. Although a few small series suggest brief responses of aggressive lymphoma to DLI or withdrawal of immune suppression post-alloSCT, a graft-versus-aggressive lymphoma effect has never clearly been
demonstrated to confer long-term disease control. Successful tumour debulking prior to allogeneic SCT seems to be far more important in aggressive lymphoma than in other histologies to create a favorable effector T-cell to target tumour cell ratio in patients with these fast growing lymphomas.

Despite theoretical concerns regarding RIC allogeneic SCT for aggressive lymphoma, available non-randomized data suggests at least similar OS rates compared to myeloablative allogeneic SCT. Sorró and colleagues compared outcomes among patients with lymphoma or chronic lymphocytic leukemia given either nonmyeloablative (n=152) or myeloablative (n=68) conditioning. Outcomes were stratified by the SCT-specific comorbidity index. Patients in the nonmyeloablative group were older, had more previous treatment and more comorbidities, more frequently had unrelated donors, and more often had malignancy in remission compared with patients in the myeloablative group. Patients with indolent versus aggressive malignancies were equally distributed among both cohorts. For patients without comorbidities, even after adjustment for pre-transplantation variables, no significant differences were observed between nonmyeloablative and myeloablative SCT cohorts with respect to NRM, PFS or OS. In contrast, patients with comorbidities experienced lower NRM (p=0.009) and better survival (p=0.04) after nonmyeloablative conditioning. These differences became more significant (p<0.001 and 0.007, respectively) after adjustment for other variables. Further, nonmyeloablative patients with comorbidities had favorable adjusted progression-free survival (p=0.01) suggesting that patients with comorbidities should preferentially receive RIC allogeneic SCT.

Cesar Freytes and colleagues recently described results of non-myeloablative allogeneic SCT for 267 B-cell NHL patients relapsing after autologous HCT who were reported to the CIBMTR 1997-2006 (median follow-up 37 months). Histological subtypes included DLBCL (56%), follicular (17%), mantle cell lymphoma (27%), and the time from first to second transplant was less than 1 year in 21% of patients, between 1 and 2 years in 30% of patients, and more than 2 years in 49% of patients. In total, 63% were chemosensitive, 31% chemoresistant, and 6% untreated. The graft source was peripheral blood in 78%, and 90% involved unrelated donors. Outcome at 3 years included TRM=42%, progression=36%, and PFS=22%. Causes of death were NHL (29%), infection (19%), MOF (19%), GVHD (14%). There was a lower risk of relapse and death in patients with a KPS≥90%, >2 years between transplants, use of TBI, and CR at time of SCT.

Most recently, The EBMT reviewed their results of 101 patients with DLBCL who received an allogeneic SCT after relapse from an autologous SCT (MAC=37, RIC=64). The 3-year PFS was 42% and the OS rate was 54%. Non-relapse mortality was 41% for MAC versus 20% for RIC (p=0.05), but relapse rates were higher after RIC, particularly those patients who relapsed less than 1 year post-autologous SCT and those who were chemo-resistant. No evidence for GVT effect was seen.

Overall, full and reduced intensity allogeneic SCT for aggressive lymphoma requires further evaluation in well-designed prospective RCTs before the true benefit and role can be fully understood. Only a few conclusions can be drawn based upon currently available data:
1. Relapse rates are lower after myeloablative allogeneic SCT than autologous SCT, although this difference is less than that reported for indolent lymphoma.
2. Treatment-related mortality rates are high, in the range of 20-40%.
3. Some patients who would otherwise have died from their lymphoma achieve long-term survival following allogeneic SCT, and therefore this treatment needs to be considered an option for motivated, well-informed, transplant-eligible patients who are well enough to tolerate this intensive treatment, have relapsed non-bulky chemosensitive disease, and are not candidates for autologous SCT.
4. Data do not demonstrate any improvement in 5-year survival rates with allogeneic over autologous SCT for lymphoma, with the exception of relapsed lymphoblastic and mantle cell lymphomas.9,10 Patients with these subtypes who present with extensive blood/marrow disease should also be considered for allogeneic SCT in first remission.11 Allogeneic SCT should also be considered in the situation when a patient is a candidate for an autologous SCT but an adequate autograft could not be collected for the patient. Occasionally, patients who relapse after a prior autologous SCT could be considered for an allogeneic SCT, especially for mantle cell or indolent lymphomas.

**Guidelines for Follow-Up after Hematopoietic SCT**
EBMT/ASBMT/CIBMTR joint recommendations for screening and preventive practices of long-term survivors after hematopoietic cell transplantation have recently been published, and will not be reviewed here.12

**References:**


Indolent Lymphoma

Upfront Treatment of Poor Prognosis Indolent Lymphoma

The role of first remission HDCT/ASCT remains investigational. Three frequently-cited randomized controlled trials have generally followed a similar design where patients either received CHOP-like induction therapy and interferon maintenance or CHOP-like induction followed by HDCT +/- TBI and ASCT. The trials were of modest size (169-401 patients) and allowed crossover HDCT/ASCT at relapse in the control arms. With median follow-up times between 4 and 5 years, one study has shown statistical improvement in overall survival (86 versus 74%) while the other two studies demonstrated improved progression-free survival (65 versus 33% and 59 versus 37%) for HDCT/ASCT over interferon. Because these studies have not consistently shown improved overall survival, involve a potentially toxic, expensive treatment that can be reserved for salvage therapy, and were conducted prior to the routine use of rituximab, HDCT/ASCT is not widely accepted as standard initial therapy for follicular lymphoma.

Treatment of Relapsed/Refractory Indolent Lymphoma

General principles: Generally accepted indications for therapy of indolent lymphoma include:

- Patient symptoms (e.g. fever, night sweats, weight loss, malaise, pain, nausea)
- Significant lymphadenopathy: >7 cm mass, >3 sites and >3 cm
- Rapidly progressive, moderate-to-severe splenomegaly
- Impending organ compromise (e.g. compression, pleural/pericardial effusions, ascites)
- Cytopenias secondary to bone marrow infiltration
- Patient preference because of anxiety and poor quality of life without treatment

Patients who do not have at least one of these factors could simply be observed.
Therapeutic recommendations for recurrent follicular lymphoma need to be individualized. No one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma. Some of these include:

- **Patient factors:** Age, co-morbidity, symptoms, short versus long-term goals, preservation of future options, reimbursement versus ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (relative risk, progression-free survival, overall survival)
- **Disease factors:** Sites, grade, transformation, prior therapy, response duration (disease-free interval)

For example, previously healthy patients younger than 65 years who relapsed within 1-2 years of initial chemotherapy have a life expectancy of only 2-4 years, and are probably best managed with HDCT/ASCT or even allogeneic SCT. HDCT/ASCT probably maximizes the length of disease control for all patients younger than 65 years, regardless of length of initial remission, and as such is a reasonable treatment option for those who accept potential risks/toxicities. Conversely, some patients may be best managed by repeating their initial treatment regimen if they achieved an initial remission greater than 2 years. Other patients should be changed to a second line standard-dose chemotherapy regimen (CHOP, FND, GDP).

**Autologous Transplantation for Follicular Lymphoma**

We conducted a retrospective analysis of the first 100 consecutive patients with relapsed or refractory follicular lymphoma treated with HDT/ASCT in Calgary from 1993-2008. With a median follow-up of 65 months (range 16-178) post-ASCT, the 5-year EFS and OS rates were 56% (95%CI 46-66) and 70% (95%CI 61-79), respectively. A plateau on the EFS curve was evident starting 6 years post-ASCT. Also, the EFS post-ASCT was markedly longer than the 12-month median EFS from last therapy prior to ASCT (p<0.0001). Severe toxicities included 2 early treatment-related deaths, and 4 late deaths from secondary leukemia. Factors significantly associated with adverse EFS and OS were:

- Follicular Lymphoma International Prognostic Index (FLIPI) score 2-5 versus 0-1
- Elevated LDH
- Lack of rituximab within 6 months prior to ASCT

The year of ASCT divided further into the 3 time periods of 1993-1999, 2000-2003, and 2004-2008, reflective of varying rituximab availability in our health region, also showed a significant association with 5 year EFS (38 vs. 56 vs. 64% respectively, p=0.038). Independent predictors of EFS and OS in multivariate analysis were rituximab therapy within 6 months of ASCT and FLIPI score 0-1.

Our results support those of previous publications concerning outcomes of ASCT for relapsed or refractory follicular lymphoma, which report 5-year EFS rates ranging from 44-59% and 5-year OS
rates of 63-78%. One of the largest historical series from the EBMT registry retrospectively analyzed 693 patients with follicular lymphoma treated with ASCT and reported a 10-year PFS rate of 31% with a plateau on the PFS curve. Unfortunately, there are no large randomized trials evaluating ASCT for relapsed follicular lymphoma, however, several trials have demonstrated significantly better PFS for ASCT consolidation compared to interferon for follicular lymphoma patients in first remission. The lack of OS benefit for upfront ASCT in these studies is possibly due to cross-over to ASCT at relapse in the control arms. Available non-randomized data for relapsed follicular lymphoma patients show significantly longer progression-free survival following HDCT/ASCT than from prior therapy within the same patients. A GELA trial reported a 5-year overall survival of 58% for relapsed follicular lymphoma patients treated with ASCT relative to 38% for concurrent controls (p=0.0005), and found that ASCT at first relapse was independently associated with overall survival in multivariate analysis. The only published randomized trial evaluating HDCT/ASCT for relapsed follicular lymphoma was stopped due to poor accrual after only 89 patients were randomized. With a median follow-up of 69 months, the 5-year PFS (55 versus 15%) and OS (70 versus 45%) rates significantly favoured HDCT/ASCT. These results support a role for HDCT/ASCT in the management of selected, relapsed, chemosensitive follicular lymphoma patients. The use of rituximab prior to stem cell collection and the incorporation of RIT into the HDCT regimen may further improve upon the results of ASCT for follicular lymphoma.

Evidence is emerging that ASCT remains an effective salvage therapy for relapsed follicular lymphoma after rituximab-containing regimens and suggests that rituximab may be beneficial as part of HDT/ASCT salvage therapy. Kang and colleagues compared follicular lymphoma patients who had received rituximab prior to ASCT to a group who were rituximab-naïve, excluding patients who received rituximab as part of salvage therapy, and found no significant difference in relapse-free survival (RFS) or OS.1 Kang and colleagues reported a study of 136 high risk patients with follicular lymphoma who were randomized to up-front therapy with 6 courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or rituximab-supplemented high-dose sequential chemotherapy with autografting (R-HDS). They noted a 4-year EFS favouring R-HDS over R-CHOP (61 versus 28%, p<0.001), however OS was similar because 71% of R-CHOP failures underwent salvage R-HDS and 85% achieved a complete remission and 68% achieved 3-year EFS, again demonstrating that HDT can salvage R-chemotherapy failures.

The curative potential of ASCT for follicular lymphoma remains controversial, in part because of a lack of consensus as to the definition of cure for this disease. Oncologists frequently define cancer cure as a prolonged plateau on a RFS curve after therapy cessation. The plateaus on our EFS curve starting at 6 years and extending to 15 years post-ASCT indicate that a subset of patients may be cured. Several other studies of ASCT for follicular lymphoma have demonstrated similar long-term plateaus on EFS curves, suggesting that relapses are very unlikely to occur after 7-8 year remissions. Clear evidence of cure post-ASCT for follicular lymphoma is challenging due to the indolent nature of the disease, which requires 5-10 year follow-up to detect late relapses. Many published studies are retrospective, report data on indolent lymphomas with...
histologies other than follicular lymphoma, include many patients who are heavily pre-treated having failed 3 or more regimens, and report inadequate median follow-up times of less than 5 years, with few patients followed for 10 or more years. If ASCT is to be used as a curative strategy, it should be included as a part of primary therapy or at first relapse. Indeed, Tarella and colleagues reported outcomes for 168 high risk patients with follicular lymphoma who received HDT/ASCT as part of primary therapy and demonstrated that 48% remained in complete remission at a 10 year median follow-up, with a plateau on the disease-free survival curve starting at approximately 8 years.29

We found that an intermediate or high FLIPI score of 2-5 at the time of relapse/refractory status prior to ASCT was independently predictive of inferior EFS and OS. These results confirm those of Vose and colleagues who reported that a high risk FLIPI score (3-5) at the time of HDT was predictive of inferior outcome.18 Two additional studies also reported that an age adjusted International Prognostic Index (aaIPI) of ≥2 at HDT correlated with poor outcome after ASCT for follicular lymphoma.17,30,31 In contrast, two studies reported no correlation between FLIPI score and outcome after ASCT for follicular lymphoma, though both analyzed FLIPI at diagnosis rather than at ASCT.5,28 In our analysis, an intermediate to high risk FLIPI score at diagnosis also had no predictive value for survival post-ASCT.

Retrospective studies have demonstrated that rituximab improves outcomes when used prior to HDT-ASCT for relapsed follicular lymphoma.17,19,22,30 The only phase III trial to evaluate the role of rituximab in the setting of ASCT for follicular lymphoma is the EBMT LYM1 study, which investigated the value of in-vivo purging with rituximab 375 mg/m² weekly for 4 cycles prior to stem cell collection and the value of maintenance rituximab every 3 months for 2 years post-ASCT.32 This study randomized 280 patients with follicular lymphoma in a 2x2 design, and showed no improvement in PFS with in-vivo purging (5-year PFS 54.3 versus 47.8%, p=0.20), but improvement in PFS with maintenance rituximab (58.8 versus 42.6%, p=0.02). We also found no evidence that rituximab-based mobilization improved EFS over chemotherapy alone; however, this result is confounded by the use of rituximab with re-induction therapy prior to mobilization for many patients. The benefit of rituximab pre-ASCT may be due to an in-vivo purging effect on the autograft.17,19 Arcaini and colleagues demonstrated this purging effect by showing that none of their patients’ stem cell harvests had detectable minimal residual disease using polymerase chain reaction (PCR) amplification of the Bcl-2/IgH rearrangement after receiving a rituximab-containing regimen.19 Absence of minimal residual disease was demonstrated to lead to an improvement in PFS, a finding confirmed by several groups.16,17,19,27

Our early treatment-related mortality rate of 2%, and secondary AML/MDS rate of 4% compare favourably with other reports of HDT/ASCT for follicular lymphoma, but are still of concern. These serious adverse events caution against using HDT/ASCT as a part of initial remission consolidation. Other series report rates of secondary malignancies as high as 16-21% at 10 years with about half being fatal;5,28 though this rate may be lower with HDT regimens that exclude total body irradiation.13,23 The patients in our cohort who developed secondary AML/MDS had all received prior fludarabine or chlorambucil, and total body irradiation in the HDT regimen.
Avoidance of these exposures may decrease the incidence of secondary AML/MDS for this patient population.

References:


Allogeneic Transplantation for Follicular and Other Indolent Lymphoma

Despite prolonged OS from diagnosis, patients with indolent B-cell NHL are rarely cured by conventional chemotherapy.\(^1\) Following relapse, most patients live with the presence of disease and intermittent toxicity from repeated courses of therapy until their death, often within 5 years of relapse.\(^2\) As such, many otherwise healthy individuals prefer to maximize the chance of prolonged PFS with high dose therapy and HSCT;\(^3\)-\(^7\) a result possibly improved when rituximab is used with stem cell mobilization or transplantation.\(^8\),\(^9\) It must be acknowledged, however, that most SCT data are retrospective, and subject to selection bias. Compared to autoSCT outcomes, CIBMTR data suggest that alloSCT is associated with significantly lower relapse rates but similar OS rates due to much higher TRM from GVHD and opportunistic infections.\(^10\),\(^11\) Specifically, the CIBMTR reported results on 904 patients undergoing alloSCT (176), purged autoSCT (131), or unpurged autoSCT (597) for follicular lymphoma, showing that 5-year TRM rates were 30\%, 14\%, and 8\%, 5-year relapse rates were 21\%, 43\%, and 58\%, and 5-year OS were 51\%, 62\%, and 55\%, respectively, with no association between GVHD and lymphoma relapse after alloSCT.\(^10\) There are no data from large prospective, randomized controlled trials comparing autoSCT to alloSCT, or different high dose conditioning regimens for indolent lymphoma.

Data from the CIBMTR suggest that a second autoSCT is feasible and can confer long-term benefit in some patients, usually those who relapse more than one year after the prior autoSCT.\(^12\) It is also possible to perform an alloSCT after prior autoSCT failure, although CIBMTR results suggest 3 and 5 year PFS rates of only 20 and 5\%, respectively.\(^13\)

CIBMTR data showing significantly lower rates of grades III–IV acute GVHD and improved PFS for 179 patients who received rituximab within 6 months of alloSCT compared to 256 patients who did not receive prior rituximab.\(^14\) TRM may potentially be further reduced with non-myeloablative conditioning (NST), also called reduced intensity conditioning (RIC),\(^15\) however data derived from large numbers of patients receiving NST reported to the CIBMTR demonstrate 1 year TRM rates slightly over 20\%, and higher relapse rates than myeloablative alloSCT.\(^16\)

Quality of life (QOL) studies in the SCT setting tend to report that early impairments in QOL largely return to pre-SCT levels by day 100, over half of patients report good to excellent QOL one year post-SCT, autoSCT patients tend to recover faster than alloSCT, and that reduced QOL and impaired functional status post-alloSCT is most strongly associated with the presence of chronic GVHD.\(^17\),\(^18\)

Calgary Results of FluBu and Autologous or Allogeneic SCT for Indolent Lymphoma

A prospective phase II study was conducted to evaluate autoSCT and alloSCT stem cell sources depending upon availability of appropriate sibling donor, following uniform RICE (rituximab, ifosfamide, carboplatin, etoposide) re-induction and novel myeloablative FluBu (fludarabine, busulfan) conditioning, for patients with mantle cell lymphoma in first remission or first relapse, or indolent lymphoma in first or second relapse. Sixty-eight patients (autoSCT=36, syngeneic=1, alloSCT=31) were accrued from June 2001 to December 2006, with a 10 month median PFS, and 1\% 5-year PFS rate following their last chemotherapy treatment. Following RICE, the overall
response rate was 69%, and 24 of 39 patients (62%) cleared marrow of lymphoma. Treatment-related mortality following FluBu was 0% and 6% at 100 days, but 0% and 26% at 1 year post-autoSCT and alloSCT, respectively. At a median follow-up of 60 months, the respective 5 year overall survival (71% vs. 58%, logrank p=0.086) and PFS (46% vs. 47%, logrank p=0.843) rates were similar for auto/synSCT and alloSCT, while the 1 year post-SCT quality of life assessment favored autoSCT.

References:


Additional Reading


Hodgkin Lymphoma

Pathologic Classification
The histological sub-classification of Hodgkin disease is based on the light microscopic H&E interpretation. If problems with differential diagnosis arise, staining for CD15, CD30, T-cell and B-cell panels and EMA may be helpful. For lymphocyte predominant Hodgkin disease, CD20, CD45, +/- CD57 are recommended.

WHO Classification of Histologic Subtypes\(^1,2\)
- Nodular Lymphocyte Predominant Hodgkin Disease (LPHD)
- Classical Hodgkin Lymphoma:
  - Nodular Sclerosis Hodgkin Disease (NSHD)
  - Mixed Cellularity Hodgkin Disease (MCHD)
  - Lymphocyte Depletion Hodgkin Disease (LDHD)
  - Lymphocyte-rich classical Hodgkin Disease (LRCHD)

Autologous SCT for Hodgkin Lymphoma
Two randomized trials support the role of high-dose therapy (HDT) and ASCT over conventional dose salvage therapy with mini-BEAM (carmustine, etoposide, cytarabine, melphalan) or dexamethasone-BEAM in relapsed/refractory Hodgkin lymphoma,\(^3,4\) although optimal re-induction and HDT regimens are unknown.\(^5-14\) A commonly used salvage regimen for Hodgkin lymphoma in Canada is GDP (gemcitabine, dexamethasone, cisplatin). Kuruvilla and colleagues from Toronto retrospectively compared the outcomes of 68 Hodgkin lymphoma patients treated with either GDP or mini-BEAM as salvage therapy, followed by HDT/ASCT in responding patients.\(^14\) The response rate to GDP prior to ASCT was similar to mini-BEAM at 62% and 68%, respectively, however, the PFS at 1.5 years was superior with GDP (74% vs. 35%). Moccia and colleagues from the British Columbia Cancer Agency recently presented results of salvage GDP for 83 Hodgkin lymphoma patients whose characteristics included 82% International Prognostic Score (IPS) 0-3, 88% first salvage, 36% refractory. Of the 67% patients who had response assessment available, 7% achieved CR/CRu, 64% PR, and 69 pts (83%) proceeded to HDT/ASCT. With a median follow-up of 30 months from starting GDP, 2-year PFS was 58%.\(^15\) Recently, Josting and colleagues published the results of the HDR-2 randomized controlled trial in which patients responding after 2 cycles of DHAP (dexamethasone, cytarabine, cisplatin) were randomized to either standard BEAM-ASCT or sequential high dose therapy (SHDCT: cyclophosphamide, methotrexate, etoposide) before BEAM-ASCT.\(^16\) Patients randomized in this study were chemosensitive and 60% had relapsed after an initial remission duration of over 1 year. Nevertheless, the 3-year freedom from treatment failure rate was only 62%, and was similar between the arms.

Calgary previously reported a 5-year event-free survival (EFS) rate of approximately 50% for 23 patients with relapsed/refractory Hodgkin lymphoma who were treated with single agent high-dose melphalan and ASCT.\(^17\) This rate is similar to that reported for multi-agent high-dose chemotherapy regimens.\(^3,4,18,19\) Calgary results of double high-dose therapy with DICEP (dose-
intensified cyclophosphamide 5.25 g/m², etoposide 1.05g/m², and cisplatin 105 mg/m²) re-induction followed by high dose melphalan 200mg/m² and ASCT for 73 consecutive patients with relapsed (n=43) or refractory (n=30) classical Hodgkin lymphoma treated between June 1995 and November 2009 have been reviewed and submitted for publication in 2011. DICEP chemotherapy resulted in successful stem cell mobilization in 71 patients (97%), with a median CD34+ cell collection of 15.6 x10⁶/kg. With a median follow-up of 56 months post-DICEP, the 5-year PFS and OS rates were 61% [95%CI 49-72%] and 80% [95%CI 69-89%], respectively. The 5 year PFS was 65% versus 30% for DICEP responders versus non-responders (logrank p=0.003) and 89% for IPS 0-1, 56% for IPS 2-3, and 24% for IPS 4-7 (logrank p<0.001). Response to DICEP and relapse IPS were the only two factors that independently predicted PFS and OS in multivariate analyses. Treatment-related mortality was 1%.

Results of DICEP compare favourably to reports of other salvage regimens, which tend to report ORR below 75% and 5 year PFS rates below 50%. The ORR with DICEP was 86% despite the fact that that response was assessed only 4-5 weeks after a single cycle of salvage therapy, and without the use of PET which may have upgraded some PRs to CRs. Perhaps the most encouraging results were seen for primary refractory disease patients. Prior reports of high dose therapy/ASCT for refractory Hodgkin lymphoma include a 3-year PFS rate of 38% from the Autologous Bone Marrow Transplant Registry, and 5-year freedom from second failure rate of 31% from the German Hodgkin Study Group. Most studies suggest that the length of initial remission duration is associated with outcome of salvage high dose therapy/ASCT, however, this is not a universal finding. In our study, however, initial time to progression failed to impact either PFS or OS with a 5-year PFS rate of 57% for refractory Hodgkin lymphoma, suggesting that DICEP-high dose melphalan/ASCT overcomes relative chemo-resistance and provide superior outcomes in patients with primary refractory disease.

Second Hematopoietic SCT for Hodgkin Lymphoma
Smith and colleagues from the CIBMTR reported a 5-year PFS rate of 30% for patients with either Hodgkin lymphoma (n = 21) or non-Hodgkin lymphoma (n=19) receiving a second ASCT after relapse following a prior ASCT, suggesting that a second ASCT can possibly induce long term disease control for some patients who are not cured by prior high dose therapy. In another study, a 5-year OS rate of 46% was reported using tandem transplantation in poor prognosis relapsed or refractory Hodgkin lymphoma patients. Clear evidence, however, must await randomized controlled trials, which have not evaluated this strategy of tandem high dose therapy for relapsed Hodgkin lymphoma.

Allogeneic SCT for Hodgkin lymphoma has been reported to confer a 5 year PFS in approximately 20-35% of patients. Patients who achieve good outcomes generally have chemosensitive disease that relapsed more than 1 year post-autoSCT. Reduced intensity conditioning allogeneic SCT for Hodgkin lymphoma patients relapsing after autologous transplantation was reported by Sarina and colleagues from the GITMO group in 2008. In this study of 132 patients with a median age of 30 years (range 17-62), 75 patients were found to have a SCT donor and 68 (90%) underwent an allogeneic SCT, including 36 matched related donors (52%), 23 matched unrelated
donors (33%), and 6 haploidentical family donors (9%). The most common high dose chemotherapy regimen was thiotepa, cyclophosphamide, and fludarabine; GVHD prophylaxis consisted of methotrexate plus cyclosporine, except for haploidentical-SCT. Seven patients with donors did not receive allogeneic SCT because of progressive disease. The cohorts of donors versus no donors were well balanced, including relapsing less than 6 months from autologous SCT. The results are shown in the table below, indicating improved PFS and OS with the allogeneic SCT. In multivariate analysis, having a donor and CR before allogeneic SCT were significant for improved OS and PFS.

Table 1. Outcomes of patients (OS, PFS, GVHD and mortality) with or without a donor

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Donor (N=75)</th>
<th>No Donor (N=57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year OS</td>
<td>70% (77% if SCT)</td>
<td>38.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>2 year PFS</td>
<td>42% (47% if SCT)</td>
<td>10%</td>
<td>0.03</td>
</tr>
<tr>
<td>acute GVHD, grade 2-4</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chronic GVHD</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment-related mortality</td>
<td>12%</td>
<td></td>
<td></td>
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</table>

References:


Stem Cell Graft

The section on the stem cell graft has been removed from these guidelines and transferred to the section on “Donor Management, including Stem Cell Mobilization”.

Allogeneic Stem Cell Transplantation for Lymphoma

General Comments¹-⁵

Potential benefits of allogeneic over autologous SCT for lymphoma have not been evaluated by randomized controlled trials. As such it is difficult to determine when this more expensive and toxic treatment should be recommended. IBMTR and EBMT registry data do not demonstrate any improvement in 5 year survival rates with allogeneic over autologous SCT for lymphoma, with the exception of relapsed lymphoblastic and mantle cell lymphomas. Patients with these subtypes who presented with extensive blood/marrow disease should also be considered for allogeneic SCT in first remission. Allogeneic SCT should also be considered for multiply relapsed indolent lymphoma (2nd or 3rd relapse), or in the situation when a patient is a candidate for an autologous SCT but an adequate autograft could not be collected for the patient. Occasionally, patients who relapse after a prior autologous SCT could be considered for an allogeneic SCT, especially for mantle cell or indolent lymphomas, and occasionally for Hodgkin lymphoma.

References:


Calgary Stem Cell Transplantation Results for Lymphoma

Autologous SCT for Aggressive Lymphoma

Figure 1. Progression-free survival of DLBCL treated with autologous HSCT in Calgary (n=268)

Figure 2. Progression-free survival of DLBCL treated with autologous HSCT in Calgary (n=258)
**Figure 3.** Time to positivity for DLBCL treated with autologous HSCT in Calgary (n=268)

**Figure 4.** Progression-free survival for (R)DICEP +/- HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma (n=113)
Figure 5. Progression-free survival after (R)DICEP +/- HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma (n=113)

Figure 6. Progression-free survival after (R)DICEP +/- HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma (n=113)
In Calgary, we analyzed 115 patients with refractory/relapsed DLBC or large T-cell non-Hodgkin lymphoma who received DICEP salvage therapy. Of these patients, 104 (90%) proceeded to HDCT/ASCT. Initial time to relapse < 1yr, elevated LDH, ECOG 2-4, and aaIPI=3 were more common in the 11 patients who did not proceed to ASCT. For example, of the 25 patients with aaIPI=3, only 17 (68%) proceeded to ASCT compared with 87 of 90 patients (97%) with aaIPI=0-2. We also compared the results of the 104 patients who received DICEP then HDCT/ASCT with the other 44 Calgary patients who received HDCT/ASCT during the same time period (1995-2009) but did not receive DICEP. Clinical factors more common in DICEP than no DICEP groups included:

- age >60 13.5% vs. 40.9% (p=0.0002)
- TTP<1yr 72.1% vs. 47.7% (p=0.004)
- refractory 29.8% vs. 6.8% (p=0.002)
- bulk >10cm 24.3% vs. 9.1% (p=0.042)

Despite generally worse prognostic factors in the DICEP group, PFS rates were not significantly different between the groups (logrank p=0.11).
Figure 8. Survival after DICEP then HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma in Calgary 1995-2009 (n=113)

Figure 9. Time to positivity after DICEP then HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma in Calgary 1995-2009
Figure 10. Time to positivity after DICEP then HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma in Calgary 1995-2009

Figure 11. Time to positivity after DICEP then HDCT/ASCT for relapsed/refractory aggressive histology non-Hodgkin lymphoma in Calgary 1995-2009
Figure 12. Progression-free survival after high dose thiotepa/busulfan-based conditioning and ASCT for primary CNS lymphoma in Calgary (n=28)

Figure 13. Survival after high dose thiotepa, busulfan, cyclophosphamide and ASCT for PCNSL in Calgary 1998-2010 (n=26)
Figure 14. Overall survival for HIV – PCNSL patients in Alberta less than 65 years of age from 1998-2008 (n=50)

Figure 15. Survival for patients with secondary CNS lymphoma treated in Alberta with high dose thiotepa/busulfan-based conditioning and ASCT (n=20)
Figure 16. Progression-free survival for uncommon B-cell lymphoma treated with autologous HSCT in Calgary (n=23)

Figure 17. Survival for patients with relapsed/refractory classical Hodgkin lymphoma treated with DICEP then melphalan/ASCT in Calgary (n=73)
**Figure 18.** Event-free survival for patients with relapsed/refractory classical Hodgkin lymphoma treated with DICEP then melphalan/ASCT in Calgary, categorized by IPS (n=73)

**Figure 19.** Event-free survival for patients with relapsed/refractory classical Hodgkin lymphoma treated with DICEP then melphalan/ASCT in Calgary (n=73)
Autologous Stem Cell Transplantation for Follicular Lymphoma

**Figure 20.** Progression-free survival for patients with follicular lymphoma treated with HSCT in Calgary (n=170)

**Figure 21.** Event-free survival for the initial 100 patients treated with ASCT for relapsed/refractory follicular lymphoma in Calgary between September 1993 and October 2008
Figure 22. Event-free survival for patients treated with rituximab within 6 months of ASCT for relapsed/refractory follicular lymphoma in Calgary between July 2000 and October 2008, categorized by TBI conditioning.

Figure 23. Event-free survival for patients treated with ASCT for relapsed/refractory follicular lymphoma in Calgary between September 1993 and October 2008, categorized by treatment.
Figure 24. Event-free survival for patients treated with rituximab within 6 months of ASCT for relapsed/refractory follicular lymphoma in Calgary between July 2000 and October 2008

Figure 25. Event-free survival for the initial 100 patients treated with ASCT for relapsed/refractory follicular lymphoma in Calgary between September 1993 and October 2008
Stem Cell Transplantation for Mantle Cell Lymphoma

**Figure 26.** Progression-free survival for patients with mantle cell lymphoma treated with HSCT in Calgary (n=74)

**Figure 27.** Overall survival for patients with mantle cell lymphoma treated with HSCT in Calgary (n=74)
Figure 28. Event-free survival for patients <70yo with mantle cell lymphoma treated with SCT in Calgary between 1994 and 2009 (n=49)

Figure 29. Overall survival from diagnosis for patients with mantle cell lymphoma treated with SCT in patients <70yo in Calgary between 1994 and 2009 (n=77)
Allogeneic Stem Cell Transplantation for Lymphoma

**Figure 30.** Progression-free survival for allogeneic/syngeneic HSCT for indolent lymphoma (n=78)

**Figure 31.** Progression-free survival for allogeneic/syngeneic HSCT for aggressive lymphoma (n=33)
Figure 32. Overall survival for allogeneic SCT for relapsed/refractory Hodgkin lymphoma in Calgary (n=15)

Figure 33. Event-free survival after treatment with FluBu (ATG) and AlloSCT or AutoSCT for relapsed/refractory follicular lymphoma in Calgary (n=51)
Figure 34. Overall survival after treatment with FluBu (ATG) and AlloSCT or AutoSCT for relapsed/refractory follicular lymphoma in Calgary (n=51)
Salvage Chemotherapy Regimens for Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
</tr>
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</table>
| VIP     | Dexamethasone 10mg IV q6h days 1-4  
Ifosfamide 1.5 g/m² (max 1.75g) over 60min days 1-3  
Cisplatin 25-35mg/m² IV over 1h days 1-3  
Etoposide 100-125mg/m² over 1h days 1-3  
Mesna 300 mg/m² over 5-10 min prior to first dose of Ifosfamide, then 300 mg/m² IV at 4h and 600mg/m² po (or 300 mg/m² IV) at 8h post-Ifosfamide x 4 days.  
Cycles: Q21-28d |
| GDP     | Gemcitabine 1000mg/m² IV days 1 and 8  
Decadron 40mg po days 1-4  
Cisplatin 75mg/m² IV |
| DICEP   | Dexamethasone 10mg IV q8h x 10 doses  
Cyclophosphamide 1.75 g/m² IV over 2 hrs days 1-3  
Etoposide 350mg/m² IV over 2 hrs days 1-3  
Cisplatin 35mg/m² IV over 2 hrs days 1-3  
Mesna 1.75g/m² IV over 24 hrs days 1-3  
Septra for PCP prophylaxis  
Cycles: Once only |
| MICE    | Dexamethasone 10mg IV q8h x 10 doses  
Cyclophosphamide 1.5 g/m² IV over 2 hrs days 1-3  
Etoposide 200mg/m² IV over 2 hrs days 1-3  
Mesna 1.5g/m² IV over 24 hr days 1-3  
Septra for PCP prophylaxis  
Cycles: Once only |

Stem Cell Mobilization Regimens for Lymphoma

<table>
<thead>
<tr>
<th>Indication</th>
<th>Regimen</th>
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<tbody>
<tr>
<td>Relapsed Hodgkin Lymphoma</td>
<td>DICEP</td>
</tr>
<tr>
<td>Peripheral T-Cell Lymphoma</td>
<td>DICEP</td>
</tr>
<tr>
<td>Relapsed/Refractory DLBCL</td>
<td>R-DICEP</td>
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<tr>
<td>High Risk DLBCL in PR1 (eg.DHL or IPI=3-5)</td>
<td>R-DICEP</td>
</tr>
<tr>
<td>SCNSL</td>
<td>R-DHAP</td>
</tr>
<tr>
<td>PCNSL</td>
<td>R-AraC</td>
</tr>
<tr>
<td>Mantle Cell Lymphoma</td>
<td>R-DHAP (or R-AraC if unable to tolerate cisplatin)</td>
</tr>
<tr>
<td>Relapsed Follicular or other indolent NHL</td>
<td>R-C2g/m² or RC2HOP or RC2EOP (non-bulky, chemosensitive relapsed disease), or R-DICEP (bulky, refractory, or clinically aggressive)</td>
</tr>
</tbody>
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High Dose Chemotherapy Regimens for Stem Cell Transplantation

See chapter on Conditioning.
Symptomatic Myeloma and AL Amyloidosis: Indications for Stem Cell Transplantation

Presented by: Jason Tay and Victor Zepeda

Summary

1. An autologous stem cell transplant (ASCT) should be offered to patients with symptomatic myeloma who are ≤65 years old without significant co-morbidities who 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.
   - We do not recommend ASCT for individuals ≥70 years.
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
   - 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/m²
   - 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. The use of combination lenalidomide with a proteasome inhibitor as maintenance is reasonable in patients with high risk disease.
9. Allogeneic transplant is not indicated outside a clinical trial.
10. ASCT may be offered to selected patients with systemic AL amyloidosis who meet the following 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%.
11. Induction chemotherapy for patients with AL amyloidosis should be recommended for patients with >10% monoclonal plasma cells in the bone marrow at presentation.

12. 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). 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.

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

Rationale for use of autologous 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 support 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 of time 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\(^13,14\).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>SDT versus HDT (p-value)</th>
<th>Median PFS (mths)/3 yr PFS</th>
<th>3 or 4 year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo et al. 2014(^{15})</td>
<td>402</td>
<td>&lt;65</td>
<td>15.7 vs. 20</td>
<td>22.4 vs. 43 (p&lt;0.001)</td>
<td>65.3 vs. 81.6 (p=0.02)</td>
</tr>
<tr>
<td>Gay et al. 2015(^{16})</td>
<td>389</td>
<td>≤65</td>
<td>?20s vs. 30s</td>
<td>28.6 vs. 43.3 (p&lt;0.001)</td>
<td>84 vs. 87%</td>
</tr>
<tr>
<td>Cavo et al. 2017(^{17})</td>
<td>1503</td>
<td>≤65</td>
<td>75 vs. 84</td>
<td>57% vs. 64% (p=0.002)</td>
<td>NR</td>
</tr>
<tr>
<td>Attal et al. 2017 IFM/DFCI2009(^{18})</td>
<td>700</td>
<td>≤65</td>
<td>48 vs. 59 (p=0.03)</td>
<td>36 vs. 50 (p&lt;0.001)</td>
<td>82 vs. 81 (p=0.87)</td>
</tr>
</tbody>
</table>

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\(^{19-22}\) 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\(^{18}\).
Table 3: Review of RCTs Comparing Upfront or Delayed ASCT

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Response</th>
<th>Median EFS/PFS (mths)</th>
<th>Median OS (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermand et al. 1998</td>
<td>202</td>
<td>≤56</td>
<td>NR</td>
<td>39 vs. 13 p=0.02</td>
<td>64.6 vs. 64 p=0.92</td>
</tr>
<tr>
<td>Attal et al. 2017 IFM/DFCI2009</td>
<td>700</td>
<td>≤65</td>
<td>59% vs. 48% (CR)</td>
<td>50 vs. 36 p&lt;0.001</td>
<td>81% vs. 82% at 4yrs p=NS</td>
</tr>
</tbody>
</table>

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. 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. In addition, there have been movements to consider physiologic age as opposed to chronologic age. As such, it is reasonable to consider ASCT in patients >65 with careful attention to comorbidities and assessments of frailty.

Patient Variables:
See AHS BMT guidelines section: Patient Eligibility

Depth of Response:
In general depth of response pre-ASCT correlates with post-ASCT outcomes. 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. 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.

In the “novel therapy” era, the MRC XI 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:**
Figure 1 illustrates ASCTs performed in Calgary over 20 years, including the proportion of 2nd ASCT (planned tandem, delayed ASCT or stem cell boost). There were 537 ASCTs for symptomatic myeloma, with 66 of those ASCTs being 2nd ASCTs. On average, 12.29% of all ASCTs are 2nd ASCTs for symptomatic myeloma, where 6.33%, 3.33% and 2.61% are for delayed 2nd ASCT, Tandem ASCT and stem cell boost respectively.

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 discussed on a case by case basis.

**Figure 1:**

![Number of ASCTs over 20 years - Calgary](chart.png)
Conditioning regimen

The current standard for conditioning is Melphalan 200mg/m² following a RCT demonstrating that Melphalan 200mg/m² (Mel200) was superior to Melphalan 140mg/m² (Mel140) with 8 Gy Total Body Irradiation. A large database study from EBMT suggest that Mel200 may 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.

More recently, Rousell 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. Additionally, Qazilbash et al. evaluated the combination of Mel140+Busulfan 130mg/m² vs. Mel200 in a RCT with the combination therapy associated with an improved PFS (65 months vs. 34 months).

The dose of melphalan should be reduced to 140mg/m² in individuals with renal dysfunction or on dialysis. Further, consideration could be given to a 140mg/m² melphalan dosing in those who >65 years with deemed frailty.

Table 4: Review of RCTs Comparing Conditioning Regimens in ASCT

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yrs) Median</th>
<th>CR (%)</th>
<th>Mel200 versus “other” (p-value)</th>
<th>Median EFS/PFS</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreau et al. 2002 IFM 9502</td>
<td>282</td>
<td>&lt;65</td>
<td>NA</td>
<td>EFS of 20.5 mths vs. 21 mths (p=0.6)</td>
<td>65.8 vs. 45.5 (at 45mths) p=0.05</td>
<td></td>
</tr>
<tr>
<td>Rousell et al. 2017 IFM 2014-02</td>
<td>300</td>
<td>58</td>
<td>21 vs. 23</td>
<td>76% vs. 79% (at 18 mth PFS)</td>
<td>93 vs. 93 (at 2 years)</td>
<td></td>
</tr>
<tr>
<td>Qazilbash et al. 2017</td>
<td>204</td>
<td>58-59</td>
<td>26 vs. 33</td>
<td>PFS of 34.4 mths vs. 64.7 mths (p=0.013)</td>
<td>NS at (p=0.94)</td>
<td></td>
</tr>
</tbody>
</table>

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. 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. Two meta-analyses would confirm these observations.
Table 5: Review of historic RCTs Comparing Tandem ASCT with Single ASCT

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

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. 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.49

These findings were also echoed by the preliminary findings in the EMN02/HO95 MM study, 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 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 6: Review of recent RCTs Comparing Tandem ASCT with Single ASCT

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Tandem versus single/other</th>
<th>Randomized Gps</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadtmauer et al. 2016 STAMINA</td>
<td>758</td>
<td>&lt;71yrs</td>
<td>Mel200 x1 - R maint</td>
<td>52 mths</td>
<td>83 mths</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mel200 x2 - R maint</td>
<td>57 mths</td>
<td>86 mths</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mel200 x1- RVD conso- R maint</td>
<td>57 mths</td>
<td>82 mths</td>
<td></td>
</tr>
<tr>
<td>Cavo et al. 2016 EMN02/HO95</td>
<td>1503</td>
<td>≤65yrs</td>
<td>Mel200 x1 - +/- RVD - R maint</td>
<td>64% (3yr PFS)</td>
<td>82% (3yr PFS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mel200 x2 - +/- RVD - R maint</td>
<td>73% (3yr PFS)</td>
<td>89% (3yr PFS)</td>
<td></td>
</tr>
</tbody>
</table>
**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 effects on OS is less clear.

Indeed, the above mentioned BMT-CTN 0702 STAMINA study\(^{50}\) did not demonstrate benefit of consolidation therapy. In contrast, preliminary data from the EMN02/HO95 MM study\(^{51}\) suggest a PFS benefit with 2 cycles of lenalidomide, bortezomib and dexamethasone (VRD) consolidation without OS benefit.

**Table 7: Review of recent RCTs Comparing Consolidation Therapy with No Consolidation Therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Randomized Gps</th>
<th>Median PFS (mths)</th>
<th>Median OS (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadtmauer et al. 2016</td>
<td>758</td>
<td>&lt;71yrs</td>
<td>Mel200 x1 - R maint</td>
<td>52 mths</td>
<td>83 mths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mel200 x2 - R maint</td>
<td>57 mths</td>
<td>86 mths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mel200 x1- RVD conso- R maint</td>
<td>57 mths</td>
<td>82 mths</td>
</tr>
<tr>
<td>Sonneveld et al. 2016</td>
<td>903</td>
<td>≤65yrs</td>
<td>RVD consolidation x 2</td>
<td>65% at 3yrs</td>
<td>86% at 3yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No consolidation</td>
<td>60% at 3yrs</td>
<td>87% at 3yrs</td>
</tr>
</tbody>
</table>

**Maintenance post-ASCT**

A typical maintenance therapy is low dose with limited toxicity administered over a prolonged period of time 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 has been considered standard of care following the publications by CALGB\(^{52}\) and IFM\(^{53}\). 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\(^{33}\) 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\(^{54-58}\).
The effect of maintenance bortezomib post-ASCT has also been evaluated. The HOVON-65/GMMG-HD4 study suggests that patients with del 17p might benefit from a proteasome inhibitor maintenance. More recently, the TOURMALINE MM3 study 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 8: Review of recent RCTs Comparing Maintenance Therapy with Lenalidomide with No Maintenance Therapy

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

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. In contrast, there have been numerous observational studies that support the use of a 2nd salvage ASCT. 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 9: Review of recent RCTs Comparing Maintenance Therapy with Proteosome Inhibition with No Maintenance Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Proteosome Inhibition versus other (p-value)</th>
<th>Median PFS (mths)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldschmidt et al. 2018 HOVON-65/GMMG-HD4</td>
<td>82</td>
<td>57</td>
<td>36 vs. 24 CR</td>
<td>35 vs. 28 (p=0.002)</td>
<td>61% vs. 55% at 5yrs</td>
</tr>
<tr>
<td>Dimopoulos et al. 2018 TOURMALINE MM3</td>
<td>65</td>
<td>57</td>
<td>12 vs. 7 MRD -ve</td>
<td>26.5 vs. 21.3 (p=0.002)</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 10: Review of RCTs of 2nd salvage ASCT.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Overall Response (%)</th>
<th>Median PFS (mths)</th>
<th>3-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook et al. 2014 NCRI myeloma X Relapse</td>
<td>297</td>
<td>61</td>
<td>83 vs. 75</td>
<td>19 vs. 11 (p&lt;0.001)</td>
<td>80.3 vs. 62.9 (p=0.19)</td>
</tr>
</tbody>
</table>

Role of allogeneic transplant

Evidence for a graft-versus-myeloma effect has been weak. Allogeneic transplants (myeloablative) is 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. In general, there is a lack of meaningful benefit with an ASCT-RIC allogeneic transplant approach to myeloma care. Allogeneic transplant in relapsed disease is poorly tolerated with marginal effectiveness over other available therapies.

Table 11: Review of RCT and quasi-RCTs comparing studies Tandem ASCT vs. ASCT-RIC Allo
Tandem ASCT vs. ASCT-RIC Allo (p-value)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean/Median Age (yrs)</th>
<th>CR (%)</th>
<th>Median PFS/EFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreau et al. 2008 IFM99-03 and IFM99-04</td>
<td>284</td>
<td>58 vs. 54 (p=0.006)</td>
<td>38 vs. 62</td>
<td>22mths vs. 19mths EFS</td>
<td>48mths vs. 34mths</td>
</tr>
<tr>
<td>Rosinol et al. 2008 PETHEMA</td>
<td>752</td>
<td>55 vs. 52</td>
<td>11 vs. 40 (p=0.001)</td>
<td>31mths vs. NR PFS (p=0.08)</td>
<td>34mths vs. 58mths (p=0.9)</td>
</tr>
<tr>
<td>Krishnan et al. 2011 BMT-CTN0102</td>
<td>710</td>
<td>&lt;70</td>
<td>45 vs. 58</td>
<td>46% vs. 43% at 3 yrs (p=0.671)</td>
<td>80% vs. 77% at 3 yrs (p=0.191)</td>
</tr>
<tr>
<td>Giaconne et al. 2011</td>
<td>162</td>
<td>55</td>
<td>26 vs. 55</td>
<td>2.4yrs vs. 2.8yrs EFS (p=0.005)</td>
<td>4.25yrs vs. NR (p=0.001)</td>
</tr>
<tr>
<td>Gahrton et al. 2013 EBMT-NMAM2000</td>
<td>357</td>
<td>≤69</td>
<td>41 vs. 50</td>
<td>12% vs. 22% at 8 yrs (p=0.027)</td>
<td>36% vs. 49% at 8 yrs (p=0.154)</td>
</tr>
<tr>
<td>Knop et al. 2014</td>
<td>199</td>
<td>53</td>
<td>31 vs. 59</td>
<td>23mths vs. 35mths PFS (p=0.005)</td>
<td>72mths vs. 70mths (p=NS)</td>
</tr>
</tbody>
</table>

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. Light-chain (AL) amyloidosis is the most common form of systemic amyloidosis, accounting for 70% of patients with amyloidosis. 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. AL amyloidosis is a disease of the elderly with a median age at diagnosis of 63 years.
There is a male predominance, with men accounting for 55% of cases\(^8^2\). 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\(^8^3\).

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\(^8^4\). 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\(^8^5\). In brief, 672 consecutive patients receiving ASCT for AL amyloidosis were divided into three cohorts on the basis of 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 v 58 v 54 years for cohorts 3, 2, and 1, respectively; \(P < .001\)). More patients received pre-transplantation therapy in cohort 3 compared with earlier time periods (49% v 38% v 42% for cohorts 3, 2, and 1, respectively; \(P = .02\)). Hematologic response was higher in cohort 3 (84% v 79% v 69% for cohorts 3, 2, and 1, respectively; \(P = .002\)). Median overall survival for the entire cohort was 122 months and improved over time (not reached v 120 months v 75 months for cohorts 3, 2, and 1, respectively; \(P < .001\)). Treatment-related mortality declined over time (2.4% v 8.6% v 14.5% for cohorts 3, 2, and 1, respectively; \(P < .001\)).

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\(^8^6\). High-dose dexamethasone was introduced later in 1997\(^8^7\). 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\(^8^8\). However, no cardiac biomarker selection was made on those patients and 29 centers were included for the study.
Requirements for safe ASCT currently include:\(^{83,84,89-91}\):

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 m\(^2\) 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\(^{92}\). 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\(^{93}\) 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%\(^{94}\).

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\(^{95}\).
Among 415 AL patients, 35% had induction prior to ASCT at the Mayo Clinic\textsuperscript{96}. Post-ASCT hematologic CR plus VGPR rates were significantly higher in those with baseline BMPC ≤ 10% compared to BMPC >10% (58% versus 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\textsuperscript{97}. 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\textsuperscript{36} 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.\textsuperscript{98}. 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\textsuperscript{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. 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 on 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. 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. 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 2: Recommended algorithm for ASCT in AL amyloidosis at Tom Baker Cancer Center.

AL amyloidosis (auto-SCT eligible)

- BMPC≥ 10% or symptomatic MM:
  - CyBorD induction (2-3 cycles)
  - Melphalan 200 mg/m2

- BMPC<10%:
  - Melphalan 200 mg/m2
References


39. Ali H, Jyoti B, Paneesha S, et al. Efficacy and Safety of Melphalan 140mg/m<sup>2</sup> or 200 mg/m<sup>2</sup> for autologous stem cell transplantation in elderly Pre-Dialysis and Dialysis Patients with Multiple Myeloma. Blood 2016;128:5822-.
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50. 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:LBA-1-LBA-.


Hematopoietic Cell Transplantation for Severe Aplastic Anemia
Presented by: Lynn Savoie. Revised by: Andrew Daly

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 antithymocyte 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 HCT from matched siblings or matched unrelated donors will consist of fludarabine, cyclophosphamide and rabbit antithymocyte globulin. Recipients receiving transplants from matched unrelated donors will receive this regimen augmented with an additional 200 cGy TBI. Additional GVHD prophylaxis will consist of methotrexate on day 1, 3, 6, 11 and cyclosporine for at least 6 months.
- Conditioning for haploidentical HCT will consist of rabbit antithymocyte globulin, fludarabine, low dose cyclophosphamide, and 200 cGy TBI (400 cGy if no previous immunosuppressive therapy). GVHD prophylaxis will consist of post-transplant cyclophosphamide, mycophenolate mofetil until day 35 and tacrolimus until 1 year.
- Bone marrow will be the preferred source of stem cells in aplastic anemia.
- Patients with recurrence of SAA after stem cell transplantation may be considered for repeat transplantation or immunosuppressive therapy.

Background

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 10⁹ / L
  - Platelets < 20 x 10⁹/L
  - Reticulocyte index < 1.0

**Results with Standard Treatment⁵⁻¹⁷**

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**

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

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.

**Bone Marrow Transplantation in SAA¹⁷⁻²⁶**

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

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

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.
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.\textsuperscript{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\%.\textsuperscript{33} Further improvement appears to have been achieved by including rabbit antithymocyte globulin into the conditioning. The Johns Hopkins (Baltimore) group reported on 16 patients with relapsed/refractory SAA (13 haploidentical and 3 unrelated), age 17-69, who received ATG, fludarabine, low dose cyclophosphamide, 200 cGy TBI, marrow graft, and posttransplant cyclophosphamide, MMF and tacrolimus. Overall survival with a median follow up of 21 months was 100\% (16/16), and no graft failure or moderate to severe cGVHD occurred. Additional 6 patients were transplanted according to this protocol with similar results, except moderate to severe cGVHD developed in one patient (Amy DeZern, pers.com., May 2019). 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,\textsuperscript{35} 1/8 after 300 cGy,\textsuperscript{36} and 1/17 after 400 cGy TBI\textsuperscript{37}). 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. This is consistent with the current approach by the Johns Hopkins group.

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

![Percent survival over time for patients with aplastic anemia](image-url)
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. 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). 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). We plan to use fludarabine 30 mg/m² 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. Patients receiving transplants from unrelated or mismatched donors will receive this regimen augmented with 200 cGy based on results of a retrospective study by the EBMT-SAA working party.

As of 2016 only three patients have been transplanted in Calgary using the above approach. It is still too early to determine whether this change has resulted in improved outcomes.

For haploidentical transplants, we will use the Baltimore protocol. 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/m²/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 one year. They will also receive mycophenolate mofetil 15 mg/kg tid (max 1 g tid) from day +5 to day +35.
Table 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Conditioning</th>
<th>Product</th>
<th>Graft Failure</th>
<th>aGVHD II-IV</th>
<th>cGVHD</th>
<th>TRM</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacigalupo</td>
<td>38</td>
<td>Flu/CY/rATG</td>
<td>BM=36; PBSC=2</td>
<td>18%</td>
<td>11%</td>
<td>27%</td>
<td></td>
<td>72 (2 years)</td>
</tr>
<tr>
<td>Kang</td>
<td>5</td>
<td>Flu/CY/rATG</td>
<td>BM</td>
<td>0</td>
<td>0 (1/5, grade I)</td>
<td>0</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Gupta</td>
<td>7</td>
<td>Flu/CY/alemtuzumab</td>
<td>BM</td>
<td>0</td>
<td>3/7</td>
<td>1/6</td>
<td>2/7</td>
<td></td>
</tr>
<tr>
<td>Chan</td>
<td>5</td>
<td>Flu/CY/ATG</td>
<td></td>
<td>0</td>
<td>80%</td>
<td>80%</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Urban</td>
<td>3</td>
<td>Flu + other</td>
<td>PBSC/CD34+ cells</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vassiliou</td>
<td>8</td>
<td>Alemtuzumab/CY/TBI</td>
<td>MUD=7; haplo sib=1</td>
<td>0</td>
<td>25% (grade II)</td>
<td>0</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

**MRD**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Conditioning</th>
<th>Product</th>
<th>Graft Failure</th>
<th>aGVHD II-IV</th>
<th>cGVHD</th>
<th>TRM</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>George</td>
<td>35</td>
<td>Flu/CY ± ATG</td>
<td>G stim; BM=7; PBSC=28</td>
<td>2.8%</td>
<td>29% (I-IV)</td>
<td>32%</td>
<td>17.1% (day 100)</td>
<td>82</td>
</tr>
<tr>
<td>Resnick</td>
<td>13</td>
<td>Flu/CY/ATG</td>
<td>BM=4; PBSC=9</td>
<td>0</td>
<td>8.3%</td>
<td>12.5%</td>
<td></td>
<td>84 (5 years)</td>
</tr>
<tr>
<td>Koh</td>
<td>8</td>
<td>Flu/TBI</td>
<td>PBSC; MRD=7; MUD=1</td>
<td>0</td>
<td>37.5%</td>
<td>60%</td>
<td>25%</td>
<td>75</td>
</tr>
<tr>
<td>Rzepeki</td>
<td>5</td>
<td>Flu/alemtuzumab</td>
<td>BM=2; PBSC=2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Srinivasan</td>
<td>26</td>
<td>Flu/CY/ATG</td>
<td>PBSC; MRD=22; MMRD=4</td>
<td>0</td>
<td>65%</td>
<td>56%</td>
<td>3.8%</td>
<td>92</td>
</tr>
<tr>
<td>Gupta</td>
<td>33</td>
<td>CY/alemtuzumab</td>
<td>BM=32; PBSC=1</td>
<td>24%</td>
<td>14%</td>
<td>4%</td>
<td>6/33</td>
<td>81 (5 years)</td>
</tr>
<tr>
<td>Gomez-Almaguer</td>
<td>23</td>
<td>Bu/CY/Flu</td>
<td>PBSC=23</td>
<td>26%</td>
<td>17.3%</td>
<td>26%</td>
<td></td>
<td>2/23</td>
</tr>
</tbody>
</table>

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)\textsuperscript{33}

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

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


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), Fludarabine (30 mg/m² daily from day -6 to -2), Cyclophosphamide (14.5 mg/kg daily on day -6 and -5), and TBI (4 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).

**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). 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. 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. The resultant clinical manifestations of SCD are summarized in table 1.

Table 1. Clinical manifestations of sickle cell disease

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

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; have led to significant improvements in survival in children with SCD. 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. 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. In another recent American prospective observational cohort, those with SCA had a median survival of 58 years. 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. There is no convincing evidence to suggest that hydroxyurea alters the incidence or course of chronic SCD-related cardiopulmonary disease. 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. 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.

In adults, there are fewer published reports of allo-HCT for SCD. However, encouraging early results with both myeloablative and 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. 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. 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

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>Donors/Graft</th>
<th>Conditioning and GVHD prophylaxis</th>
<th>Engraftment</th>
<th>GVHD</th>
<th>TRM</th>
<th>SCD-Specific Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myeloablative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>MSD / PBSC</td>
<td>Flu/Mel/ATG MTX/Tac</td>
<td>2/2</td>
<td>1 acute/1 chronic</td>
<td>2/2</td>
<td>No acute SCD complications</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>MSD / BM</td>
<td>Bu/Cy/ATG MTX/Csa</td>
<td>15/15</td>
<td>Acute: 7 grade II 1 grade III Chronic: 2 mod-severe</td>
<td>1/15</td>
<td>14/15 “normal” QoL &amp; no immune suppression</td>
</tr>
<tr>
<td>14</td>
<td>22</td>
<td>MSD (17) or MUD (5) / BM</td>
<td>Flu/Bu/ATG MTX/Csa</td>
<td>22/22 (1 late graft failure)</td>
<td>Acute: 4 grade 2-3 Mod-Severe Chronic: 3</td>
<td>2/22</td>
<td>No SCD recurrence post HCT. ↑ HR-QoL and ↓ pain.</td>
</tr>
<tr>
<td><strong>Non-myeloablative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>MSD / PBSC</td>
<td>Alem/TBI Sirolimus</td>
<td>26/30</td>
<td>None</td>
<td>0/30</td>
<td>↓TRV ↓Hospitalization ↓Narcs No recurrent neurologic events 15/26 off sirolimus @ med 2.1 yrs</td>
</tr>
<tr>
<td>16</td>
<td>13</td>
<td>MSD / PBSC</td>
<td>Alem/TBI Sirolimus</td>
<td>12/13</td>
<td>None</td>
<td>0/13</td>
<td>↑QoL ↓BNP ↑FEV1&amp;FVC 4/12 off sirolimus at med f-up 22 mos</td>
</tr>
<tr>
<td>35</td>
<td>17</td>
<td>Haplo (14) or MSD (3) / BM</td>
<td>ATG/Flu/Cy/TBI200/PTCy/MMF/Tacro or Sirol</td>
<td>11/17</td>
<td>No gr 2-4 aGVHD, No mod-sev cGVHD</td>
<td>0/17</td>
<td>10/17 disease-free (transfusion-independent, off narcotics)</td>
</tr>
<tr>
<td>36</td>
<td>8</td>
<td>Haplo / PBSC</td>
<td>ATG/Flu/Cy/TBI300/PTCy/MMF/Sirol</td>
<td>7/8</td>
<td>2 gr 2-4 aGVHD, 1 mod-sev cGVHD</td>
<td>1/8</td>
<td>6/8 disease-free</td>
</tr>
<tr>
<td>37</td>
<td>17</td>
<td>Haplo / BM</td>
<td>ATG/Flu/Cy/TBI400/PTCy/MMF/Sirol</td>
<td>16/17</td>
<td>5 gr 2-4 aGVHD, 1 mod-sev cGVHD</td>
<td>0/17</td>
<td>16/17 disease-free</td>
</tr>
<tr>
<td>38</td>
<td>20</td>
<td>MSD / PBSC</td>
<td>ATLG/Flu/Cy/TBI200/Bu/PTCy/Sirol</td>
<td>20/20</td>
<td>None</td>
<td>0/20</td>
<td>20/20 disease-free</td>
</tr>
</tbody>
</table>

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.
However, 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 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. 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. 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.

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 unrelated donors remains investigational and should not be pursued outside of a clinical trial. In this setting, matched unrelated donors are considered “alternative” donors. The use of MUDs has only 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. Haploidentical allo-HCT with post-transplant cyclophosphamide is promising. Initially, it was hampered by high rates of graft failure. 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, and only one developed graft failure. Similar results were reported from Chicago. We will use the Baltimore protocol, 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. 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.21 Other end organ complications like sickle hepatopathy, sickle nephropathy, cerebrovascular events and acute chest syndrome are also associated with mortality.22 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).21

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, 18

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).23
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, ie, 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, ie, 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.\(^{24}\) 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


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 neurologists experienced with the use of AHSCAT in MS and a transplant physician.
- For transplant technique, we follow the Ottawa protocol, ie, mobilization with cyclophosphamide + GCSF, CD34 enrichment, conditioning with busulfan + cyclophosphamide + Thymoglobulin, 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®. 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). 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.

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 its use has decreased considerably in the wake of relatively high rates of serious adverse events including cardiac dysfunction, leukemia and bone marrow damage. In 2006, Natalizumab (Tysabri®) was approved for use in RRMS in the context of marked failure on conventional agents. 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. 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. There did appear to be a small increase in breast cancer cases in the Ocrelizumab group, but the numbers were small, and this is being evaluated in the post-marketing setting to determine if it is real or a statistical anomaly. This agent was approved by Alberta Blue Cross as a first-line agent in April 2019. 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 Blue Cross as third-line). These agents include:

Fingolimod/Gilenya®:
Gilenya® was the first oral agent in RRMS 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, preventing lymphocyte egress from lymphoid tissues and thus reducing auto-aggressive lymphocyte infiltration into the central nervous system (CNS). In pivotal trials, there was a 54% relative reduction in relapses versus placebo (52% versus Avonex®), as well as significant reductions in MRI lesion load, and markers of disability progression. 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 lymphopenia due to its mechanism of action. It, like all agents mentioned below is considered a second-line/escalation agent in Canada. 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. 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. 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). More recently, additional risks including acute acalculous cholecystitis and stroke during infusions have been reported.

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. 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.

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. 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. 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. 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®)

**First-Line Management of Aggressive Inflammatory Pseudo-progression in Multiple Sclerosis**
- Definition of aggressive inflammatory pseudo-progression:
  - Very large expanded disability status scale (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®)**
- Cladribine (Mavenclad®)*

*only approved and covered for use in relapsing patients
**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 201333):

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 functional system score (FSS) changes >1 in motor/cerebellar/brainstem/sphincter/sensory domains, but EDSS still <6.0
  OR
- Milder relapse breakthrough but couples 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 neurologists 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

1. 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).

Special Circumstances for Users of Natalizumab/Ocrelizumab/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

2. 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 the 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.

Autologous Hematopoietic Cell Transplant Details

**Stem cell mobilization** is achieved with cyclophosphamide, filgrastim and dexamethasone. Cyclophosphamide, 2500 mg/m² IV over 1 h, is given in BMT clinic. Antiemetics and hydration are given per our standard practice; Mesna, 2500 mg/m² IV, should be given in two divided doses, the first one concurrently with cyclophosphamide and the second one 4 h 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 $10 \times 10^6$/kg ($\sim 5 \times 10^6$/kg after CD34 cell enrichment). The minimum CD34 cell yield is $5 \times 10^6$/kg ($\sim 2.5 \times 10^6$/kg after CD34 cell enrichment). Only if $>2 \times 10^6$ CD34 cells/kg are available after CD34 cell enrichment, the patient can proceed into the autologous transplantation.

**Graft processing:** Both unmanipulated and CD34 cell-enriched grafts have been used. It is currently not known whether CD34 cell enrichment is necessary. We use CD34 cell enrichment as the Ottawa protocol, the results of which we wish to replicate, has used it. For stem cell collection, we target $10 \times 10^6$/kg CD34 cells. Of the collected product, 10% ($1 \times 10^6$/kg CD34 cells) are cryopreserved as a backup for graft failure. The remaining 90% ($9 \times 10^6$/kg CD34 cells) are immunomagnetically enriched for CD34 cells. The CD34 rich fraction is cryopreserved and later used as the graft. The CD34 negative fraction is cryopreserved in 3 bags (equal cell numbers for simplicity) as a backup for intractable viral infections.

**Conditioning:** Many different regimens have been used (Table 1). We use the Bu+Cy+ATG (Ottawa) conditioning (Table 2).
Table 1. Results of recent studies with >20 patients

<table>
<thead>
<tr>
<th></th>
<th>Burt (US) 2009&lt;sup&gt;34&lt;/sup&gt;</th>
<th>Burt (US) 2019&lt;sup&gt;35&lt;/sup&gt;</th>
<th>Krasulova (Czechia) 2010&lt;sup&gt;36&lt;/sup&gt;</th>
<th>Fassas (Greece) 2011&lt;sup&gt;37&lt;/sup&gt;</th>
<th>Bowen (US) 2012&lt;sup&gt;38&lt;/sup&gt;</th>
<th>Mancardi (Italy) 2012&lt;sup&gt;39&lt;/sup&gt;</th>
<th>Shevchenko (Russia) 2012&lt;sup&gt;40&lt;/sup&gt;</th>
<th>Atkins (Canada) 2016&lt;sup&gt;41&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>21</td>
<td>52 (51 in DMT arm with 31 crossover)</td>
<td>26</td>
<td>35</td>
<td>26</td>
<td>74</td>
<td>95</td>
<td>24</td>
</tr>
<tr>
<td>% RRMS</td>
<td>100%</td>
<td>100%</td>
<td>42%</td>
<td>3%</td>
<td>4%</td>
<td>45%</td>
<td>44%</td>
<td>50%</td>
</tr>
<tr>
<td>Age (median)</td>
<td>33 y</td>
<td>35.6 y</td>
<td>33 y</td>
<td>40 y</td>
<td>41 y</td>
<td>36 y</td>
<td>~34 y</td>
<td>34 y (24-45)</td>
</tr>
<tr>
<td>EDSS (median)</td>
<td>3.1</td>
<td>3.4</td>
<td>6.0</td>
<td>6.0</td>
<td>7.0</td>
<td>6.5</td>
<td>1.5 – 8.0</td>
<td>3.0 – 6.0</td>
</tr>
<tr>
<td>Duration of MS (y, median)</td>
<td>5 y</td>
<td>5 y</td>
<td>7 y</td>
<td>7 y</td>
<td>?</td>
<td>11 y</td>
<td>?</td>
<td>6.5 y</td>
</tr>
<tr>
<td>Mobilization</td>
<td>Cy + GCSF</td>
<td>Cy + GCSF</td>
<td>Cy + GCSF</td>
<td>Cy + GCSF</td>
<td>GCSF + Pred</td>
<td>Cy + GCSF</td>
<td>GCSF</td>
<td>Cy + GCSF</td>
</tr>
<tr>
<td>CD34 selection</td>
<td>No</td>
<td>No</td>
<td>50% Yes</td>
<td>No (most pts)</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Conditioning</td>
<td>Cy + Alem or rATG</td>
<td>Cy + rATG</td>
<td>BEAM ± rATG</td>
<td>BEAM or Bu, + rATG</td>
<td>TBI + Cy + hATG</td>
<td>BEAM + rATG</td>
<td>BM or BEAM, + hATG</td>
<td>Bu + Cy + rATG</td>
</tr>
<tr>
<td>Follow up (y)</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>TRM</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>6% (2 pts)</td>
<td>4% (1 pt)</td>
<td>3% (2 pts)</td>
<td>0%</td>
<td>4% (1 pt)</td>
</tr>
<tr>
<td>EDSS trend</td>
<td>Improvement</td>
<td>Improvement</td>
<td>?</td>
<td>Worsening</td>
<td>Worsening</td>
<td>Stabilization</td>
<td>Stabilization</td>
<td>Stabilization</td>
</tr>
<tr>
<td>% pts with post-HCT clinical relapse</td>
<td>24%</td>
<td>2% y1</td>
<td>8% y1-2</td>
<td>10% y1-3</td>
<td>?</td>
<td>4%</td>
<td>15%</td>
<td>?</td>
</tr>
<tr>
<td>% pts with post-HCT Gd-enhancing lesions</td>
<td>14%</td>
<td>?</td>
<td>?</td>
<td>&lt;20%</td>
<td>16%</td>
<td>3%</td>
<td>?</td>
<td>0%</td>
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<tr>
<td>Progression-free survival*</td>
<td>77%</td>
<td>94%</td>
<td>29% (~80% for RRMS)</td>
<td>25%</td>
<td>44%</td>
<td>66% (71% for RRMS)</td>
<td>82% (~97% for RRMS)</td>
<td>70%</td>
</tr>
<tr>
<td>Disease activity-free survival**</td>
<td>62%</td>
<td>78.5%</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>70%</td>
</tr>
</tbody>
</table>

Abbreviations: RRMS = relapsing remitting multiple sclerosis, rATG = rabbit ATG, 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

** Survival free of EDSS progression, clinical relapse and MRI activity
### Table 2. Transplant Conditioning/Infusion Regimen used in Calgary

<table>
<thead>
<tr>
<th>Day</th>
<th>-10</th>
<th>-9</th>
<th>-8</th>
<th>-7</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan* ~2.4 mg/kg/day IV</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>GCSF ~0.5 ug/kg/d from d7 till ANC&gt;1/nl</td>
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* Busulfan 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 pharmacokinetics (PK) 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 busulfan area under the curve (AUC) <4000 umol.min/L starting day -8 for an overall exposure 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 medical judgement or institutional policy. Aprepitant, however, is to be used only with significant vomiting and when other options have been ineffective. Hydration with Normal Saline, approximately 2 liters/m²/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
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 at 2 years posttransplant 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 months posttransplant per our Standard Practice (see chapter “Bacterial and Pneumocystis Prophylaxis”)
- Vaccinations per our Standard Practice (see chapter “Vaccination”)
References

## Appendix A: Patient Monitoring

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<th>Baseline/Eligibility</th>
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* EDSS = Extended disability status scale (0-10), MSFC = Multiple sclerosis functional composite. Both arranged by Neurology.

** Male patients will be offered sperm banking, female patients will be offered fertility clinic consult.

*** Only if blood cell counts are abnormal

**** Pretransplant, HSC, 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

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BMT Standard Practice Manual
Last Revised: April 9, 2019
Effective: April 22, 2019
### Appendix B: Calgary Experiences as of March 2019

<table>
<thead>
<tr>
<th>UPN</th>
<th>Year of autoHCT</th>
<th>Mobilization</th>
<th>CD34 selection</th>
<th>Conditioning</th>
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* Relapse, progression, or new or enhancing MRI lesions
Scleroderma/ Systemic Sclerosis (SSc)

Presented by: Jan Storek

Summary

- Autologous HCT for SSc is indicated if
  - Age <65, ideally younger
  - <5 y from the first non-Raynaud symptom, ideally <1 y
  - 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 (RVSP >55 mmHg by echo or mean PAP >30 mmHg by RHC)
  - No heart involvement.
  - 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.

Scleroderma/ Systemic Sclerosis Manifestations

- Skin involvement
  o Thickening
    - Localized cutaneous scleroderma (“morphea”)
      - Not an indication for HCT due to good prognosis
    - Limited cutaneous scleroderma (hands/distal forearms/face) / CREST syndrome (calcinosis of skin, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, teleangiectasia)
      - Associated with anti-centromere antibody (ACA) (60%)
      - Controversial indication for HCT at present due to better prognosis (without HCT) compared to diffuse cutaneous scleroderma, and minimal data on HCT. Reasonable to do HCT if interstitial lung disease.
    - Diffuse cutaneous scleroderma (involves also proximal skin)
      - Associated with Scl-70 antibody (30%)
      - Indicated for HCT if moderate to severe (mRSS >20, see Figure 1 for mRSS assessment) or if associated with lung disease
  o Other skin manifestations
    - Edema (early)
    - Contractures (late)
    - Pruritus
    - Hyper/hypopigmentation (“salt-and-pepper”)
    - Loss of appendicular hair
- Ulcers
- Calcinosis

- Lung involvement
  - Interstitial lung disease / fibrosing alveolitis
    - Indicated for HCT, particularly if rapidly progressing, but FVC and DLCO must be >40% predicted
  - Pulmonary artery hypertension
    - Relative contraindication to HCT
  - Lung cancer (5 fold higher incidence compared to general population)
    - Contraindication to HCT
  - Smoking
    - Both SCOT and ASTIS study showed that ever smokers had worse outcome than non-smokers
    - We consider present smoking as a contraindication to HCT

- Renal crisis
  - Renal failure
  - Hypertension
  - Proteinuria
  - Microangiopathic hemolysis/thrombocytopenia
  - Renal crisis needs to be partially controlled (with ACE inhibitors) before HCT

- Heart involvement
  - Myocarditis → fibrosis; myocardial ischemia; pericarditis/effusion
  - LVEF <40 or 50% or tricuspid annular plane systolic excursion (TAPSE) <1.8 cm on echocardiography or any sign of heart involvement with scleroderma on MRI are considered contraindications to HCT

- Involvement of other organs (usually has no impact on whether HCT is indicated)
  - Systemic
    - Fatigue/weakness, may be associated with ↑CK
    - Pain (in skin? joints?)
  - Vascular
    - Raynaud
    - Teleangiectasia
  - Gastrointestinal
    - Esophageal hypomotility and incompetence of the LES → chronic esophagitis, stricture, Barrett’s esophagus, pulmonary microaspiration
    - Stomach: Gastric Antral Venous Ectasia (GAVE, “watermelon stomach”) → anemia
      - GAVE needs to be successfully treated (eg, with Argon Plasma Coagulation) before HCT
    - Intestines: Diarrhea or constipation, bacterial overgrowth with malabsorption
    - Anorectum: Fecal incontinence
Joints
- Stiff, aching, tendon friction rub – due to inflammation → fibrosis around tendons/periarticular soft tissue
- Polyarthritis (rare), with erosions on X-ray similar to rheumatoid arthritis

Neuromuscular
- Myositis
- Peripheral neuropathy, including autonomic
- CNS disease rare

Genital
- Erectile dysfunction
- Dyspareunia due to vaginal dryness / narrow introitus

Pathogenesis
- Poorly known
- T cell, endothelial cell and fibroblast abnormalities
- Autoantibodies – marker of immune dysregulation or active role in pathogenesis?
  - Antibodies binding to fibroblasts
    - Anti-Scl-70 (anti-topoisomerase on fibroblast surface)?
    - Anti-PDGFR with profibrotic activity?
  - Whether autoantibodies persist after autoHCT is controversial
- “GVHD” due to fetal T cells in skin of women with SSc post-pregnancy

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

Prognosis without HCT
- Survival ~80% at 2 y, ~60% at 5 y, ~40% at 10 y per Altman et al; consistent with more recent studies
- Survival particularly low with
  - Diffuse scleroderma
  - Heart, Lung or Kidney involvement
  - For diffuse scleroderma without or with only mild internal organ involvement, rapid Skin Thickness Progression Rate (STPR)
    - 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

**Therapy Other than HCT**

- Systemic immunosuppressive / antifibrotic / anticytokine agents - all studies retrospective or non-randomized prospective (thus dubious efficacy), except for cyclophosphamide, which was shown to have dubious efficacy in randomized studies, and for MMF, which has efficacy similar to cyclophosphamide.
  - 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). There was no difference at 2 y.
  - Methotrexate
  - Corticosteroid (caveat: can induce renal crisis)
  - MMF
  - Rituximab?
  - Tocilizumab?
  - Antifibrotics?

- Organ/Symptom-based therapies
  - Pruritus – antihistamines
  - Raynaud / digital ulcers – Ca channel blocker, avoiding cold environment
  - Contractures – physiotherapy
  - Renal crisis – ACE inhibitor
  - Esophageal dysmotility – proton pump inhibitor, metoclopramide
  - Malabsorption/diarrhea due to bacterial overgrowth – antibiotics
  - PAH – oxygen, diuretic, PAP lowering agents (bosentran, sildenafil, iloprost), lung transplantation
  - Arthritis – NSAID, hydroxychloroquine
  - CHF – ACE inhibitor, implantable cardioverter-defibrillator

**Autologous HCT**

Multiple non-randomized and 3 randomized studies of autoHCT for SSc published (Table 1 and SCOT study). From these studies it can be surmised that

- AutoHCT is superior over pre-2015 conventional therapy (eg, oral or monthly IV cyclophosphamide) for
- SSc involving skin + lungs, if FVC or DLCO 40-80% predicted or rapid decline of FVC (>10% over 12-18 mo), particularly if patient never smoked, or
- Scleroderma without lung involvement, if mRSS >20 with high ESR/CRP or rapid skin thickness progression rate
- Disease duration <5 years, ideally <1 year
  - No data for patients with longer disease duration. With other autoimmune disease, duration appears to matter.\(^{20-23}\)
  - Pretreatment with systemic immunosuppressive drugs may not be a contraindication\(^{24}\)
- No heart involvement
  - May not be a contraindication in the future with non-cardiotoxic conditioning\(^{25}\)
- No hypoxia
- No moderate/severe PAH (RVSP >55 mmHg by echo or mean PAP >30 mmHg by RHC; RVSP 45-55 mmHg by echo requires RHC)
- If GAVE, needs to be successfully treated before HCT

**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 y) 3-10%
  - Organ failure, particularly heart and lung
  - Infections
- Late toxicity
  - MDS/AML
  - Solid cancer (increased incidence with SSc alone)
  - Second autoimmune disease (thyroiditis, immune cytopenia)

**Method**
- Optimal drugs/doses for stem cell mobilization and transplant conditioning are unknown, intermediate intensity conditioning may be optimal.\(^{26}\) Role of CD34 selection is uncertain, may be unimportant.\(^{27}\)
- Two protocols have been widely used. ASTIS protocol,\(^{28}\) with conditioning based on cyclophosphamide 200 mg/kg, is typically used in Europe. SCOT protocol,\(^{19}\) with conditioning based on cyclophosphamide 120 mg/kg + TBI 8 Gy, is typically used in the USA.
- The SCOT protocol appears 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\(^{19}\) and Sullivan: manuscript in preparation for SCOT, refs\(^{28-30}\) for ASTIS).
Consistent with that, of 14 patients who underwent autoHCT in Calgary between 2016 and 2019 according to the ASTIS protocol, except without CD34 selection, 4 developed SSc relapse and 1 to 3 developed a posttransplant autoimmune disease (1 new rheumatoid arthritis, 1 relapse of preexisting SLE, 1 possible antiphospholipid syndrome). We decided to use SCOT protocol as of 2020.

In Calgary as of 2020, we use the SCOT protocol:

**Mobilization**

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* 16 ug/kg/d sc, rounded to a combination of 300 or 480 ug vials; 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**

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* Total body irradiation 8 Gy in 4 fractions (2 fractions a day, min 5 h between fractions) with shielding of lungs and kidneys to 2 Gy. TBI average dose rate should be 7 to 15 cGy/min. Premedicate with antiemetics ondansetron + lorazepam, also give prn dimenhydrinate + prn metoclopramide; ** Cyclophosphamide 60 mg/kg body weight (if actual body weight is higher than ideal body weight, then adjusted ideal body weight is used, calculated as ideal body weight + (0.40 x (actual body weight – ideal body weight)) in 250 mL D5W infused over 2 h, with Mesna (60 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 [can be omitted on day -3, if ATG with methylprednisolone as premedication is given before Cy] + aprepitant + prn dimenhydrinate + prn metoclopramide); *** ATGAM (15 mg/kg in 500 ml D5W infused over 4 h [the volume may be higher in overweight patients to accommodate max Atgam concentration of 4 mg/ml) with premedication (Methylprednisolone 1 mg/kg before each infusion + acetaminophen + diphenhydramine + meperidine pm). First dose of Atgam is preceded by Atgam skin test (0.02ml of a 1:1000 v/v saline dilution of Atgam intradermally). If skin test is positive (≥10 mm wheal or erythema in 10 min), no ATG will be given.
Alternatively (eg, in patients with a contraindication to TBI), the ASTIS protocol can be used:

**Mobilization**

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>≥12</th>
<th>≥13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy*</td>
<td>2.5 g/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF**</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apheresis of MNCs***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

* Cyclophosphamide (2.5 g/m² dose dissolved in 500 mL D₅W and infused over 2 h) with Mesna (500 mg/m² IV x 3, the first dose to be added into the Cy bag, the second and the third dose infused as IVPB at 4 and 8 h after starting Cy), 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 (granisetron + dexamethasone + aprepitant + prn dimenhydrinate + prn metoclopramide + prn prochlorperazine)

** 300-900 ug per dose depending on weight per SPM chapter on Mobilization; with prn codeine

*** Start when blood CD34 count is >20 x 10⁶/L. Target to collect 8 x 10⁶/kg CD34 cells. Perform CD34 selection using CliniMACS. Target 5 x 10⁶/kg CD34 cells for infusion. Cryopreserve.

**Conditioning**

<table>
<thead>
<tr>
<th>Day</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy*</td>
<td>50 mg/kg</td>
<td>50 mg/kg</td>
<td>50 mg/kg</td>
<td>50 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit ATG**</td>
<td></td>
<td></td>
<td></td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Methyl-prednisolone</td>
<td></td>
<td></td>
<td></td>
<td>1 mg/kg x 2</td>
<td>1 mg/kg x 2</td>
<td>1 mg/kg x 2</td>
<td></td>
</tr>
<tr>
<td>Stem cell infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Cyclophosphamide (50 mg/kg ideal body weight in 250 mL D₅W 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 (2.5 mg/kg in 500 ml D5W infused over 4 h) with premedication (Methylprednisolone 1 mg/kg before each infusion and 1 mg/kg at the end of each infusion + acetaminophen + diphenhydramine + meperidine pm)

**Special management notes**

- Discontinue DMARDs (eg, MMF, MTX, cyclophosphamide) 2 weeks before mobilization to maximize the likelihood of a high CD34 cell yield
- Avoid rapid intravascular volume changes, particularly fluid overload, and electrolyte concentration extremes (could trigger CHF or arrhythmia due to subclinical/subechocardiographic myocardial sclerosis)¹,²⁵
- Avoid hypertension (could trigger renal crisis) – use lisinopril or enalapril

**Supportive care post-transplant**

- Prednisone 0.5 mg/kg/d from day 6 to day 21, then tapered by day 37, to prevent engraftment syndrome and serum sickness
- GCSF from day 7 till engraftment per our SPM
o Valacyclovir from start of conditioning till 2 y per our SPM
o Septra from engraftment till 1 y per our SPM, possibly extension to 2 y if CD4 < 200/ul at 1 y
o Levofloxacin from day 0 till engraftment (risk of cardiac mortality with sepsis)
o Fluconazole from day 1 till day 28 (risk of esophageal candidiasis)
o EBV and CMV PCR weekly till day 100 (risk of PTLD, particularly with rabbit ATG) and preemptive therapy per SPM
o Vaccination per our SPM

Allogeneic HCT

• Case reports suggest efficacy. 31-33
• The only case series is a CIBMTR registry study of 12 cases with follow up of surviving patients of at least 1 year. 34 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 Re 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.

Pre-Transplant Tests/ Appointments (to be compared within 3 months before stem cell mobilization)

• Dr. Caylib Durand (Rheumatology) appointment, his exam includes mRSS
• Dental, including Panorex X-ray
• Sperm Bank or Fertility Gynecologist if patient interested in fertility preservation
• Esophageal manometry (SHC)
• GI consult including EGD by Drs. Matt Woo or Dorothy Li (SHC)
• ECG, if history of palpitations or fainting, then Holter
• Echocardiogram (Requisition should ask for echocardiogram with strain, and state that this is a scleroderma patient undergoing pre-hematopoietic cell transplant evaluation).
• Cardiac MRI including gadolinium (scleroderma heart disease?)
• Cardiooncology appointment (ideally Dr. Brian Clarke) + Right heart catheterization (to be arranged by Dr.Clarke or another cardiooncologist)
• PFT: Spirometry, DLCO, 6MWT (ideally ILD protocol, as it measures O2sat continuously as opposed PAH protocol that measures O2sat only at beginning and end, endpoints are distance walked and nadir O2sat)
• Chest CT (contiguous and high resolution)
• V/Q scan (rule out pulmonary embolism)
• Oxygen saturation ideally by forehead probe; if <92%, then ABG
• CBC+dif; if abnormal, then MD may order BMA including flow cytometry and cytogenetics (myelodysplasia?)
• Chemistries including CRP, ANA, CK, TSH, NTproBNP, Troponin T (high sensitivity), IgM, IgG, IgA
• Serology for HIV, HSV, VZV, CMV, EBV, HepB, HepC
• Pregnancy test (pre-menopausal women only)
• INR, PTT
• Urinalysis (random)
• Urine albumin:creatinine ratio (from spot urine)
• Scleroderma associated autoantibodies (“Scleroderma Profile” at Mitogen Advanced Diagnostics)

Post-Transplant Tests/appointments (at 6 months, and 1,2,3,4,5 years)
• Dr. Caylib Durand (Rheumatology) appointment, his exam includes mRSS
• Esophageal manometry (SHC)
• GI appointment with Drs. Matt Woo or Dorothy Li (SHC)
• Echocardiogram. Please put the diagnosis (scleroderma) on the requisition.
• PFT: Spirometry and DLCO; 6MWT (ideally ILD protocol) is needed only if abnormal before transplant
• Oxygen saturation ideally by forehead probe, if <92%, then ABG
• CBC+dif
• Chemistries including CRP, ANA, CK, TSH, NTproBNP, Troponin T (high sensitivity), IgM, IgG, IgA
• Urinalysis (random)
• Urine albumin:creatinine ratio (from spot urine)
• Scleroderma associated autoantibodies (“Scleroderma Profile” at Mitogen Advanced Diagnostics)
• Estradiol and anti-mullerian hormone (females), AM free testosterone (males), FSH and LH (both females and males) – 1 year posttransplant only
• CD4 T cell count – 1 year posttransplant only

Research Tests Pre- and Post-Transplant (only for pts who signed informed consent)
• Dysphagia questionnaire (SHC)
• Esophageal manometry post-transplant (SHC)


Summary

- High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is indicated in second- or third line therapy (ie. 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 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/ASCT as part of initial salvage therapy. These patients include:
  - incomplete response to first-line cisplatin-based therapy
  - primary platinum refractory disease
  - 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 do not benefit from HDCT/ASCT if they have:
  - a late relapse >2 years after completing initial chemotherapy
  - relapsed/refractory primary mediastinal non-seminomatous GCT
  - very high risk disease (≥ 5 points) according to the International Prognostic Factor Study Group Score.

There is no role for HDCT in the first-line treatment of patients with germ cell tumor.

- Stem cell mobilization is planned with the second cycle of salvage chemotherapy, usually using 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.
- Standard HDCT 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 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). Patients who do not achieve long-term remission with initial chemotherapy are still 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 the Phase II setting in well-selected patients. Another salvage approach is the use of high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT).

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. 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. Patients with primary mediastinal nonseminomatous GCTs (NSGCTs) and late relapses were not included due to previously observed poor outcomes with HDCT in these subgroups. Four year PFS was 63% for the study cohort. Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with non-seminomatous germ-cell tumors were disease-free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy.

Table 1. Results of multivariate cox proportion-hazards analysis and prognostic score

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
<th>B Regression Coefficient</th>
<th>Prognostic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third-line or subsequent chemotherapy</td>
<td>2.19 (1.35-3.56)</td>
<td>0.002</td>
<td>0.78</td>
<td>3</td>
</tr>
<tr>
<td>Platinum-refractory disease</td>
<td>1.74 (1.01-3.00)</td>
<td>0.05</td>
<td>0.55</td>
<td>2</td>
</tr>
<tr>
<td>IGCCCG high-risk stage</td>
<td>1.67 (1.00-2.78)</td>
<td>0.05</td>
<td>0.51</td>
<td>2</td>
</tr>
</tbody>
</table>

PM-NSGCT and late relapses (>2 years) were excluded. Adverse factors for DFS: IGCCCG poor-risk classification at initial diagnosis; Platinum-refractory disease, defined as tumor progression within 4 weeks after the most recent cisplatin-based chemotherapy; Receipt of HDCT as third-line or subsequent chemotherapy. DFS is approximately 80, 60, 40% for patients with low-risk, intermediate-risk and high-risk Einhorn scores.
HDCT vs CDCT for relapsed GCT

The IT-94 randomized Phase III trial compared HDCT to conventional dose chemotherapy (CDCT) in the salvage setting. This multicenter international study was conducted in Europe between 1994 and 2001, and 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 majority of patients were treated during the initial salvage setting, unlike most HDCT Phase II trials;
- Patients refractory to first-line platinum-containing chemotherapy were excluded;
- Only one cycle of HDCT was provided, using relative lower doses of carboplatin, 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 2010. Approximately equal numbers of patients were treated with CDCT and HDCT respectively. Overall, PFS and OS were found to be superior for patients treated with HDCT as compared with CDCT. On multivariate analysis, important prognostic factors were identified that allowed patient stratification into five well-defined prognostic categories. These data have since been used to develop a new prognostic model for initial salvage therapy (see...
later). Within these prognostic categories, PFS and OS remained superior for HDCT in each class with the exception of OS in the low-risk group.

**Common Recommendation:**
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, could receive CDCT, usually with TIP. Patients 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 salvage HDCT. For patients treated with CDCT in the initial salvage setting, HDCT remains an option in the third-line setting, should subsequent relapses occur.

**2-3 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 [43]. 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 cisplatin 20mg/m², etoposide 75 mg/m², and ifosfamide 1.2 g/m² for 5 days (VIP) plus three additional cycles of high-dose carboplatin 1,500 mg/m² and etoposide 1,500 mg/m² (CE) given in three divided doses over 3 days followed by reinfusion of autologous peripheral blood progenitor cells (PBPCs) 2 days later. Cycles were to be repeated at intervals of 21 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 in four divided doses over 4 days followed by reinfusion of autologous PBPCs 2 days later. Patients with a creatinine clearance between 70 mL/min and 100 mL/min were scheduled to receive HDCT at a reduced dose of carboplatin 1,200 mg/m² and etoposide 1,200 mg/m² in arm A, and carboplatin 1,600 mg/m², etoposide 1,600 mg/m², and cyclophosphamide 1,300 mg/m² in arm B. Patients with brain metastases received whole brain irradiation at a dose of 40 Gy immediately after random assignment in addition to their planned treatments.

Overall, 108 and 103 patients were randomly assigned to arms A and B, respectively. The study was stopped prematurely because of excess treatment-related mortality in arm B (14%) compared with that in arm A (4%; \( P = .01 \)). As of December 2010, nine (5%) of 211 patients were lost to follow-up; 94 (45%) of 211 are alive and 88 (94%) of 94 patients are progression free. These investigators found no statistically significant differences in event-free survival (EFS), Progression-free survival (PFS) or OS between the two groups. Five-year PFS is 47% (95% CI, 37% to 56%) in arm A and 45% (95% CI, 35% to 55%) in arm B (HR, 1.16; \( P = .454 \)). Five-year OS is 49% (95% CI, 40% to 59%) in arm A and 39% (95% CI, 30% to 49%) in arm B (HR, 1.42; \( P = .057 \)). 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 (80 vs 61%). 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.

**Figure 2.** Progression-free survival after sequential or single high-dose chemotherapy

![Progression-free survival graph](image)

**Figure 3.** Overall survival after sequential or single high-dose chemotherapy

![Overall survival graph](image)
Table 2. Residual tumor resections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm A (n=108)</th>
<th>Arm B (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>All residual tumour resections*</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Mediastinum</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Histology of resected specimen</td>
<td>39</td>
<td>100</td>
</tr>
<tr>
<td>Only necrosis</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>Vital undifferentiated cancer†</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>Mature teratoma</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Patients may have had resections at multiple sites, † Patients may have had other elements such as necrosis and/or teratoma present as well.

Table 3. Survival rates according to prognostic categories

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>No.</th>
<th>%</th>
<th>Rate of PFS at 2 Years (5)</th>
<th>Rate of OS at 3 Years (5)</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First salvage: very low risk</td>
<td>17</td>
<td>8</td>
<td>92</td>
<td>82</td>
<td>55 to 94</td>
<td>55 to 94</td>
</tr>
<tr>
<td>Arm A</td>
<td>8</td>
<td>4</td>
<td>63</td>
<td>63</td>
<td>24 to 86</td>
<td>23 to 86</td>
</tr>
<tr>
<td>Arm B</td>
<td>9</td>
<td>4</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>First Salvage: low risk</td>
<td>32</td>
<td>15</td>
<td>64</td>
<td>59</td>
<td>44 to 79</td>
<td>40 to 74</td>
</tr>
<tr>
<td>Arm A</td>
<td>18</td>
<td>9</td>
<td>69</td>
<td>61</td>
<td>40 to 86</td>
<td>35 to 79</td>
</tr>
<tr>
<td>Arm B</td>
<td>14</td>
<td>7</td>
<td>58</td>
<td>56</td>
<td>27 to 80</td>
<td>26 to 77</td>
</tr>
<tr>
<td>First Salvage: Intermediate risk</td>
<td>79</td>
<td>38</td>
<td>52</td>
<td>52</td>
<td>40 to 63</td>
<td>40 to 62</td>
</tr>
<tr>
<td>Arm A</td>
<td>42</td>
<td>20</td>
<td>51</td>
<td>55</td>
<td>35 to 65</td>
<td>39 to 68</td>
</tr>
<tr>
<td>Arm B</td>
<td>37</td>
<td>18</td>
<td>54</td>
<td>49</td>
<td>36 to 69</td>
<td>32 to 63</td>
</tr>
<tr>
<td>First salvage: high risk</td>
<td>37</td>
<td>18</td>
<td>34</td>
<td>32</td>
<td>19 to 50</td>
<td>18 to 47</td>
</tr>
<tr>
<td>Arm A</td>
<td>18</td>
<td>9</td>
<td>50</td>
<td>56</td>
<td>26 to 70</td>
<td>31 to 75</td>
</tr>
<tr>
<td>Arm B</td>
<td>19</td>
<td>9</td>
<td>14</td>
<td>11</td>
<td>2 to 37</td>
<td>2 to 28</td>
</tr>
<tr>
<td>First salvage: very high risk</td>
<td>7</td>
<td>3</td>
<td>None</td>
<td>None</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Second or subsequent salvage</td>
<td>30</td>
<td>14</td>
<td>24</td>
<td>30</td>
<td>11 to 41</td>
<td>15 to 47</td>
</tr>
<tr>
<td>Arm A</td>
<td>15</td>
<td>7</td>
<td>33</td>
<td>40</td>
<td>12 to 56</td>
<td>17 to 63</td>
</tr>
<tr>
<td>Arm B</td>
<td>15</td>
<td>7</td>
<td>15</td>
<td>20</td>
<td>2 to 38</td>
<td>5 to 42</td>
</tr>
<tr>
<td>No unequivocal classification</td>
<td>9</td>
<td>4</td>
<td>76</td>
<td>67</td>
<td>33 to 94</td>
<td>28 to 88</td>
</tr>
</tbody>
</table>

Note. Arm A, sequential high-dose chemotherapy; Arm B, single high-dose chemotherapy.
Abbreviations: OS, overall survival; PFS, progression-free survival.
**Prognostic Models**

Recently, 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. Patients with salvage treatment administered as consolidation of first-line therapy without progression were excluded. 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 histology (seminoma vs nonseminoma); primary tumor site (mediastinal vs retroperitoneal vs gonadal); response to first-line chemotherapy (CR vs PR vs other); progression-free interval following first-line chemotherapy, α-fetoprotein (AFP) level at salvage, HCG level at salvage and the presence of nonpulmonary visceral metastases. Each factor was assigned a point value and a sum score calculated for each patient. Scores were divided into five groups (very low risk, low risk, intermediate risk, high risk and very high risk) with distinct PFS and OS rates. The large, international and multicenter population of patients included in this study and the ability of the model to predict outcomes to both HDCT and CDCT initial salvage approaches will allow this model to be more widely applicable than the prior prognostic systems. Indeed, this is now widely considered the new standard predictive model in the relapsed/refractory setting.

**Table 4. Prognostic models: international prognostic factor study group score**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary site</strong></td>
<td></td>
</tr>
<tr>
<td>Gonadal</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal (NSGCT)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Response to first-line therapy</strong></td>
<td></td>
</tr>
<tr>
<td>CR/PR-</td>
<td>0</td>
</tr>
<tr>
<td>PR+/SD</td>
<td>1</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
</tr>
<tr>
<td><strong>Progression-free interval after first-line therapy</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 3 months</td>
<td>0</td>
</tr>
<tr>
<td>≤ 3 months</td>
<td>1</td>
</tr>
<tr>
<td><strong>Serum hCG level</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 1000 IU/l</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 1000 IU/l</td>
<td>1</td>
</tr>
<tr>
<td><strong>Serum AFP level</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>≤1000 ng/ml</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 1000 mg/ml</td>
<td>2</td>
</tr>
<tr>
<td><strong>Liver, bone or brain metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

*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*

<table>
<thead>
<tr>
<th>Histology</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>-1</td>
</tr>
<tr>
<td>NSGCT/mixed</td>
<td>0</td>
</tr>
<tr>
<td>Stratification</td>
<td>Points</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Very low risk</td>
<td>-1</td>
</tr>
<tr>
<td>Low risk</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1</td>
</tr>
<tr>
<td>High risk</td>
<td>2</td>
</tr>
<tr>
<td>Very high risk</td>
<td>3</td>
</tr>
</tbody>
</table>

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.

Calgary Results

**Figure 4.** Survival after ASCT for a relapsed/refractory metastatic germ cell tumor of the testis in Calgary Feb 2001-Jan 2018. (n=22)
References


Summary

- A uniform approach to pretransplant conditioning is a prerequisite for an academic bone marrow transplant program wishing to produce consistent results.
- Intravenous busulfan is an integral component to many of the conditioning regimens used by the Alberta Blood and Marrow Transplant Program (ABMTP). Variable excretion and metabolism of this agent may result in additional toxicity and measurement of pharmacokinetic parameters with the first dose will be carried out in every case.
- When busulfan is combined with fludarabine and total body irradiation in a high-intensity regimen (busulfan 3.2 mg/kg x 4 doses) additional toxicity has been noted with high busulfan exposures. Busulfan exposure of 3750 micromol·minute/L will be targeted in this regimen based on a preconditioning test dose. When used in a high-intensity regimen without TBI, busulfan exposure of 4500 micromol·minute/L is targeted. When used in a reduced intensity regimen pharmacokinetics may be measured but dose adjustments are not made.
- Dosage adjustments are made according to the formula in Appendix B.
- The recommended conditioning regimens for conditions treated by the ABMTP are listed in Table 1. Details of these regimens are included in Appendix A.

Introduction

High-dose chemotherapy is used in stem cell transplantation in order to eliminate residual macroscopic or microscopic disease. In transplantation from allogeneic donors pretransplant conditioning also induces an immunosuppressed state enabling engraftment of allogeneic hematopoietic stem cells. Doses of drugs used in conditioning regimens have generally been escalated to the point at which extramedullary toxicity becomes dose-limiting, accounting for the high rates of non-hematological toxicity seen with stem cell transplantation. Reduced-intensity regimens have been developed to exploit the immunological graft-versus-malignancy effect while avoiding the risks associated with intensive conditioning in patients not felt suitable for myeloablative transplantation.

Drugs Used for Conditioning

Busulfan

Busulfan is a bifunctional 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 (AUC) of 3750 micromol * minutes/L is targeted due to the association of higher exposures with increased toxicity[1-3]. When busulfan is administered without TBI, an exposure of 4500 micromol*minutes/L is targeted[4]. The protocol for dosage adjustment is shown in Appendix B. Busulfan is administered at a constant rate of 80 mg/hour to facilitate pharmacokinetic modeling.

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.

**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[5]. 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. Its 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 chromosomnal 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.

**Carmustine (BCNU)**
Carmustine is a nitrosurea alkylating agent. Its excretion is primarily renal (60-70%).
Common toxicities of carmustine include nausea, vomiting and constipation. A black box warning points out that pulmonary toxicity may occur at high cumulative doses (> 1400 mg/m² lifetime exposure), and that this toxicity may occur many years after treatment.

**Cytarabine (AraC)**

Cytarabine is a nucleoside analog and antimetabolite. It acts in a cell-cycle dependant manner to inhibit DNA synthesis in S-phase. It is incorporated into DNA and inhibits DNA polymerase. Cytarabine undergoes extensive metabolism in the liver (primarily by adenosine deaminase) and is excreted predominantly as the inactive metabolite AraU by the kidney.

Common toxicities include conjunctivitis, cytopenias, nausea and vomiting. Patients may experience hypersensitivity reactions that include skin rash and fever. Hand-foot syndrome (a painful rash of the palms and soles that may progress to bulla formation and desquamation) has been seen in recipients of high-dose cytarabine. Cerebellar toxicity may occur at high doses (> 1.5 gm/m² per dose) and is age dependent.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Conditioning</th>
<th>GVHD Prophylaxis*</th>
<th>Product Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML, ALL, MDS, Myelofibrosis, CML, CLL and NHL** (matched sib, URD)</td>
<td>Flu-Bu(3750)-TBI400</td>
<td>ATG-CyA-Mtx</td>
<td>PBSC</td>
</tr>
<tr>
<td>Recipients who have received TBI previously</td>
<td>Flu-Bu(4500)</td>
<td>ATG-CyA-Mtx</td>
<td>PBSC</td>
</tr>
<tr>
<td>Backup for Flu-Bu(3750)-TBI400 in case of Flu shortage</td>
<td>Bu-Cy</td>
<td>ATG-CyA-Mtx</td>
<td>PBSC</td>
</tr>
<tr>
<td>AML, ALL, MDS, Myelofibrosis, CML, CLL and NHL** (haploidentical)</td>
<td>Flu-Bu(3750)-TBI400</td>
<td>PTCy-MMF-Tacro</td>
<td>PBSC</td>
</tr>
<tr>
<td>Second allogeneic transplant for relapse (same donor)</td>
<td>VP16-TBI500</td>
<td>CyA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Second allogeneic transplant for relapse (new donor)</td>
<td>VP16-TBI500</td>
<td>CyA-Mtx</td>
<td>PBSC</td>
</tr>
<tr>
<td>Second allogeneic transplant for graft failure</td>
<td>Flu-TBI500</td>
<td>ATG-CyA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Aplastic Anemia (matched sib)</td>
<td>Flu(120)-Cy(120)</td>
<td>ATG-CyA-Mtx</td>
<td>Marrow</td>
</tr>
<tr>
<td>Aplastic Anemia (matched unrelated)</td>
<td>Flu(120)-Cy(120)-TBI200</td>
<td>ATG-CyA-Mtx</td>
<td>Marrow</td>
</tr>
<tr>
<td>Aplastic Anemia (haploidentical)</td>
<td>Flu(150)-Cy(29)-TBI200****</td>
<td>PTCy-MMF-Tacro</td>
<td>Marrow</td>
</tr>
<tr>
<td>Hemoglobinopathy (matched sib)</td>
<td>TBI300</td>
<td>Alemtuzumab-Sirolimus</td>
<td>PBSC</td>
</tr>
<tr>
<td>Hemoglobinopathy (haploidentical)</td>
<td>Flu(150)-Cy(29)-TBI400</td>
<td>PTCy-MMF-Sirolimus</td>
<td>Marrow</td>
</tr>
<tr>
<td>Reduced Intensity***</td>
<td>Flu-Bu(3.2 mg/kg x 2)</td>
<td>CyA-Mtx</td>
<td>PBSC</td>
</tr>
<tr>
<td>Reduced Intensity (NHL, HL)***, ****</td>
<td>Flu-Mel (RIC)</td>
<td>CyA-Mtx</td>
<td>PBSC</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Melphalan 200</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Plasma cell dyscrasia other than MM</td>
<td>Melphalan 200, or Melphalan 200 + Bortezomib</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Aggressive NHL (LBCL, PTCL)</td>
<td>(R)EM or (R)BuMel</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Indolent NHL (FL, MZL, LPL, CLL/SLL)</td>
<td>(R)Mel 180-TBI 500 cGy</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>(R)Mel 180-TBI 500 cGy</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Melphalan 200</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Thiopeta 600 mg/m2 + Bu 9.6 mg/m2</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Secondary CNS lymphoma</td>
<td>(R) Thiopeta 500 mg/m2 + Bu 9.6 mg/m2 + Melphalan 100 mg/m2</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Double-hit lymphoma</td>
<td>R-Bu-Mel</td>
<td>NA</td>
<td>PBSC</td>
</tr>
<tr>
<td>Germ Cell Tumor</td>
<td>Carbo-VP16</td>
<td>NA</td>
<td>PBSC</td>
</tr>
</tbody>
</table>

* NB Methotrexate is never given to recipients of umbilical cord blood transplants for GVHD prophylaxis; ** Flu-Bu without TBI should be given to recipients who have received TBI in the past; *** Anticipate near 100% prevalence of cGVHD at 1 year posttransplant. Thus, reduced intensity conditioning should be applied only if the risk of toxicity from high dose busulfan is greater than the morbidity of cGVHD; **** For patients with comorbidities (liver, lung, nervous system) or prior high-dose busulfan; slowly-progressive, non-bulky lymphoma. May be used with or without ATG for GVHD prophylaxis, although the impact of ATG on relapse rates with RIC conditioning has not been assessed in detail; ***** TBI dose is 200 cGy if previous immunosuppressive therapy and 400 cGy (in a single fraction) if no previous immunosuppressive therapy.

**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; PTCy = posttransplant cyclophosphamide; MMF = mycophenolate mofetil.
References


Appendix A. Conditioning Protocol Details

**Flu-Bu (3750)-TBI400**
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 targeted busulfan exposure of 3750 µmol·min/L
TBI 400 cGy delivered to midplane in two divided doses on day -1 or 0 (before graft infusion), at least 6 hours apart.

**Flu-Bu (4500)**
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 targeted busulfan exposure of 4500 µmol·min/L

**Bu-Cy**
Busulfan 3.2 mg/kg IV on days -8, -7, -6, -5. Avoid daily AUC >6,000 umol.min/L (avoid overall AUC >24,000 umol.min/L). The last dose of busulfan should be given in the morning of day -5 to ensure >>24 h interval between busulfan and cyclophosphamide infusions.
Cyclophosphamide 60 mg/kg IV on days -3, -2.
*This conditioning should be used only in case of fludarabine shortage. It has been found in two randomized studies to result in similar overall survival as Flu+Bu, however, whether it is equivalent to Flu+Bu+4GyTBI is not known. Moreover the busulfan toxic AUC of >6,000 umol.min/L has been determined in combination with fludarabine; it is not known whether it applies also to Bu+Cy. 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.*

**VP16-TBI**
Etoposide 60 mg/kg on day -4
TBI 500 cGy delivered to midplane in a single fraction on day 0 (before graft infusion)

**Flu-Bu (RIC [reduced intensity conditioning])**
Fludarabine 50 mg/m2 on days -6 to -2
Busulfan 3.2 mg/kg/day on days -3 and -2; no PK-based dose adjustment

**Flu(120)-Cy(120)**
Fludarabine 30 mg/m2/day on days -6 to -3
Cyclophosphamide 60 mg/kg on days -4 and -3

**Flu(120)-Cy(120)-TBI200**
Fludarabine 30 mg/m2/day on days -6 to -3
Cyclophosphamide 60 mg/kg on days -4 and -3
TBI 200 cGy delivered to midplane in a single fraction on day 0
**Flu(150)-Cy(29)-TBI (Baltimore)**
Fludarabine 30 mg/m2/day on days -6 to -2
Cyclophosphamide 14.5 mg/kg on days -6 and -5
TBI 200 or 400 cGy delivered to midplane in a single fraction on day -1
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

**TBI300 (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..

**Flu-Mel (RIC)**
Fludarabine 30 mg/m2 days -5 to -2
Melphalan 140 mg/m2 day -1

**Mel 200**
Melphalan 200 mg/m2 on day -1

**Mel-Vel**
Melphalan 200 mg/m2 on day -1
Bortezomib 1.3mg/m2 on days -5, -2, +1, +4

**R-BEAM**
Rituximab 375 mg/m2 IV on day -6
Carmustine 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

**BEAM**
Carmustine 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

**Mel 180 – TBI 500**
Melphalan 180 mg/m2 on day -1
TBI 500 cGy to midplane on day 0
**R – Mel 180 – TBI 500**
Rituximab 375 mg/m² IV on day -1
Melphalan 180 mg/m² on day -1
TBI 500 cGy to midplane on day 0

**Thiotepa-Bu**
Thiotepa 300 mg/m² on days -6 and -5
Busulfan 3.2 mg/kg/day on days -4 to -2 targeted to achieve busulfan AUC of 4500 µmol·min·L⁻¹

**R-Thiotepa-Bu-M**
Rituximab 375 mg/m² IV on day -7
Thiotepa 250 mg/m² on days -6 and -5
Busulfan 3.2 mg/kg/day on days -4 to -2 targeted to achieve busulfan AUC of 4500 µmol·min·L⁻¹
Melphalan 100 mg/m² on day -1

**Flu-TBI**
Fludarabine 50 mg/m² on days -6 to -2
TBI 500 cGy to midplane on day -1 or 0

**R-Bu-Mel**
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 4500 µmol·min·L⁻¹
Melphalan 140 mg/m² on day -1

**Carbo-Etoposide**
Carboplatin 700 mg/m²/day on days -5 to -3
Etoposide 750 mg/m²/day on days -5 to -3
Hydration: NS 3L/m²/day beginning evening of day -6 and ending day -2

**R-Etoposide-Melphalan**
Rituximab 375 mg/m² IV day -4
Etoposide 60mg/kg day -4
Melphalan 180mg/m² day -2
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·L⁻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. Dosage adjustments are made by comparing the AUC obtained from the test or first dose with the desired AUC according to the formula:

\[
\text{Adjusted Dose (mg)} = \frac{\text{Actual Dose (mg)} \times \text{Target AUC (µmol·min·L}^{-1})}{\text{Observed AUC (µmol·min·L}^{-1})}
\]

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. Busulfan target AUC is 3750 µmol·min·L⁻¹ for patients receiving TBI as part of the preparative regimen. For patients not receiving TBI the target is 4500 µmol·min·L⁻¹. 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 avoid daily AUC >6,000 umol.min/L (avoid overall AUC >24,000 umol.min/L).
Complications
Acute GVHD: Prevention and Treatment
Presented by: Ahsan Chaudhry

Summary

- **Prophylaxis**: Standard GVHD prophylaxis consists of Thymoglobulin 4.5 mg/kg, Cyclosporine A 2.5 mg/kg IV bid (adjusted to maintain trough levels between 200-400 mcg/L) from day -1 until day 56 (tapered to zero by day 84) and methotrexate on day 1, 3, 6 and 11 (Table 3).
- Adjustments to standard prophylaxis are made in certain circumstances. These include omission of thymoglobulin (second transplants for relapse, RIC, cord blood transplants) and omission of methotrexate (cord blood transplants). GVHD prophylaxis is omitted entirely for recipients of syngeneic transplants.
- Post-transplant Cyclophosphamide will be used for haplo-identical transplants (with calcineurin inhibitor+ mycophenolate).
- **Diagnosis and Grading**: Acute GVHD should ideally be confirmed histologically prior to instituting therapy. Nevertheless acute GVHD is a clinical diagnosis.
- The 1994 Consensus Conference grading system should be used to grade acute GVHD.
- **Therapy**: Treatment of grade 1 acute GVHD is topical treatment or observation.
- Treatment of grade 2-4 is po prednisone 2.0-2.5 mg/kg daily (or equivalent iv methylprednisolone). Grade 2a can be treated with oral beclomethasone dipropionate (1mg qid) + budesonide (3mg bid) + po prednisone 1 mg/kg (or equivalent); if no response in 10 days, increase prednisone to 2.0-2.5 mg/kg.
- Responding patients should be tapered as follows: from 2.0-2.5 mg/kg/day prednisone (or equivalent) x 7 days taper at a rate of 10% every 5 days until off of corticosteroids. Faster taper is recommended for patients with grade 2a aGVHD.
- Patients whose aGVHD worsens in any organ system by one or more stages after 3 days of treatment, or whose aGVHD does not improve by one or more grade after 7 days of treatment are considered steroid-refractory and should receive second-line treatment. A responding patient whose aGVHD worsens while taking more than 0.6 mg/kg prednisone is also considered steroid refractory.
- Second-line treatment for steroid-refractory GVHD is ruxolitinib, starting with 5-10 mg bid and reducing the dose if side effects. Steroids and calcineurin inhibitors are continued.

Background

Despite over 30 years of experience in allogeneic stem cell transplantation, graft-versus-host disease (GVHD) remains the main cause of death of patients in remission after this treatment. To minimize the risk of developing acute GVHD (aGVHD), more and more precise HLA typing is carried out, often to the level of single nucleotides. Differences in minor antigens, however, may lead to activation of alloreactive T-lymphocytes, which then results in tissue injury and the clinical manifestations of aGVHD. Acute GVHD remains a frequent complication of allogeneic stem cell transplantation. Risk
factors may include HLA disparity, transplantation from an unrelated donor, female-to-male transplants, recipient or donor age, or seropositivity for certain herpes viruses.

The main target organs for aGVHD are the skin, liver and gastrointestinal tract. Clinical features range from localized erythematous skin rash to bullae and moist desquamation. Acute liver injury, in the form of mildly abnormal liver enzymes to severe hyperbilirubinemia, or secretory diarrhea may occur. Acute GVHD occurs in 30 – 60% of transplants from HLA matched siblings and up to 80% of transplants from matched, unrelated donors. While mild and moderate GVHD have little impact on transplant-related mortality (TRM), clinically severe aGVHD (IBMTR severity index C or D, i.e., similar to grade 3 or 4) is associated with a pronounced increase in the relative risk of TRM (4.34 (3.33-6.57) and 11.9 (9.12-15.5), respectively) and a commensurate decrease in overall survival.

Grading of Acute GVHD

While multiple grading systems have been developed for aGVHD, only two have achieved widespread clinical use. A system was initially proposed by Glucksberg and subsequently modified by Thomas that first graded severity by organ system. Overall severity was determined based upon the combination of individual organ stages. The original staging system was based on 61 recipients of bone marrow transplants from HLA-matched siblings performed in a single center.1 This was subsequently modified in a consensus conference, in which data on 8,249 patients from 12 transplant centers was reviewed. This has become the standard grading system used in most transplant centers, including our own.2 More recently the CIBMTR has reported a diversity of outcomes for patients within the same Glucksberg grade but different patterns of organ involvement, suggesting that the grading system could be improved.3 In suggesting this system they propose that aGVHD could be graded according to the peak severity of a single organ, and this system has shown a better correlation between treatment failure and severity of aGVHD. Grade 2a is defined by rash<50% BSA and stool <1000 L/d or only upper GI sx and no liver involvement. The table below shows the 1994 Consensus conference grading system in use in our program.

Table 1. Consensus organ staging and overall clinical grading for acute GVHD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No rash</td>
<td>Total bilirubin &lt; 34 umol/L</td>
<td>No diarrhea</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash &lt;25% body surface area</td>
<td>Total bilirubin 34 to 50</td>
<td>Diarrhea 500 – 1000 mL/day or nausea with positive gastric biopsy.</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25 – 50% body surface area</td>
<td>Total bilirubin 51 to 100</td>
<td>Diarrhea 1000 – 1500 mL/day</td>
</tr>
<tr>
<td>3</td>
<td>Maculopapular rash &gt; 50% body surface area</td>
<td>Total bilirubin 101 to 250</td>
<td>Diarrhea 1500 – 2000 mL/day</td>
</tr>
<tr>
<td>4</td>
<td>Generalized exfoliative, ulcerative or bullous dermatitis</td>
<td>Total bilirubin ≥250</td>
<td>Diarrhea &gt;2000 mL/day or severe abdominal pain or ileus</td>
</tr>
</tbody>
</table>
Table 2. Grading of acute GVHD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>And</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>1-2</td>
<td>And</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>Or</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>2 - 3</td>
<td>Or</td>
<td>2 – 4</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>Or</td>
<td>4</td>
</tr>
</tbody>
</table>

Prevention of Acute GVHD

Once established, aGVHD has a high mortality rate and is a cause of significant morbidity among stem cell transplant recipients. Both pharmacological and immunological, chiefly T-cell depletion, methods have been developed to prevent aGVHD. Each of these methods is associated with risks, toxicities and costs. The most widely used strategy for prevention of aGVHD employs a combination of Cyclosporine A and methotrexate. While methotrexate has been associated with high rates of mucositis, several studies have demonstrated improved outcomes of transplantation using the combination compared with Cyclosporine A alone. Other strategies have replaced methotrexate with mycophenolate mofetil or sirolimus, resulting in lower rates of mucositis and more rapid engraftment. These alternate strategies have so far not shown an improvement in overall survival. We will continue to use Cyclosporine A and Methotrexate, in addition to Thymoglobulin.

Depletion of donor T-cells from the stem cell product has been shown to significantly decrease rates of acute GVHD at the expense of higher rates of rejection, relapse and infection. The use of T-cell depleting techniques with narrow specificity appears to be associated with better leukemia-free survival than techniques based on more broadly-depleting antibodies. Other disadvantages of ex vivo T-cell depletion are its high reagent and labor costs, making its routine use unsuitable in a resource-constrained environment. The in vivo depletion of T-cells from both donor and recipient using T-cell depleting antibodies has been shown in a number of studies to reduce the incidence of both acute and chronic GVHD without adversely affecting survival. In our program the routine use of Thymoglobulin has led to better outcomes among recipients of stem cell products from unrelated donors and others. We will continue to offer prophylactic Thymoglobulin 4.5 mg/kg IV over three days for prevention of acute GVHD, together with cyclosporine and methotrexate as shown in Table 3.
Table 3. Standard immunosuppressive agents for prevention of acute GVHD.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine*</td>
<td>2.5 mg/kg every 12 hours</td>
<td>-1 until oral feasible</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>6.25 mg/kg every 12 hours</td>
<td>Until day +56, then taper to zero by day +84</td>
<td>PO</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15 mg/m²</td>
<td>Day + 1</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>10 mg/m²</td>
<td>Day + 3</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>10 mg/m²</td>
<td>Day + 6</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>10 mg/m²</td>
<td>Day + 11</td>
<td>IV</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>0.5 mg/kg</td>
<td>Day -2</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>2 mg/kg</td>
<td>Day -1</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>2 mg/kg</td>
<td>Day 0</td>
<td>IV</td>
</tr>
</tbody>
</table>

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

Methotrexate Administration and Adjustment Guidelines

The first dose of methotrexate will be 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 (Table 4) or hepatic (Table 5) dysfunction, mucositis, and fluid collections (below).

Table 4. Dosage adjustments based on direct bilirubin

<table>
<thead>
<tr>
<th>Direct Bilirubin (micromoles/litre)</th>
<th>% Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 34</td>
<td>0</td>
</tr>
<tr>
<td>34-50</td>
<td>25</td>
</tr>
<tr>
<td>51-100</td>
<td>50</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 5. Dosage adjustments based on creatinine clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/minute)</th>
<th>% Dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>0</td>
</tr>
<tr>
<td>40-50</td>
<td>50</td>
</tr>
<tr>
<td>&lt;40</td>
<td>100</td>
</tr>
</tbody>
</table>

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 q6h 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.

Alternatives to Cyclosporine and Methotrexate
Patients with compromised renal function (CrCl < 40 mL/min) should receive methylprednisolone or prednisone instead of cyclosporine. The dosing is as follows:

- 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 who develop renal failure before day 11 should receive prednisone as above and mycophenolate mofetil (MMF, 1 g bid until day 35) instead of cyclosporine and methotrexate.

Post-Transplant Cyclophosphamide (PTCy)
There is evidence that PTCy in combination with a calcineurin inhibitor and MMF is effective for prevention of both acute and chronic GVHD in haploidentical transplantation. For HLA matched sibling and unrelated donor transplantation, PTCy (alone or in combination) has not yet been compared to our conventional GVHD prophylaxis (Thymoglobulin+MTX+CsA) in prospective studies. Therefore, we use PTCy-based GVHD prophylaxis (Table 6) only in the setting of haploidentical HCT.

Table 6. Dosing of cyclophosphamide, tacrolimus, mycophenolate and MESNA.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>50 mg/kg (actual, &gt;30% -&gt; AIBW)</td>
<td>+3, +4</td>
<td>½ L in NS IV</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.06 mg/kg (ideal) bid</td>
<td>+5 until +84</td>
<td>PO (trough 5-15)</td>
</tr>
<tr>
<td>MMF</td>
<td>1 g bid</td>
<td>+5 until +35</td>
<td>PO/IV</td>
</tr>
<tr>
<td>MESNA</td>
<td>12.5 mg/kg (actual/AIBW)</td>
<td>+3, +4</td>
<td>QID iv</td>
</tr>
</tbody>
</table>

Abbreviations: AIBW = adjusted ideal body weight; NS = normal saline; IV = intravenous; PO = per oral; QID = 4 times a day.
First-Line Treatment of Acute GVHD

Corticosteroids remain the cornerstone of treatment of aGVHD and patients who fail to respond to these agents experience high mortality and poor outcomes. Complete responses to corticosteroids occur in 25-40% of patients, with lower rates of complete response for patients with clinically more severe disease. A typical corticosteroid regimen for patients with clinically-significant (grade 2 - 4) aGVHD involves administering prednisone 2.0 to 2.5 mg/kg (or an equivalent dose of methylprednisolone) for up to two weeks, then tapering in patients whose aGVHD responds. Milder forms of aGVHD may be treated with less intensive regimens: Grade 2a can be treated with oral beclomethasone dipropionate (nonabsorbable steroid) plus either 0.5mg/kg/d or 1mg/kg/d prednisone. Grade 1 aGVHD (skin only, rash <50% BSA) does not require systemic therapy and may be treated with a topical steroid (e.g., betamethasone valerate 0.1% cream bid).

It is essential that patients whose GVHD is unlikely to respond to conventional treatment be identified early, as delaying the institution of second-line therapy exposes patients to the unnecessary risks of high-dose steroids and delays the institution of potentially beneficial treatment. If an organ system worsens by one or more stages after 3 days of treatment, or if GVHD has not improved by one or more grade after 7 days of treatment, GVHD will be considered steroid resistant and second-line treatment will be instituted. See below for second-line regimens. For grade 2a treated with 1 mg/kg prednisone + oral beclomethasone and no response by day 10 then increase to 2.0-2.5 mg/kg prednisone before concluding steroid refractory.

Patients whose aGVHD responds to corticosteroids should not remain on high doses unnecessarily, given the well-known toxicity of this class of drugs. Responding patients should be tapered as follows: 2.0-2.5 mg/kg/day (prednisone equivalent) x 7 days then tapered at a rate of 10% every 5 days, until they are off corticosteroids.

Second-Line Treatment of Acute GVHD (Steroid-Refractory)

Favourable outcomes following second-line therapy for aGVHD have been infrequent with any therapy.

A recently published multicenter trial reported that ruxolitinib was superior to standard care (other immunosuppressive therapies) for glucocorticoid-refractory acute GVHD (grades II to IV) [20]. In this trial, 309 patients ≥12 years old were randomly assigned (1:1) to ruxolitinib (10 mg by mouth, twice daily) versus the investigator’s choice of therapy. At day 28, compared with the control group, ruxolitinib achieved superior rates of overall response (62 versus 39%; odds ratio 2.64; 95% CI 1.65-4.22) and complete response (CR; 34 versus 19%). Superiority of ruxolitinib was maintained at day 56 (40 versus 22%) and its benefits were seen with all grades of disease and affected organs, but the cross-over design precluded conclusions about an impact on survival. Treatment was discontinued in
72 percent of patients receiving ruxolitinib and in 85 percent of patients in the control group; most discontinuation was due to lack of efficacy. The most common grade ≥3 toxicity with ruxolitinib was thrombocytopenia, anemia, and cytomegalovirus infection.

Ruxolitinib is administered twice daily by mouth; the usual dose is 10 mg twice daily, but some experts suggest starting at 5 mg twice daily and increasing to 10 mg twice daily after ≥3 to 7 days of treatment, if the absolute neutrophil count (ANC) and platelet count have not declined by ≥50 percent relative to the first day of treatment [27]. Dose adjustments of ruxolitinib may be required for cytopenias and for renal or hepatic impairment. Toxicity includes cytopenias, liver dysfunction, neurologic complaints, reactivation of viral infections, and bacterial or fungal infections.

For patients who have a response, ruxolitinib may be tapered gradually after eight weeks. 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.

Inhibition of JAK1/2 signaling results in reduced proliferation of donor effector T cells, suppression of pro-inflammatory cytokine production in response to alloantigen, as well as impairment of APC’s in vitro and vivo. In mouse models of GVHD, ruxolitinib improved survival and reduced GVHD grade and serum levels of proinflammatory cytokines. Graft versus leukemia effects have been maintained in both lymphoid and myeloid murine leukemia models. Previous published human experience was limited to a retrospective study of 95 SR GvHD patients from 19 centres. 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; notable side effects included cytopenias and CMV reactivation. Our local experience with ruxolitinib for SR aGVHD since 2016 includes 16 patients with 5 CR, 6 PR/stable and 5 refractory (all GI).
References


Chronic Graft Versus Host Disease
Presented by: Jan Storek

Summary

Diagnosis of Chronic GVHD:
- At least one diagnostic clinical sign of chronic GVHD or at least one distinctive sign confirmed by biopsy or other relevant tests (e.g., Schirmer’s test <5 mm, PFT+ CT findings of bronchiolitis obliterans), and exclusion of other possible diagnoses. For diagnostic and distinctive clinical signs, see Appendix 1.
- Acute vs Chronic GVHD?
  - If skin/GI/liver manifestations of GVHD (see Common signs in Appendix 1) without a diagnostic/distinctive sign of cGVHD (at any time between HCT and now), it is aGVHD.
  - If skin/GI/liver/eye/mouth/lung/genital/other organ manifestations of GVHD with a diagnostic/distinctive sign of cGVHD (at any time between HCT and now), it is cGVHD.

Scoring (staging) of Chronic GVHD:
- According to NIH Consensus Conference (see Appendix 2). An organ score from 0 to 3 is assigned to each organ. Global score (1=mild, 2=moderate or 3=severe) is then determined based on the organ scores as follows:
  - Mild cGVHD: \( \leq 2 \) organs involved with max organ score 1, plus lung score 0
  - Moderate cGVHD:
    - Neither mild nor severe
  - Severe cGVHD:
    - \( \geq 1 \) organ with a score of 3, or
    - Lung score 2 or 3

First-Line Therapy:
- Mild cGVHD: No therapy, or topical/ancillary therapy
- Moderate or Severe cGVHD:
  - Prednisone 1mg/kg/day, or
  - Prednisone 1mg/kg/day + cyclosporine A in therapeutic dose (target level 200-400 ng/mL)
  - Duration of prednisone therapy (including taper): At least 6-9 months.

Criteria For Failure of First-Line Therapy:
- Progression despite prednisone 1 mg/kg/day for 2 weeks
- Stable disease despite prednisone 1 mg/kg/day for 4-8 weeks
- Inability to taper prednisone below 0.5 mg/kg/day
Second Line Therapy:
- Add one of the following immunosuppressive modalities:
  - extracorporeal photopheresis (first choice if logistically feasible)
  - sirolimus
  - B cell targeting therapy like rituximab or ibrutinib
  - tyrosine kinase inhibitor like imatinib
  - ruxolitinib

Infection Prophylaxis:
- Extend standard VZV and Pneumocystis/pneumococcal prophylaxis until ≥3 mo after discontinuation of immunosuppressive therapy (systemic and topical), when cGVHD is inactive.
- The need for topical or systemic fungal prophylaxis is controversial; we do not use it routinely.
- No live vaccine until at least 3 months after discontinuation of immunosuppressive therapy (systemic and topical), when cGVHD is inactive.

For details, see Infection Prophylaxis and Vaccination sections of this Standard Practice Manual.

Background

Chronic graft-versus-host disease (cGVHD) is a frequent and highly polymorphic complication of allogeneic stem cell transplantation often resembling autoimmune and other immunologic disorders. The incidence of cGVHD ranges from ≤30 to ≥70%. In Alberta, ~20% allo-HCT recipients whose GVHD prophylaxis consists of 4.5 mg/kg Thymoglobulin, methotrexate and cyclosporine develop cGVHD needing systemic immunosuppression (Ousia, manuscript in preparation). Median time of onset is 3 to 5 months after transplant, but can occur also at <3 months or >1 year after transplant. About half of patients experience disease involving 3 or more organs. Treatment is usually prolonged; it may take 1-2 years or more to successfully discontinue immunosuppressive therapy. Chronic GVHD is the primary cause of late non-relapse mortality; this is probably not only due to GVHD but also due to toxicity of immunosuppressive drugs and immune deficiency predisposing to infections.1,2 Chronic GVHD has a substantial impact on quality of life of survivors.3

The pathophysiology of cGVHD differs from that of acute graft-versus-host disease (aGVHD), and even now it remains poorly understood. Possibly, failure of negative selection of T cells in the thymus with breaking of immune tolerance to self-antigens plays a role in the pathogenesis. B cells and regulatory T cells may also play a role.4

Risk factors for cGVHD include:
- Prior aGVHD
- HLA mismatched/unrelated donor (in the absence of ATG or PTCy prophylaxis)
- Older patient age in non-ATG literature. Younger patient age per one Albertan-Australian study with ATG prophylaxis58
- Older donor age
• Transplantation from a female donor to a male recipient (especially if the donor is parous)
• Blood stem cell graft source
• Absence of total body irradiation in conditioning per one Albertan-Australian study with ATG prophylaxis

Diagnosis and Staging of Chronic GVHD

Chronic GVHD is a complex medical condition with a broad spectrum of clinical presentations. It was originally described in 1980, and time of onset was used to distinguish acute and chronic GVHD (before vs. after day 100). Changes in the clinical practice of bone marrow transplantation have affected this arbitrary distinction, as patients may present with classical aGVHD after day 100 after reduced-intensity conditioning. Currently the diagnosis of cGVHD is based on clinical manifestation (irrespective of time of onset) and requires:

1. Distinction from aGVHD
2. Presence of at least 1 diagnostic clinical sign of cGVHD or presence of at least 1 distinctive sign confirmed by biopsy or other relevant tests
3. Exclusion of other possible diagnoses

Appendix 1 lists the diagnostic and distinctive clinical signs of cGVHD. Diagnostic signs are sufficient to establish a diagnosis of cGVHD. They include such features as scleroderma, oral lichen-planus, poikiloderma, esophageal webs, bronchiolitis obliterans (diagnosed by lung biopsy) and fasciitis. They should be distinguished from distinctive signs, which are not normally seen in aGVHD but are not sufficiently specific to make a diagnosis of cGVHD. Distinctive signs include features such as depigmentation of skin, xerostomia or keratoconjunctivitis sicca and require confirmation of diagnosis by biopsy or other relevant tests (eg, Schirmer’s test, pulmonary function tests, CT).

Diagnosis of cGVHD can be made before day 100 if the patient presents with diagnostic or distinctive clinical signs. On the other hand, GVHD presenting with only classical features of aGVHD (diffuse maculopapular rash, erythroderma, vomiting, diarrhea or jaundice) after day 100 should be classified as late aGVHD. Coincidental occurrence of features of acute and chronic GVHD is called “overlap syndrome” (which is a subcategory of cGVHD); whereas cGVHD without classical features of aGVHD is called “classical cGVHD”. Higher mortality follows the overlap syndrome compared to classical cGVHD. Chronic GVHD (both overlap syndrome and classical cGVHD) are associated with lower mortality compared to late aGVHD.

Scoring (Staging) of Chronic GVHD

The original staging system was designed by Shulman et al. and distinguished “limited” (skin and/or liver) and “extensive” (involving other organs) forms. Its ingenious simplicity and easy applicability kept the system in use for nearly 30 years and some transplant centers are still using it. In an effort to make staging more accurate for prognosis, the NIH Consensus Conference proposed the “Clinical
Scoring of Organ Systems & Global Assessment of Disease Severity” (see Appendix 2).\(^6\) It is becoming used in transplant centers world-wide not only for research purposes but also in daily clinical routine. We use the NIH scoring system, version 2015.\(^59\)

**Why is correct diagnosis and scoring of cGVHD important?**
- FACT accreditation
- Assessing response to therapy
- Endpoint of local retrospective, prospective, and mechanistic studies
- Endpoint of CIBMTR retrospective studies

**Factors Predicting Survival**
The NIH scoring system appears to be the major predictor of nonrelapse mortality. In the only prospective multiinstitutional study available so far, which unfortunately has a short follow up (<1 ½ years), mild cGVHD (at its onset) was followed by 3% mortality, moderate cGVHD by 14% mortality, and severe cGVHD by 38% mortality at 2 years.\(^55\) In a retrospective single-center (Toronto) study with longer follow up (median 3 years), mild cGVHD (at its onset) was followed by ~15% mortality, moderate cGVHD by ~30% mortality, and severe cGVHD by ~50% mortality at 5 years.\(^54\) Apart from disease extent (NIH score), multiple risk factors have been reported to predict patients’ survival. Two of them, thrombocytopenia at diagnosis of cGVHD and progressive onset (acute GVHD present at diagnosis of chronic GVHD), are most consistently reported across the studies.\(^10,11,56\) A cGVHD risk scoring system was published most recently.\(^12\) Using risk score of 10 variables, it identifies 6 risk groups stratifying the 5-year non relapse mortality between 5% and 72% and 5-year overall survival between 91% and 4%. This system, constructed from retrospective data, needs further validation.

**Prophylaxis of Chronic GVHD**
The major risk factor for development of cGVHD is previous aGVHD. The prophylactic use of calcineurin inhibitors with methotrexate or other immunosuppressive drugs after transplant has decreased the aGVHD, but had little or no impact on the incidence and severity of cGVHD.\(^13,14\) Ex vivo T cell depletion prevents GVHD, but may be associated with a high risk of relapse, graft failure or infections. Rabbit anti-thymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy) prevent cGVHD. We use ATG (Thymoglobulin) as it is the only GVHD prophylaxis proven in randomized studies to decrease cGVHD incidence without increasing relapse.\(^60\)

**Treatment of Chronic GVHD**
The goals of chronic GVHD management are to prevent death and disability, relieve symptoms while allowing for the development of immunological tolerance. An assessment of clinical response requires the distinction active cGVHD from inactive GVHD with irreversible organ damage. Using currently available therapy, effective control of symptoms within first 3-6 months is not predictive for induction
of immunological tolerance and cure of cGVHD, defined by withdrawal of all systemic treatment without a subsequent flare of cGVHD.\textsuperscript{18}

**First Line Therapy**

**Mild cGVHD:**
The relationship between the presence of mild/limited cGVHD and low relapse rate is well documented\textsuperscript{19}; the use of systemic immunosuppression can diminish graft-versus-leukemia effect. While systemic therapy is not indicated for this group of patients, ancillary (e.g. topical) therapy may be used. These patients may need close follow-up to recognize clinical deterioration and an indication for systemic treatment.

**Moderate or Severe cGVHD:**
This level of cGVHD requires prolonged systemic immunosuppressive treatment. Evidence exists supporting use of steroids in this indication, however, a randomized study has never been conducted, and steroid-free approaches have never been tested.\textsuperscript{20} Addition of another immunosuppressive drug to prednisone does not improve outcome. In a double blind, randomized study, the combination of prednisone with azathioprine showed a higher response rate than prednisone with placebo, but overall survival of patients in the combination arm was inferior.\textsuperscript{21} Koc \textit{et al.} provide a randomized study comparing prednisone and cyclosporine (every other day) with prednisone alone in patients with newly-diagnosed extensive cGVHD and platelet count more than 100,000/μL.\textsuperscript{22} The combination treatment did not result in differences in treatment-related mortality, overall survival, relapse or need for additional immunosuppressive drugs between the two groups. Glucocorticoid-related morbidity, as reflected by reduced rates of avascular necrosis, was reduced in the combination arm. Bone marrow was used as a graft in this study; similar data are lacking for PBSC or other alternative grafts increasingly used nowadays. In spite of these results, some experts still recommend to use prednisone plus calcineurin inhibitor as first line therapy, particularly in patients with severe cGVHD or platelet count less than 100,000/μL or patients who are likely to develop side effects of prednisone.\textsuperscript{23}

Adding yet another immunosuppressive modality to prednisone plus-minus calcineurin inhibitor in the setting of first line therapy is not recommended, as so far no studies have proved any benefit of addition of third agent into first-line combination.\textsuperscript{25,26} A study of Martin \textit{et al.} was discontinued prematurely because its interim analysis did not show any improvement in patients’ outcome after addition of MMF into treatment combination.\textsuperscript{27}

The initial dose of prednisone 1mg/kg/day is widely used and no studies are available comparing efficacy of different doses. Some experts suggest keeping the initial dose of steroids for 2-4 weeks and then tapering to half dose over 2-4 months. Depending on therapeutic response, a dose of 0.5 mg/kg/day might be either continued for next 2-4 months or tapered further by 10%-20% per month. If
cGVHD flares during this period, increasing a dose by 1 or 2 taper steps may be enough to control the symptoms.

In transplant settings, there are no data comparing efficacy of equivalent doses of steroids given either daily or every other day. This issue was addressed in studies looking at the treatment of children with nephritic syndrome and adults with proctocolitis and once- and twice-daily regimens were equally effective.\textsuperscript{23,24}.

No systemic immunosuppressive therapy may be considered for moderate cGVHD if only one organ/site shows clinically significant but not major disability (maximum score 2), or if three or more organs/sites are involved but show no clinically significant functional impairment (maximum score of 1 in all affected organs/sites). In such cases, ancillary (eg, topical) therapy can be used.

**Progressive cGVHD:**
Patients developing cGVHD directly progressing from acute GVHD are usually already treated with combination of steroids and a calcineurin inhibitor (CNI). The dose of CNI should be increased to therapeutic and the dose of prednisone should be increased to 1mg/kg/day. If the patient is already on such doses of CNI and prednisone, a second line agent (see below) should be added.

**Failure of First Line Therapy:**
Failure of first-line therapy is considered in the situation in which cGVHD progresses despite 2 weeks of treatment with prednisone at a dose of 1mg/kg/day, or when the disease remains stable after 4-8 weeks of prednisone 1 mg/kg/day. The inability to taper prednisone below 0.5mg/kg/day may also be considered as failure of therapy. Failure of prednisone or a significant toxicity of prednisone are indications for addition of second line therapy.

**Second Line Therapy**
The evidence for efficacy of any second line treatment is weak, as Phase 3 studies are lacking. With current approaches (as of 2017), treatment success defined as achievement of complete (CR) or partial response (PR) at 1 year without next systemic treatment has been observed in fewer than 20% of patients.\textsuperscript{61} No therapeutic option is clearly superior to others and empirical attempts are made to identify the best treatment for an individual patient. The choice of therapy depends both on the patient’s medical condition and preferences. Our priority for second line therapy is clinical trials, whenever available.

Assessment of response and next line therapy: Unless cGVHD has progressed, assessment of response should be performed at 2-3 months into therapy. Response is defined as improved manifestations of cGVHD or ability to taper prednisone (or other immunosuppressive therapy). If no response, a common, though unproven approach is adding additional immunosuppressive agents, one at a time. Agents toxic to the patient are discontinued, unless clearly efficacious. Extracorporeal
photopheresis (ECP), if ineffective, is discontinued.

**Extracorporeal Photopheresis (ECP):**
Retrospective analyses of small series show high response rates (up to 80%), especially in patients with cutaneous manifestation of steroid refractory chronic GVHD, including scleroderma.\(^{29-31}\) Risks of ECP are only those related to inserting and maintaining the central venous catheter. Because of the relatively low risk profile, and because ECP is the only second line therapy with efficacy, albeit small, documented in randomized studies,\(^{62,63}\) ECP is our first choice second line therapy, except when precluded by logistics (eg, patient lives too far from Calgary). Recommended schedule is 3x a week, or Monday through Friday (daily) every other week. If no clinical benefit within 3 months, discontinue ECP.

**Sirolimus:**
Sirolimus combines immunosuppressive properties and antiproliferative effect on fibroblasts and smooth muscle cells.\(^{31}\) In phase II trials, its response rate ranges between 51% and 81% and its use does not seem to increase relapse rate.\(^{35}\) Recommended initial dosing is 1-2 mg/day and the target therapeutic trough level is 5-15 ng/mL. The initial dose of sirolimus must be significantly reduced in patients concomitantly treated with azole or macrolide antibiotics. Major side effects of mTOR inhibitors are hyperlipidemia, headache, poor wound healing, renal dysfunction, edema, cytopenias and hemolytic-uremic syndrome.\(^{36}\) Hemolytic-uremic syndrome is particularly problematic in patients treated concurrently with calcineurin inhibitors. Sirolimus should not be used in the first 1-2 months after transplant, particularly when busulfan is used for conditioning and methotrexate is used for aGVHD prophylaxis. In a retrospective study, when sirolimus was used for acute GVHD prophylaxis in addition to methotrexate after busulfan-based conditioning, there was a high incidence of venoocclusive disease/sinusoidal obstruction syndrome.\(^{66}\)

**Calcineurin Inhibitors (CNIs):**
CNIs are often used in combination with steroids in first-line therapy of cGVHD; their use in that indication is based mostly on expert opinion and clear data showing their benefit are lacking. They may be a reasonable option for patients who are refractory to first-line prednisone. After addition of tacrolimus in patients with refractory cGVHD, overall response rate was 35-46% in two small studies.\(^{37,38}\) The major side effects of CNIs, including nephrotoxicity, hypertension and microangiopathic hemolytic-uremic syndrome, are well known.

**Mycophenolate Mofetil (MMF):**
In case series, the response rates to MMF is reported between 40% and 75%.\(^{39-42}\) 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.\(^{43}\) Some recent studies also raised concerns about higher risk of infectious complications in relation to MMF.\(^{41,42}\)
Rituximab:
Rituximab was initially reported to be effective in patients with cGVHD-associated immune phenomena, objective responses of cGVHD were seen in more than 70% of patients, mainly with cutaneous and musculoskeletal manifestations. True response rate in steroid-dependent/refractory patients is probably on the order of 50% (30% CR, 20% PR). Usual therapeutic scheme consist of 4 courses of rituximab at a dose of 375 mg/m², but significantly lower doses may be equally effective. Side effects include infusion reactions, mild hypogammaglobulinemia and late neutropenia.

Imatinib:
Imatinib, a tyrosine kinase inhibitor, has been shown to inhibit the platelet-derived growth factor receptor (PDGFR) and transforming growth factor beta (TGF-β) pathways and to have antifibrotic activity. The first case report in this area described a patient who was treated with imatinib for relapse of CML after allogeneic stem cell transplant and experienced an improvement of his concurrent bronchiolitis obliterans. 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 and gastrointestinal cGVHD. Myelosuppression, fluid retention and dyspnea are the most common side effects.

Ruxolitinib:
Ruxolitinib, a Jak1/2 inhibitor, at 5-10 mg bid orally, was associated in one retrospective study with a response in 19/19 patients (1 CR, 18 PR). Responses occurred within 2 weeks of treatment initiation, and were associated with meaningful reduction of steroid dose. No toxicities leading to dose reduction or discontinuation were reported. In other settings, ruxolitinib is known to lead to cytopenia and probably also GI/liver toxicity.

Ibrutinib:
Ibrutinib, a BTK inhibitor, at 420 mg qd orally, was studied in 42 patients. Five patients were not evaluable for response due to early discontinuation. Responses occurred in 28 (67%) of the 37 evaluable patients (9 CR, 19 PR), and were associated with meaningful steroid dose reduction. 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.

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).\textsuperscript{68}
# Ancillary Therapy for Chronic GVHD and/or Steroid Treatment Complications

<table>
<thead>
<tr>
<th>Organ/Site</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| **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:  
  o artificial saliva / lubricants (*Moistir, Oralbalance, Biotene*)  
  o salt water / baking soda or *Club soda* rinses  
  o 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:  
  o upper GI – beclomethasone dipropionate oral solution 1mg/mL; 1mL po QID  
  o lower GI – budesonide 3 mg po TID  
• Enzyme supplementation: pancreolipase (*Cotazym, Pancrease MT, Creon, Ultrase, Viokase*)  
• GI reflux management  
• Esophageal dilatation |
<table>
<thead>
<tr>
<th>Organ/Site</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>• Surveillance for infection (PJP, viral, fungal, bacterial)</td>
<td>• Ursodeoxycholic acid (if pruritus due to cholestasis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• inhaled corticosteroids: budesonide (<em>Pulmicort</em>), fluticasone (<em>Flovent</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SABA: salbutamol (<em>Ventolin</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LABA: formoterol (<em>Oxeze</em>), salmeterol (<em>Serevent</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Combo: formoterol + budesonide (<em>Symbicort</em>), salmeterol + fluticasone (<em>Advair</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticholinergics: tiotropium (<em>Spiriva</em>)</td>
</tr>
<tr>
<td>Musculo-</td>
<td>• Surveillance for decreased range of motion</td>
<td>• Physical therapy</td>
</tr>
<tr>
<td>skeletal</td>
<td>• Bone densitometry</td>
<td>• Treatment of osteoporosis, if present</td>
</tr>
<tr>
<td></td>
<td>• Calcium supplementation</td>
<td></td>
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<tr>
<td></td>
<td>• Vitamin D supplementation</td>
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</tr>
</tbody>
</table>

**Infectious Prophylaxis**

Patients with chronic GVHD are immunosuppressed and their treatment with currently available therapy 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 and vaccination).
References


64. Khoury HJ et al: Ruxolitinib: a steroid sparing agent in cGVHD. BMT, in press.


Appendix 1: Signs and Symptoms of Chronic GVHD (adapted from Jagasia et al., 2015)\textsuperscript{59}

<table>
<thead>
<tr>
<th>Organ/ Site</th>
<th>Diagnostic (sufficient to establish the diagnosis of cGVHD)</th>
<th>Distinctive (seen in cGVHD but insufficient alone to establish a diagnosis)</th>
<th>Other Features*</th>
<th>Common (seen with both aGVHD and cGVHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (see photos below)</td>
<td>• Poikiloderma &lt;br&gt;• Scleroderma / morphea &lt;br&gt;• Lichen sclerosus (morphea with overlying hypopigmented, finely wrinkled skin) &lt;br&gt;• Lichen planus</td>
<td>• Depigmentation &lt;br&gt;• Papulosquamous lesions</td>
<td>• Sweat impairment &lt;br&gt;• Ichthyosis &lt;br&gt;• Keratosis pilaris &lt;br&gt;• Hypopigmentation &lt;br&gt;• Hyperpigmentation</td>
<td>• Erythema &lt;br&gt;• Maculopapular rash &lt;br&gt;• Pruritus</td>
</tr>
<tr>
<td>Nails</td>
<td>• Dystrophy &lt;br&gt;• Longitudinal ridging, splitting or brittle &lt;br&gt;• Onycholysis &lt;br&gt;• Pterygium unguis &lt;br&gt;• Nail loss (usually symmetric)</td>
<td></td>
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</tr>
<tr>
<td>Scalp &amp; body hair</td>
<td>• New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) &lt;br&gt;• Loss of body hair &lt;br&gt;• Scaling</td>
<td>• Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) &lt;br&gt;• Premature gray hair</td>
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<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>• Lichen planus</td>
<td>• Xerostomia &lt;br&gt;• Mucocele &lt;br&gt;• Mucosal atrophy &lt;br&gt;• Ulcers &lt;br&gt;• Pseudomembranes</td>
<td></td>
<td>• Gingivitis &lt;br&gt;• Mucositis &lt;br&gt;• Erythema &lt;br&gt;• Pain</td>
</tr>
<tr>
<td>Eyes</td>
<td>• New onset of dry, gritty, or painful eyes &lt;br&gt;• Cicatricial conjunctivitis &lt;br&gt;• Keratoconjunctivitis sicca &lt;br&gt;• Confluent areas of punctuate keratopathy</td>
<td>• Photophobia &lt;br&gt;• Periorbital hyperpigmentation &lt;br&gt;• Blepharitis (erythema of the eyelids with edema)</td>
<td></td>
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</tr>
<tr>
<td>Genitalia</td>
<td>• Lichen planus or sclerosus &lt;br&gt;• Vaginal scarring/stenosis or clitoral/labial agglutination &lt;br&gt;• Phimosis or urethral/meatus scarring or stenosis</td>
<td>• Erosions &lt;br&gt;• Fissures &lt;br&gt;• Ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ/Site</td>
<td>Diagnostic (sufficient to establish the diagnosis of cGVHD)</td>
<td>Distinctive (seen in cGVHD but insufficient alone to establish a diagnosis)</td>
<td>Other Features*</td>
<td>Common (seen with both aGVHD and cGVHD)</td>
</tr>
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<td>-----------</td>
<td>-----------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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<td>------------------------------------------</td>
</tr>
<tr>
<td>GI Tract</td>
<td>• Esophageal web&lt;br&gt; • Strictures/stenosis in the upper- to mid-third of the esophagus</td>
<td>• Exocrine pancreatic insufficiency</td>
<td>• Anorexia&lt;br&gt; • Nausea/Vomiting&lt;br&gt; • Diarrhea&lt;br&gt; • Weight loss&lt;br&gt; • Failure to thrive (infants and children)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>• Bronchiolitis obliterans diagnosed with lung biopsy&lt;br&gt; • Bronchiolitis obliterans syndrome (BOS)** - diagnostic only if at least one distinctive manifestation of cGVHD in another organ</td>
<td>• Air trapping / bronchiectasis on CT</td>
<td>• Cryptogenic organizing pneumonitis&lt;br&gt; • Restrictive lung disease</td>
<td>• T.bilirubin or ALT or ALP &gt;2 times UNL</td>
</tr>
<tr>
<td>Lung</td>
<td>• Fasciitis&lt;br&gt; • Joint stiffness or contractures secondary to sclerosis</td>
<td>• Myositis or polymyositis (diagnostic if biopsy-confirmed)</td>
<td>• Edema&lt;br&gt; • Muscle cramps&lt;br&gt; • Arthralgia or arthritis</td>
<td></td>
</tr>
<tr>
<td>Muscles, fascia, joints</td>
<td>• Fasciitis&lt;br&gt; • Joint stiffness or contractures secondary to sclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematopoietic and immune</td>
<td>• Thrombocytopenia&lt;br&gt; • Eosinophilia&lt;br&gt; • Lymphopenia&lt;br&gt; • Hypo- or hyper-gammaglobulinemia&lt;br&gt; • Auto-antibodies (AIHA, ITP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>• Pericardial or pleural effusions&lt;br&gt; • Ascites&lt;br&gt; • Peripheral neuropathy&lt;br&gt; • Nephrotic syndrome&lt;br&gt; • Myasthenia gravis&lt;br&gt; • Cardiac conduction abnormality or cardiomyopathy</td>
<td></td>
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</tr>
</tbody>
</table>

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.

*Acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed.

**BOS is defined as all of the following 4 criteria:
1. $FEV_1/FVC < 0.7$
2. $FEV_1 < 75\%$ 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 Used to Describe Some Forms of Cutaneous and Mucosal 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.

![Lichen planus images]

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

![Poikiloderma image]

**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.

![Morphea image]
Appendix 2: NIH Scoring of Chronic GVHD (adapted from Jagasia *et al.*, 2015)\textsuperscript{59}

<table>
<thead>
<tr>
<th>Organ Scores</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td>No symptoms</td>
<td>&lt;19% BSA with disease signs but NO sclerotic features</td>
<td>19-50% BSA OR involvement with superficial sclerotic features “not hidebound” (able to pinch)</td>
<td>&gt;50% BSA OR deep sclerotic features “hidebound” (not able to pinch) OR impaired mobility, ulceration, or severe pruritus</td>
</tr>
<tr>
<td><strong>MOUTH</strong></td>
<td>No symptoms</td>
<td>Mild symptoms with disease signs but not limiting oral intake significantly</td>
<td>Moderate symptoms with disease signs with partial limitation of oral intake</td>
<td>Severe symptoms with disease signs on examination with major limitation of oral intake</td>
</tr>
<tr>
<td><strong>EYES</strong></td>
<td>No symptoms</td>
<td>Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 times daily) OR asymptomatic signs of keratoconjunctivitis sicca</td>
<td>Moderate dry eye symptoms partially affecting ADL (requiring drops &gt;3 times daily or puntal plugs) WITHOUT vision impairment</td>
<td>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</td>
</tr>
<tr>
<td><strong>GI TRACT</strong></td>
<td>No symptoms</td>
<td>Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (&lt;5%)</td>
<td>Symptoms associated with mild to moderate weight loss (5-15%)</td>
<td>Symptoms associated with significant weight loss &gt;15%, requires nutritional supplement for most calorie needs OR esophageal dilation</td>
</tr>
<tr>
<td><strong>LIVER</strong></td>
<td>Normal LFT</td>
<td>Bilirubin (total) normal ALT 180-300 U/L ALP ≥429 U/L</td>
<td>Bilirubin 24-72 umol/L ALT &gt;300 U/L</td>
<td>Bilirubin &gt;72 umol/L</td>
</tr>
<tr>
<td><strong>LUNGS</strong></td>
<td>No symptoms</td>
<td>Mild symptoms (shortness of breath after climbing 1 flight of steps), or FEV1 60-79%</td>
<td>Moderate symptoms (shortness of breath after walking on flat ground), or FEV1 40-59%</td>
<td>Severe symptoms (shortness of breath at rest requiring O\textsubscript{2}), or FEV1 &lt;39%</td>
</tr>
<tr>
<td><strong>JOINTS &amp; FASCIA</strong></td>
<td>No symptoms</td>
<td>Mild tightness of arms or legs, normal or mild decreased range of motion AND not affecting ADL</td>
<td>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</td>
<td>Contractures WITH significant decrease of range of motion AND significant limitation of ADL (unable to tie shoes, button shirt, dress self)</td>
</tr>
<tr>
<td><strong>GENITAL TRACT</strong>*</td>
<td>No symptoms/signs</td>
<td>Mild signs*</td>
<td>Moderate signs*</td>
<td>Severe signs*</td>
</tr>
</tbody>
</table>

*Genital signs:*

**Female genitalia:**

1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
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:**

<table>
<thead>
<tr>
<th>Mild cGVHD:</th>
<th>≤2 organs involved with max organ score 1, plus lung score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate cGVHD:</td>
<td>≥3 organs involved with max score 1, or</td>
</tr>
<tr>
<td>Severe cGVHD:</td>
<td>≥1 organ with a score of 3, or</td>
</tr>
</tbody>
</table>
CMV, VZV, HSV, HHV6
Presented by: Jan Storek

Summary

CMV (cytomegalovirus) Disease Prevention

- Monitoring and preemptive therapy: Monitor plasma CMV by quantitative PCR weekly until day 100, then monthly until 1 year posttransplant. If >25,000 IU/mL, treat preemptively with ganciclovir or valganciclovir.
- Blood products: Use CMV safe 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

- Valacyclovir from start of conditioning until 1 day before VZV vaccination.
  - VZV vaccination should occur at 2 years posttransplant or later (later in patients on prolonged therapy with immunosuppressive drugs – wait until ≥3 mo after discontinuation of immunosuppressive therapy (systemic and topical) and no cGVHD activity).

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

Cytomegalovirus (CMV)¹

Background

Epidemiology: Incidences of CMV Reactivation / CMV Disease

- Seronegative donor → Seronegative patient
  - 70% / 35% with non-CMV safe transfusions (from random donors and not leukodepleted)
  - <2% / <2% with CMV safe transfusions (from CMV seronegative donors; if from random donors, than leukodepleted and irradiated)

- Seropositive donor → Seronegative patient
  - 70% / 35% with non-CMV safe transfusions
  - 15% / 5% with CMV safe transfusions, before ganciclovir
  - 14% / 3% with CMV safe transfusions, since ganciclovir

- Seropositive donor → Seropositive patient, and Seronegative donor → Seropositive patient
  - 70% / 35% before ganciclovir
  - 70% / 10% (3-20%) since ganciclovir (<3% in the first 3 mo after T replete HCT)
- Lower incidence of CMV disease in D+R+ than D-R+ patients in the setting of in vivo T cell depletion with ATG, and approximately 20% absolute survival difference at 5 years\textsuperscript{2,3}

- **Autologous seropositive patient**
  - 50% / ≤2%

- **Syngeneic seropositive patient**
  - 50% / 0%

- **Healthy individuals**
  - 50% - 80% are infected, <5% reactivate (poorly studied), 0% develop CMV disease

**Risk factors**: Seropositivity of recipient, GVHD / immunosuppressive drugs, severe T-cell depletion

**Clinical manifestations of CMV disease**: Pneumonia, gastroenteritis, other rare manifestations (retinitis, encephalitis, hepatitis, marrow suppression)

**Prevention/Prophylaxis 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 irradiated prior to transfusion.
- CMV seronegative HCT donor is preferred for CMV seronegative recipient.\textsuperscript{4} However, the difference in survival of seropositive patients receiving grafts from seropositive vs negative donors is minor, if any.\textsuperscript{2,5}
- CMV seropositive HCT donor is preferred for CMV seropositive recipient.\textsuperscript{2-4,6} Survival difference (between HCT from seropositive vs seronegative donors) appears to be marked in patients with lymphoid malignancies receiving myeloablative HCT with ATG-based GVHD prophylaxis (HR 3.1, p<0.001, Ousia, manuscript in preparation). The survival difference in the setting of ATG-based GVHD prophylaxis appears to be minor, if any, in patients with myeloid malignancies (HR 1.3, p=0.20, Ousia, manuscript in preparation). The survival difference is virtually zero in the setting of haploidentical HCT with posttransplant cyclophosphamide-based GVHD prophylaxis.\textsuperscript{7}
- In the setting of a myeloablative HCT for a lymphoid malignancy with 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.\textsuperscript{2}
- 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.\textsuperscript{8}
Preemptive Therapy with Ganciclovir/Valganciclovir

Benefits: Reduction of CMV disease incidence in seropositive patients from 33% to <20%. One third of CMV diseases are pneumonias that are ~50% fatal.

Risks: Neutropenia (30-60% patients) → bacterial and fungal disease, late CMV disease; both risks are more likely with prolonged therapy.

Preemptive strategy in Alberta
- CMV DNA monitoring in plasma from day 0 to day 100 weekly, then monthly to one 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 (induction treatment, i.e., b.i.d.).
  - 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 U/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.
    - With this threshold, our incidence of CMV disease has been 3.8%, and our incidence of CMV pneumonia <1%. The incidence of CMV disease has been highest in D-R+ patients (11.2%), second highest in D+R+ patients (3.6%), and low in D+R- patients (0.8%) and D-R- patients (0%).
  - Continue induction until a down-going trend of CMV PCR results, then switch to maintenance (q.d.). For example, if ganciclovir induction was started for 80,000 IU/mL, switch to maintenance after <80,000 IU/mL.
  - Treat until <5,000 IU/mL at least twice, but treat for at least 3 weeks (e.g., one week of induction and 2 weeks of maintenance).
  - Prolonged maintenance can be considered for patients at high risk of CMV disease (e.g., active GVHD, or recurrent CMV DNAemia requiring preemptive therapy).
  - 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.

Ganciclovir/valganciclovir dosing, and management of toxicity
- Induction with ganciclovir 5 mg/kg IV twice daily, or valganciclovir 900 mg p.o. twice daily, for 7 days.
Longer induction is needed if after the 7 day induction CMV DNAemia has not dropped. In that case continue induction until DNAemia has started to decline.

If DNAemia has not declined after 2-3 weeks of induction, suspect ganciclovir resistance.

- Maintenance with ganciclovir 5 mg/kg IV once daily or valganciclovir 900 mg p.o. once daily, for at least 2 weeks.
- 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.

**CMV Disease Diagnosis and Therapy**

- 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:

<table>
<thead>
<tr>
<th>Viral load range (IU/mL)</th>
<th>Neg (0 to &lt;150)</th>
<th>150 to 10^3</th>
<th>10^3 to 10^4</th>
<th>10^4 to 10^5</th>
<th>&gt;10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% viral culture positive (pos/total)</td>
<td>0.33% (1/306)</td>
<td>6% (2/33)</td>
<td>27% (6/22)</td>
<td>40% (4/10)</td>
<td>100% (4/4)</td>
</tr>
</tbody>
</table>

- 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) ¹

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 since acyclovir prophylaxis

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) \( \rightarrow \) 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/ Prophylaxis 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 followed by VZV vaccination, as this strategy appears effective for eliminating post-herpetic neuralgia (Fig. 1).[^5]
- Give valacyclovir until VZV vaccination, which should occur at 24 months posttransplant in patients free of active cGVHD and off of immunosuppressive therapy.
- For patients with longer duration of immunosuppressive therapy, continue valacyclovir until VZV vaccination, which should occur at ≥3 months after the discontinuation of immunosuppressive therapy (systemic and topical), when cGVHD is inactive.
- Valacyclovir should not be taken on the day of VZV vaccination or thereafter as it could minimize the immune response to the vaccine by killing the live vaccine. Take the last dose of valacyclovir on the day preceding the day of vaccination.
- 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/m² po twice daily.
- If patient is on ganciclovir/valganciclovir/foscarnet/cidofovir, hold acyclovir/valacyclovir.

**Table 1.** Pediatric patients treated with acyclovir/valacyclovir

<table>
<thead>
<tr>
<th>HSV Recipient Serostatus</th>
<th>VZV Recipient Serostatus</th>
<th>Start and End of Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive or Negative</td>
<td>Positive</td>
<td>From day 0 until VZV vaccination (24 months or later)</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>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.</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>No prophylaxis. Consider immunizing VZV-seronegative contacts with VZV vaccine.</td>
</tr>
</tbody>
</table>

Exposure prevention for VZV (recommendation only):

- 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.
- Vaccinate 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 (recommendation only):
- 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

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)
- Prevention: Insufficient data exist whether prophylaxis or preemptive therapy with ganciclovir or foscarnet is indicated. In Alberta, we use no prophylaxis or preemptive therapy.
- Therapy of HHV6 disease: Ganciclovir or foscarnet, same dose as for CMV disease.
References

Appendix A: Cumulative Incidence of Post-Herpetic Neuralgia

Figure A1. 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.5
Epstein - Barr Virus/ Posttransplant Lymphoproliferative Disorder
Presented by: Jan Storek

Summary

Epstein - Barr Virus (EBV) Monitoring:
- Use RealStar assay (the only EBV DNAemia 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 375 mg/m² i.v. (2nd, 3rd and 4th doses can be given as 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 diagnosis of PTLD by biopsy, or as EBV DNAemia >30,000 IU/mL and at least one 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. The rituximab and tapering of immunosuppression can be skipped for a PTLD diagnosed after preemptive therapy (preemptive therapy failure).
- Second line therapy: Donor lymphocyte infusion (10⁵ T cells/kg) if no GVHD and if donor is EBV seropositive. If active GVHD or if donor is EBV seronegative, use chemotherapy.

Background

Epstein - Barr virus¹ ³
- EBV is a gamma-herpes virus infecting primarily pharyngeal epithelial cells and B cells.
- Over 90% 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, 82% HCT recipients reactivate EBV (have EBV detectable in blood by PCR).
    - First reactivation on median day 33 (11 – 318).
    - Maximum EBV DNAemia: median ~50,000 IU/ml
    - Maximum EBV DNAemia reached on median day 55 (14 – 398).
  - (Data based on Kalra et al: submitted)

- 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)
  - 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

**Risk Factors for Developing EBV PTLD after HCT**
- T cell depletion ex vivo, without concurrent B cell depletion.
- Antithymocyte globulin (ATG) / high ATG levels.
- Unrelated/mismatched donor
- GVHD (not applicable in Alberta with ATG - >80% PTLDs occur in absence of GVHD, median day 54) (ref8 and Kalra, submitted)
- D+R- EBV serostatus (ref9 and Kalra, submitted)
- Second transplant
- Immunocompromised recipient pretransplant (i.e., SCID)

**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 DNAemia 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.

- 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:
1. EBV specific T cells\textsuperscript{10-12} (not available in Alberta)
   - 70-100\% efficacy
No toxicity; however, costly/impractical due to long manufacturing (weeks) or non-persistence (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)

2. Rituximab:
- 50-100% efficacy (?) – preponderance of single arm studies – see Table 1 below13-16

**Table 1. Efficacy of rituximab prophylaxis, preemptive therapy, prompt therapy and therapy.**

<table>
<thead>
<tr>
<th>Given as</th>
<th>N</th>
<th>Efficacy endpoint</th>
<th>Efficacy endpoint achieved (% patients)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis (200 mg on d5)</td>
<td>55 vs 68ctrl total patients</td>
<td>EBV not high PTLD incidence</td>
<td>86 vs 51% (p&lt;.001) 0% vs 3% (N.S.)</td>
<td>No impact on overall survival</td>
<td>Dominietto BMT 201217</td>
</tr>
<tr>
<td>Preemptive Therapy</td>
<td>93 w high EBV</td>
<td>EBV undetectable</td>
<td>83%</td>
<td>2 patients died of PTLD</td>
<td>Garcia-Cadenas BMT 201518</td>
</tr>
<tr>
<td></td>
<td>55 w high EBV</td>
<td>EBV not high</td>
<td>91%</td>
<td>3 patients died of PTLD</td>
<td>Coppoletta BMT 201116</td>
</tr>
<tr>
<td></td>
<td>19 w high EBV</td>
<td>EBV undetectable</td>
<td>89%</td>
<td></td>
<td>Blaes BBMT 201019</td>
</tr>
<tr>
<td></td>
<td>49 vs 85ctrl total pts</td>
<td>PTLD incidence Mortality 2° PTLD</td>
<td>6 vs 12% (N.S.) 0 vs 6% (N.S.)*</td>
<td>Impact on overall survival not reported</td>
<td>VanEsser Blood 200214</td>
</tr>
<tr>
<td>Prompt Therapy</td>
<td>5 w PTLD</td>
<td>Regression</td>
<td>100%</td>
<td></td>
<td>Wagner Blood 200415</td>
</tr>
<tr>
<td></td>
<td>6 w PTLD</td>
<td>“complete remission”</td>
<td>67%</td>
<td></td>
<td>Kinch SJID 200720</td>
</tr>
<tr>
<td></td>
<td>21 w PTLD</td>
<td>Sustained regression</td>
<td>76%</td>
<td></td>
<td>Kalra/Roessner in preparation</td>
</tr>
<tr>
<td>Therapy</td>
<td>12 w PTLD</td>
<td>Sustained CR</td>
<td>67%</td>
<td></td>
<td>Faye BJH 200121</td>
</tr>
<tr>
<td></td>
<td>146 w PTLD</td>
<td>“cure or improvement”</td>
<td>63%</td>
<td></td>
<td>Styczynski Transpl Inf Dis 200922</td>
</tr>
<tr>
<td></td>
<td>144 w PTLD</td>
<td>Not dying due to PTLD</td>
<td>61%</td>
<td></td>
<td>EBMT registry Styczynski CID 201323</td>
</tr>
</tbody>
</table>

* Significant difference when only patients with high EBV DNAemia were compared.

Toxicities/disadvantages of rituximab:
Infusion reactions
- Hypo-IgM/IgG
- Neutropenia,\textsuperscript{17} which may be clinically significant\textsuperscript{24,25}
- Vaccination onset needs to be moved to at least 6 months after the last rituximab dose

3. 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\textsuperscript{23}

4. Purging grafts of B cells (theoretical)

5. Alemtuzumab instead of ATG
- Alemtuzumab may be associated with more CMV disease and other non-EBV viral infections.\textsuperscript{30}
  - 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.\textsuperscript{31}

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, below). The addition of the taper of immunosuppression is an extrapolation from the study of Styczynski et al\textsuperscript{23} showing overall survival benefit in the setting of therapy (not preemptive therapy). The use of preemptive therapy in patients whose conditioning includes ATG is in line with EBMT guidelines.\textsuperscript{32}

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

<table>
<thead>
<tr>
<th>EBV DNAemia (max)*</th>
<th>Undetectable</th>
<th>&lt;10,000/ml</th>
<th>10,000 – 100,000/ml</th>
<th>100,000 – 1,000,000/ml</th>
<th>&gt;1,000,000/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with PTLD of total patients in the max DNAemia range (%)</td>
<td>0/56 (0 %)</td>
<td>0/43 (0 %)</td>
<td>0/103 (0 %)</td>
<td>25/82 (30 %)</td>
<td>18/22 (81 %)</td>
</tr>
<tr>
<td>Number of patients with fatal PTLD of total patients in the max DNAemia range (%)</td>
<td>0/56 (0 %)</td>
<td>0/43 (0 %)</td>
<td>0/103 (0 %)</td>
<td>3/82 (4 %)</td>
<td>2/22 (9 %)</td>
</tr>
</tbody>
</table>

* 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.**

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

* 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.

### 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/m² i.v.), until undetectable DNAemia, maximum 4 doses. In Alberta, we adopt the weekly dosing given that
  - It is in line with EBMT guidelines.
  - 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.
  - One dose only may be sufficient (in preemptive setting).
- 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.

Second Line Therapy\textsuperscript{10,33}

- To be used if no response to rituximab with immunosuppression taper in 2-4 weeks.
- If no GVHD and if donor is EBV seropositive, use DLI, starting with $10^5$ T cells/kg.
- If active GVHD or if donor is EBV seronegative, use chemotherapy.
- Future options may include:
  - EBV specific T cells from the original donor, manufactured in 1-2 days.\textsuperscript{12}
  - EBV specific T cells from a partially HLA matched 3rd party donor, off shelf.\textsuperscript{34}
  - EBV thymidine kinase inducers, making EBV-infected cells susceptible to ganciclovir.\textsuperscript{35}
References

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>1.5/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 for allogeneic HCT recipients (except for cord blood)
  - No antibacterials peri-transplant routinely (both autologous and allogeneic HCT recipients)
  - 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
  - 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 given to 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/m² 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 sulfamethoxazole and trimethoprim.

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\textsuperscript{1}. These recommendations, including Calgary-specific deviations, are summarized below.

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

- Dental consult pretransplant
- Hand washing
- 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 of systemic antibacterials: low rate of bacterial infection or fever (but no survival benefit)
  - Disadvantages:
    - Resistance
    - C. difficile
- Growth factors have marginal benefit in reducing infections and shortening hospital stay (but not improving survival) in autologous HCT recipients. Thus, in Calgary, GCSF is routinely given to autologous HCT recipients.
  In allogeneic HCT recipients, length of hospital stay is typically not limited by neutropenia, there is a theoretical concern that T cell reconstitution may be impaired by G-CSF, and GVHD may be induced/worsened by GM-CSF. Thus, in Calgary, growth factors are not routinely given to HCT recipients, except for GCSF given to recipients of cord blood.
- 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\textsuperscript{2}. When using PJP prophylaxis until approximately 6 months in allo HCT recipients not getting ATG (for GVHD prophylaxis), PJP incidence was \(\leq 1\%\). However, with ATG, in Albertan patients using PJP prophylaxis until approximately 6 months, we have noted PJP incidence of 3% (Evernden & Storek,
manuscript in preparation). 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 PJP's occurred at 7-12 months, 2 PJP's occurred at 13-24 months, and no PJP at >24 months. As approximately 30% of patients with PJP's 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 months. CD4 T cell count < 200/microliter is a well-recognized risk factor for PJP (reviewed by Messiaen PE et al5, consistent with Evernden & Storek, manuscript in preparation). Thus:

- PJP prophylaxis in Alberta is routinely given to patients from engraftment until 12 months 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 (some enteric/urinary/respiratory pathogens including S.pneumoniae, Toxoplasma, Nocardia).
  - Patients with documented allergy to sulfamethoxazole and trimethoprim may be desensitized (see Appendix). Patients who experience non-allergic toxicity to sulfamethoxazole and trimethoprim (eg, cytopenia, increased ALT, increased creatinine), should be rechallenged with sulfamethoxazole and trimethoprim 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 (eg, 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. Atovaquone as well as inhaled pentamidine have a high breakthrough PJP rate4,5.
- 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
- 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. The exception is for autologous HCT recipients who are cotrimoxazole-intolerant. In these patients it is acceptable to give only dapsone (or another anti-PJP drug) and omit penicillin. The rationale is that the incidence of pneumococcal infections after autoHCT is approximately 2-fold lower than after alloHCT\textsuperscript{6,7}, so pneumococcal prophylaxis might be redundant.

- Vaccinate patients against S. pneumoniae and with other vaccines per standard schedule (see chapter on Vaccination).

Appendix, including Figures and Tables

**Fig. 1. Incidence of Pneumococcal Sepsis after alloHCT.** From Kulkarni, S. et al. Blood 2000;95:3683-3686\textsuperscript{8}. Red line represents data on general population from Kumar D. et al: BMT 41:743-747, 2008\textsuperscript{9}.
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.
Comparison of prophylactic dosing schedules of Sulfamethoxazole+Trimethoprim and alternative anti-PJP drugs

Schneider MM et al: A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis pneumonia in patients with HIV infection\textsuperscript{11}.

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Efficacy (% developing Pneumocystis pneumonia)</th>
<th>Toxicity (% discontinuing drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentamidine inhaled monthly</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Sulfa+Trim 800+160 mg daily</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Sulfa+Trim 400+80 mg daily</td>
<td>0%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Bozzette SA et al: A randomized trial of three anti-Pneumocystis agents in patients with advanced human immunodeficiency virus infection\textsuperscript{12}.

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Efficacy (% developing Pneumocystis pneumonia per year)</th>
<th>Toxicity (% discontinuing drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone 50 mg bid</td>
<td>2.6%</td>
<td>75%</td>
</tr>
<tr>
<td>Pentamidine inhaled monthly</td>
<td>5.7%</td>
<td>12%</td>
</tr>
<tr>
<td>Sulfa+Trim 800+160 mg bid</td>
<td>1.2%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Hughes WT et al: Successful intermittent chemoprophylaxis for Pneumocystis pneumonia (in pts treated with chemotherapy for acute lymphoblastic leukemia)\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Efficacy (% developing Pneumocystis pneumonia)</th>
<th>Toxicity (% with adverse effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfa+Trim 800+160 mg daily</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>Sulfa+Trim 800+160 mg 3x/week (3 consec.days)</td>
<td>0%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Sangiolo D et al: Toxicity and Efficacy of daily dapsone as Pneumocystis jirovecii prophylaxis after HCT: A case-control study\textsuperscript{14}.

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Efficacy (% developing Pneumocystis pneumonia)</th>
<th>Toxicity (% discontinuing drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone 50 mg bid</td>
<td>1.3%</td>
<td>Not given</td>
</tr>
<tr>
<td>Sulfa+Trim 800+160 mg bid</td>
<td>0%</td>
<td>Not given</td>
</tr>
</tbody>
</table>

Souza JP et al: High rates of Pneumocystis carinii pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis\textsuperscript{15}.

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Efficacy (% developing Pneumocystis pneumonia)</th>
<th>Toxicity (% discontinuing drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone 50 mg bid 3x a week</td>
<td>7.2%</td>
<td>Not given</td>
</tr>
<tr>
<td>Sulfa+Trim 800+160 mg bid twice a week</td>
<td>0.4%</td>
<td>Not given</td>
</tr>
</tbody>
</table>
Desensitization Protocol for HCT Patients with Sulfa Allergies*

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.

*Modified from Purdy et al, Annals of Internal Medicine, 1984, 100:512-51416.
A similar protocol is well described in Pyle RC: Successful Outpatient Graded Administration of Trimethoprim-Sulfamethoxazole in Patients Without HIV and With a History of Sulfonamide Adverse Drug Reaction: Journal of Allergy and Clinical Immunology: In Practice 2014, 2:52-5817.
References


17. Pyle RC: Successful Outpatient Graded Administration of Trimethoprim-Sulfamethoxazole in Patients Without HIV and With a History of Sulfonamide Adverse Drug Reaction: Journal of Allergy and Clinical Immunology: In Practice 2014, 2:52-58
**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.
- 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 important clinical endpoints such as incidence of proven and probable invasive fungal infection and 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 2yrs). 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 separate 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 successful46.
Allogeneic HSCT Recipients, Initial Neutropenic Phase

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

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

* 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.
- Ongoing construction at our centre may increase the risk of IFI in at risk patients.
- In the two most recent trials of mould-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-chlorodeoxyadenosine) within 6 months of HCT

**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. Benefit from secondary antifungal prophylaxis has been suggested by two large retrospective studies of allogeneic HSCT recipients, and a prospective study of voriconazole in this population. 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 3 AII). Where ongoing antifungal therapy is considered prudent, clinicians must be mindful of drug interactions, especially between azoles and calcineurin inhibitors.

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. 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. AMBd receives a D1 grading in the presence of risk factors for renal toxicity and should be avoided.

• Caspofungin is as effective as L ampho B in empiric treatment of suspected invasive fungal infections.

• 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, effective therapy for candidiasis, and efficacious for prevention of break through invasive fungal disease.

• Fluconazole has no activity against Aspergillus species or other molds, and is not approved by the FDA for this indication.

• Only amphotericin B preparations and 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).
Table 2. Dose and grading of antifungal agents

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>Daily Dose</th>
<th>ECIL 3 Grading¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>L ampho B⁴⁷,⁴⁸</td>
<td>3 mg/kg</td>
<td>AI</td>
</tr>
<tr>
<td>Caspofungin⁴⁸-⁵⁰</td>
<td>50 mg</td>
<td>AI</td>
</tr>
<tr>
<td>Itraconazole⁵¹</td>
<td>200 mg i.v.</td>
<td>BI</td>
</tr>
<tr>
<td>Voriconazole⁵²,⁵³</td>
<td>2 X 3 mg/kg i.v.</td>
<td>BI</td>
</tr>
<tr>
<td>Micafungin⁵⁴,⁵⁵</td>
<td>100mg</td>
<td>BII</td>
</tr>
<tr>
<td>AMBd⁴⁷</td>
<td>0.5 - 1 mg/kg</td>
<td>BI/DI</td>
</tr>
<tr>
<td>Fluconazole⁵⁶</td>
<td>400 mg i.v.</td>
<td>CI</td>
</tr>
</tbody>
</table>

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


Graft Failure and Poor Graft Function
Presented by: Andrew Daly

Summary

Graft Failure due to Rejection
- Early recognition of graft rejection is essential to avoid unnecessary delays in retransplantation. The diagnosis requires the following:
  - Severe pancytopenia (ANC < 0.5, reticulocytes < 1%, platelets < 20) for more than two weeks beyond day +14.
  - Bone marrow biopsy showing severely hypocellular bone marrow without evidence of recurrent malignancy.<n5% donor T cells and myeloid cells, or clearly decreasing trend.
- Successful treatment requires close communication between treating physicians, workup and, where necessary, donor registries.
- Continue supportive care until repeat transplant can be carried out. The choice of donor for a second transplant depends on availability of the initial or backup donor, outcome of the first marrow harvest or stem cell collection and timing of repeat collection.

Poor Graft Function
- Poor graft function should be distinguished from rejection, as repeat conditioning is not a prerequisite for successful cellular therapy. The criteria for poor graft function are:
  - Two to three lineage cytopenias with transfusion requirement sustained for more than two weeks beyond day +14.
  - Bone marrow biopsy showing severely hypocellular bone marrow without evidence of recurrent malignancy.
  - Absence of severe GVHD.
  - Complete donor chimerism in T-cell and myeloid compartments.
- A CD34-enriched stem cell boost may improve peripheral blood counts in patients with poor graft function.
- Although the optimal dose for stem cell boosts has not been determined, there does not seem to be an advantage to administering more than 3.25 x 10^6 CD34+ cells per kg. We request collection of 5-7 x 10^6 CD34+ cells per kg in a single apheresis session to ensure that after the CD34 cell enrichment, there will be at least 3 x 10^6 CD34+ cells per kg for infusion.
- The use of cryopreserved HPC-A for preparation of CD34-selected boost products is associated with low yield and viability and we recommend the use of fresh products for this procedure.
Background

Engraftment
Engraftment is a complex process involving homing of hematopoietic stem cells to the stem cell niche, interaction with bone marrow stroma and cytokines, differentiation into maturing and lineage-committed precursors and production of mature blood elements. In addition to the potency of the stem cell product, engraftment is affected by the following factors:

1. Use of growth factor support
2. Graft source (marrow, peripheral blood or umbilical cord blood)
3. Graft composition (CD34 cell dose, CD34 subsets and CD8 cell dose)
4. Bone marrow microenvironment
5. Preformed host antibodies against disparate HLA antigens
6. Donor/host HLA mismatch

Engraftment Failure
Failure of sustained allogeneic engraftment is an uncommon but serious complication of myeloablative stem cell transplantation. The term primary engraftment failure is used to describe a situation in which engraftment fails to occur, usually in relation to a preset timeframe. Secondary engraftment failure describes a situation in which engraftment has occurred but subsequently is lost. Clinically, persistence or recurrence of pancytopenia is noted without evidence of relapse of the underlying malignancy. The diagnosis of engraftment failure requires the following:

1. Severe pancytopenia (ANC < 0.5, reticulocytes < 1%, platelets < 20) for at least 2 weeks after day +14.
2. Bone marrow biopsy showing severely hypocellular bone marrow without evidence of recurrent malignancy
3. Reemergence of host T-cells and loss of donor myeloid cells

Most cases of engraftment failure are believed to be immune-mediated, although certain viruses (parvovirus B-19, human herpes virus-6 (HHV-6), cytomegalovirus and Epstein-Barr virus) and medications (ganciclovir, Septra) are also believed to contribute on occasion. Rates of graft failure vary with stem cell source, with engraftment failure (primary and secondary) occurring in 14% of transplants using unrelated bone marrow and 8-21% engraftment failure in adults receiving umbilical cord blood transplants. Mortality rates range between 40-50%, with infection as the primary cause of death in the majority of cases.
Poor Graft Function

Engraftment failure should be distinguished from poor graft function, in which a recipient with complete donor T-cell chimerism shows persistently low blood counts in the absence of severe GVHD and relapse. The mechanism underlying poor graft function is unclear but, like engraftment failure, it may be primary (peripheral blood counts do not recover after conditioning-related nadir) or secondary (occurring at some time after engraftment).

Criteria for the diagnosis of poor graft function includes the following:

1. Two to three lineage cytopenias with transfusion requirement
2. Sustained for at least two weeks beyond day +14
3. Hypoplastic or aplastic bone marrow
4. Complete donor chimerism
5. Absence of severe GVHD and relapse

Management of Graft Failure

Due to the high mortality of sustained pancytopenia and the inevitable delays in procuring new stem cell products for repeat transplantation, early diagnosis of engraftment failure is essential. This requires a high degree of suspicion in patients at higher than average risk of graft failure combined with early diagnostic testing in suspected cases. In the case of primary engraftment failure a bone marrow biopsy and peripheral blood chimerism (sorted to test T-cells and disease phenotype cells separately) should be carried out on day +28 in the case of transplant from adult donors and day +42 in the case of umbilical cord blood transplants. The same investigations should be carried out if unexplained pancytopenia persists for more than two weeks in a previously engrafted patient.

Early management of patients with engraftment failure includes supportive care with blood transfusions and treatment of infection. Definitive management requires repeat conditioning and stem cell infusion. The choice of donor for a repeat transplant in engraftment failure depends on the availability of the initial or backup donor, the outcome of the first marrow harvest or blood stem cell collection and the timing of repeat collection. The ability to move quickly to re-transplantation depends on close communication between the clinical team, workup office and registries. The choice of conditioning regimen is shown in the ABMT Program Standard Practice Manual section on pre-transplant conditioning.
Table 1. Summary of publications describing outcome of CD34-selected stem cell boosts in poor graft function.

<table>
<thead>
<tr>
<th>Publication</th>
<th>N=</th>
<th>Time (days)</th>
<th>Content</th>
<th>Response</th>
<th>GVHD</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainardi³</td>
<td>50</td>
<td>94</td>
<td>CD34 3.15 x 10⁶/kg</td>
<td>66% (4 week)</td>
<td>NR</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79% (8 week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stasia⁴</td>
<td>41</td>
<td>NR</td>
<td>CD34 3.45 x 10⁶/kg CD3 2.5-10 x10³/kg</td>
<td>CR 75% PR 7%</td>
<td>15%</td>
<td>63% 3-year</td>
</tr>
<tr>
<td>Haen⁵</td>
<td>20</td>
<td>NR</td>
<td>CD34 4.6 x 10⁶/kg CD3 2 x10³/kg</td>
<td>NR</td>
<td>NR</td>
<td>53% 2-year</td>
</tr>
<tr>
<td>Klyuchnikov⁶</td>
<td>32</td>
<td>150</td>
<td>CD34 3.4 x 10⁶/kg CD3 9 x10³/kg</td>
<td>81% HI 22% CHR</td>
<td>19%</td>
<td>50%</td>
</tr>
<tr>
<td>Askaa⁷</td>
<td>18</td>
<td>113</td>
<td>CD34 4.9 x 10⁶/kg CD3 1.1 x10⁴/kg</td>
<td>72%</td>
<td>22%</td>
<td>48% 2-year</td>
</tr>
<tr>
<td>Ghabadi⁸</td>
<td>26</td>
<td>NR</td>
<td>Varied with mobilization</td>
<td>81%</td>
<td>23%</td>
<td>65% 1-year</td>
</tr>
</tbody>
</table>

*Time (days) from stem cell transplant to infusion of CD34 selected cells; NR = Not reported

In general the administration of CD34-selected stem cell boosts appears to be safe and is associated with improved peripheral blood counts (Table 1). The only toxicity noted with infusion of these products appears to be graft-versus-host disease, which is clinically mild (grade I-II acute GVHD) in the majority of cases. The time to peak response appears to be 1-3 months, although responses have been reported as early as 10 days after the infusion.⁵ Where it has been examined, the total dose of CD34+ cells administered in a stem cell boost has not been associated with response.³⁴⁶ The overall response (the difference between the absolute neutrophil counts at 8 weeks and prior to the infusion) appears to plateau at a threshold CD34 cell dose of 3.25x10⁶ CD34+ cells/kg.³ It is recommended that G-CSF mobilized peripheral blood stem cells (HPC-A) be collected fresh for CD34 selection as the use of cryopreserved HPC-A has been associated with low yield and viability of CD34 cells after processing.⁸
References

5. Haen, S.P., et al., Poor graft function can be durably and safely improved by CD34(+) -selected stem cell boosts after allogeneic unrelated matched or mismatched hematopoietic cell transplantation. Journal of Cancer Research and Clinical Oncology, 2015;141(12):2241-51.
Relapse of Leukemia after Transplant
Presented by: Andrew Daly

Summary

- Patients who relapse after stem cell transplant have poor prognosis. It is doubtful that repeat transplantation improves this.

- Patients with acute leukemia relapsed after transplant should be considered for donor lymphocyte infusion, palliative chemotherapy, clinical trials or palliative care. It is possible that highly selected patients with relapsed acute leukemia may benefit from a repeat transplant. These patients will typically be:
  - Young (age < 40) and fit
  - In remission for > 1 year after first transplant

- Recent non-comparative trials have demonstrated that DLI following azacitidine is feasible and may result in disease control in relapsed AML or MDS. Toxicity appears to be minimal. For patients without a history of grade 3-4 acute or moderate to severe chronic GVHD, this is our preferred strategy for highly motivated patients and is described in detail in the body of these guidelines and in the referenced publications.

- 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 four 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
  - 5 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. Patients with chemosensitive disease may be considered for repeat transplants, but it remains unclear whether this represents optimal care. This review attempts to outline areas in which a second transplant should be considered for individual patients who relapse.
Acute Leukemia
The natural history of acute leukemia that has relapsed following allogeneic bone marrow transplantation has been described in two reports. A report by Mortimer et al. described the outcome of 95 patients treated at a single center. Fewer than half of these patients received intensive chemotherapy for the purpose of reinduction of remission, and this was successful in only 15/44 patients treated. Two patients who entered remission survived for longer than 18 months. A larger report by the EBMT describes the outcome of 117 patients with acute leukemia who relapsed following allogeneic transplant. Only 32/77 patients treated with chemotherapy entered a complete remission. Patients who entered remission experienced median survival of 1 year, while those who failed reinduction survived a median of only 4.5 months. Second transplants had a negligible impact on overall survival in this cohort, as 8/9 second transplant recipients died of complications.

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.

More recently, novel therapies have been identified with activity in relapsed/refractory acute leukemia. Clofarabine, a second-generation nucleoside analogue, has shown activity in this setting. The combination of clofarabine and high-dose cytarabine shows overall response rate of 47% vs. 23% (p<0.0001) for high-dose cytarabine alone. Included in this response rate are complete responses of 12% vs. 5% (p=0.0005). While event-free survival appeared superior with the combination of clofarabine and cytarabine, overall survival was still poor and identical between the two arms of this phase III study. Azacytidine, a DNA demethylating agent with activity in MDS and AML can be safely given after stem cell transplant and survival may be prolonged in a subset of patients with “indolent” progression of AML when azacytidine is used in combination with DLI. The multikinase inhibitor sorafenib or FLT3 inhibitors such as midostaurin show activity in certain cases of relapsed AML.

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 EFS between 14-31%. While second transplants may be of benefit to some patients who relapse, it is clear that they are only offered to a minority. For instance, 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. This report clearly demonstrates that the outcome of a second transplant depends strongly on disease status at the time of second transplant, the duration of remission after the initial transplant and the age of the patient. While several reports have described the negative effect of rapid relapse after allogeneic transplant, none has been able to clearly define a true cutpoint that separates good from poor outcomes. 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.** Second Transplants for AML

![Graph showing survival outcomes for eligible and ineligible patients](image)

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.

Most reports describing the outcome of second allogeneic transplants have identified an effect of age on TRM and overall survival. None of these studies was designed to define a cut-point, and the ideal age cutoff remains unclear. The majority of these studies, however, report better outcomes for patients younger than 16 – 34. When examined in multivariate models, age usually remained a significant predictor of increased TRM and often of overall survival. Results from our program support the idea that age influences the outcome of second allogeneic transplant, with survivors of second transplants being significantly younger than those who do not survive (25.4 years vs. 40.4 years, p=0.017). In our program only 3/27 patients receiving more than one allogeneic transplant for AML experienced prolonged survival. These patients were aged 19.9, 23.8 and 31.6 years at the time of their second transplant. Within our program it would be reasonable to limit second transplants to patients below the age of 40.

Other unresolved areas include the use of reduced-intensity conditioning for patients undergoing repeat transplants. While such conditioning may result in lower conditioning-related mortality, late effects due to GVHD and infection are largely unchanged and relapse rates are higher. RIC transplants for patients with prior relapse are associated with relapse rates of between 45-70%.

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. 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 describe 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)).\textsuperscript{16} Patients received azacitidine in a five-day 100 mg/m\textsuperscript{2} or seven-day 75 mg/m\textsuperscript{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.\textsuperscript{17} These patients received azacitidine 100 mg/m\textsuperscript{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.

We will use the following schedule:

- Week 1: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 5: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 6: DLI #1 (1 x 10\textsuperscript{e6} T cells/kg)
- Week 9: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 13: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 14: DLI #2 (1 x 10\textsuperscript{e7} T cells/kg)
- Week 17: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 21: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 22: DLI #3 (5 x 10\textsuperscript{e7} T cells/kg)
- Week 25: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 29: Azaciticine 100 mg/m\textsuperscript{2}/d x 5
- Week 30: DLI #4 (1 x 10\textsuperscript{e8} T cells/kg)
Indolent Diseases: Chronic Myelogenous Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL)

In the case of 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.\(^{18}\)

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 idelalisib) 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.\(^{19}\) 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.\(^{20,21}\) 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.\(^{22}\) 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

<table>
<thead>
<tr>
<th></th>
<th>Molecular or Cytogenetic Relapse</th>
<th>Chronic Phase</th>
<th>Accelerated Phase</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Rhee</td>
<td>11/11</td>
<td>8/14</td>
<td>1/5</td>
<td>20/30 (66%)</td>
</tr>
<tr>
<td>Collins</td>
<td>3/3</td>
<td>25/34</td>
<td>5/18</td>
<td>33/42 (78%)</td>
</tr>
<tr>
<td>Drobyski</td>
<td>_</td>
<td>_</td>
<td>6/8</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>Porter</td>
<td>_</td>
<td>6/8</td>
<td>0/3</td>
<td>6/11 (54%)</td>
</tr>
<tr>
<td>Kolb</td>
<td>14/17</td>
<td>39/53</td>
<td>1/14</td>
<td>54/84 (64%)</td>
</tr>
<tr>
<td>MacKinnon</td>
<td>8/8</td>
<td>9/10</td>
<td>2/4</td>
<td>19/22 (86%)</td>
</tr>
<tr>
<td>Bacigalupo</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>10/18 (55%)</td>
</tr>
<tr>
<td>Alyea</td>
<td>_</td>
<td>15/19</td>
<td>0/5</td>
<td>15/24 (62%)</td>
</tr>
<tr>
<td>Verdonck</td>
<td>_</td>
<td>9/9</td>
<td>4/5</td>
<td>13/14 (93%)</td>
</tr>
<tr>
<td>Sehn</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>19/23 (82%)</td>
</tr>
</tbody>
</table>

*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


3. Faderl S., W.M., Rizzieri D., Schiller J. et al., Clorafabine plus cytarabine compared to cytarabine alone in older patients with relapsed or refractory (R/R) acute myelogenous leukemia (AML): Results from the phase III CLASSIC 1 trial. Journal of Clinical Oncology, 2011. 29(Suppl): Abstract 6503.


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 2 g IV every 8 hours, OR meropenem 500 mg IV every 6 hours.
  - Gentamicin 7 mg/kg (AIBW for obese) IV q24-36h, OR ciprofloxacin 750 mg po twice daily or 400 mg IV twice daily can be added, if beta lactam resistance is suspected, or for probable gastrointestinal (GI) source.
  - Above doses assume normal renal function.
- Additional empiric therapy for unstable patients:
  - Vancomycin 1 gram (or 25mg/kg) IV loading dose.
  - IV fluids, oxygen, early ICU support.
- If blood cultures negative, continue antibacterials until absolute neutrophil count (ANC) ≥0.5/nl for 2 consecutive days.
- If blood cultures positive, adjust coverage based on organism and sensitivity.
- 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 $\geq 38.5°C$ (or oral $> 38.3$), or a core temperature of $\geq 38.3°C$ (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.

Empiric Therapy

Both ASCO (American Society of Clinical Oncology) and Surviving Sepsis campaigns recommend TTA (time to antibiotic) of < 60 minutes. Mortality rates of 5-20% have been noted directly related to comorbidities and complications.

Stable Patients
1. Piperacillin/tazobactam at 4.5 grams every 6 hours is started and continues until ANC ≥ 500 cells/mm³ for 2 consecutive days despite negative blood culture. Acceptable alternatives include ceftazidime and meropenem.
2. Gentamicin at 7 mg /kg/day (AIBW) given every 24-36 hours or Ciprofloxacin (750mg po bid/400mg IV q12) may be initiated if antimicrobial resistance is suspected or GI source.
3. Ceftazidime 2 grams q8h is given to patients who may have allergy to penicillin, recognizing that 5% of patients may still cross react.
4. 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
   - Levofloxacin 500 mg IV daily (gram-negative coverage) + tobramycin 6mg/kg/day, 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 CO₂ < 32 mmHg,
- an alteration in the total leukocyte count to > 12 × 10⁹/L or < 4 × 10⁹/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.
Vancomycin is added empirically for SIRS, hospital acquired pneumonia (HAP), gram-positive bacteremia, endocarditis, meningitis and 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. Trough levels should be considered if plasma creatinine >40 mmo/L above baseline, BMI>40, age>60, duration>7d, or target 15-20 for HAP/MRSA (methicillin-resistant Staphylococcus aureus) and 10-20 for empiric therapy. First trough should be taken at steady state (pre 4th or 5th dose) and repeated after adjustment in new steady state, every 7-10d or if concurrent nephrotoxic drugs.

Vancomycin may be added 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 treatment with vancomycin (trough target 10-20) was added empirically at the outset of therapy, 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 on the basis of *in vitro* sensitivity testing.
Table 1. Reassessment criteria for patients

<table>
<thead>
<tr>
<th>Persistent fever after 3 to 5 days of treatment:</th>
<th>Afebrile after initial antimicrobial treatment with no etiology identified:</th>
<th>Positive blood cultures/focus:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Repeat blood cultures and other investigations as indicated above.</td>
<td>1. High risk patients should continue antibiotics until ANC greater than 500 cells/mm³ for 2 consecutive days.</td>
<td>1. Treat according to sensitivities if available.</td>
</tr>
<tr>
<td>2. Imaging of the chest (CT non/enhanced), abdomen/pelvis (CT enhanced/ultrasound) on day 5.</td>
<td>2. Antimicrobials are stopped for ATG (antithymocyte globulin) related fevers if afebrile and blood culture is negative after 48 hours.</td>
<td>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.</td>
</tr>
<tr>
<td>3. Empirical antifungal treatment as indicated (see chapter on Fungal prophylaxis).</td>
<td>3. Low risk patients may step down to outpatient treatment (Cipro+ Clavulin)</td>
<td>3. For documented infection with positive culture, the duration of antimicrobial therapy depends on the type, site and source of infection.</td>
</tr>
<tr>
<td>4. Add vancomycin for 48hrs if criteria are met, e.g. skin and soft tissue infection, catheter related infection, pneumonia or hemodynamic instability.</td>
<td>4. 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.</td>
<td>4. Consider central line source if &gt; 2hr difference in TTP (time to positivity).</td>
</tr>
<tr>
<td></td>
<td>5. Investigate focus appropriately and treat according to common pathogens.</td>
<td>5. Investigate focus appropriately and treat according to common pathogens.</td>
</tr>
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</table>
References


Central Venous Catheter (CVC)-Related Complications
Presented by: Ahsan Chaudhry

Summary

Line Type Preferences

Autologous Transplant Recipients:
• The recommended catheter for patients undergoing apheresis is the COOK 12.5Fr triple-lumen silicone tunneled catheter (Product Code: G13490 – lumen diameter: red 2.5x1.2mm, blue 2.5x1.2mm, white 0.5mm), and is to remain in place until after autologous transplant.
• If apheresis is not necessary, a flexible triple-lumen catheter as recommended for allogeneic transplant is acceptable.

Allogeneic Transplant Recipients:
• The recommended catheter used for allogeneic transplantation is the Bard 12.5Fr triple-lumen Hickman silicone tunneled catheter (Product Code: #0600650 – lumen diameter red 1.5mm, blue 1.0mm, white 1.0mm).
• Non-rigid 12.5F catheters are preferred for patient comfort.

Healthy Donors:
• Peripheral venous access is preferred for collection from healthy donors. Two large-bore antecubital lines will be inserted just prior to apheresis.
• If large bore antecubital lines cannot be inserted a double-lumen Quinton Mahurkars (8 or 12 French diameter, length 15 cm) will be inserted under image guidance and removed prior to the patient leaving the apheresis unit.

Prevention of CVC 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 CVCs.
• Rigorous attention to hand hygiene and aseptic technique is essential before inserting, removing, or manipulating the CVC.
• Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before CVC insertion and during dressing changes.
• Use sterile gauze or sterile, transparent, semi permeable dressing on CVC insertion site. For tunneled CVCs, dressings may be removed as per unit policy and procedure.
• Promptly remove CVC lines that are no longer being used.
• Insert CVC on right side. Avoid femoral vein.
• Remove CVC if not used or used infrequently.
Treatment of CVC Infections

Empiric Treatment:
• Collect bacterial cultures from CVC entrance/exit site and blood (central and peripheral) prior to initiating treatment.
• Vancomycin to cover *Staphylococcus aureus*, coagulase negative *Staphylococcus* and *Enterococcus sp.* (MRSA circulates periodically on our BMT unit).
• In neutropenic, markedly immunocompromised or severely ill patients, cover also Gram-negative bacilli including *Pseudomonas* (Tazocin, ceftazidime or meropenem).

Treatment of Proven or Complicated Infection:
• Treat according to IDSA guidelines as described in main text below.

Treatment of Line Occlusion (Thrombotic or Mechanical)
• Occluded CVCs 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 an x-ray and/or dye study will be carried out.

Treatment of Line Related Venous Thrombosis
• There is insufficient evidence to recommend routine removal of clinically-necessary, functioning and non-infected CVC’s in the setting of catheter-related thrombosis. If anticoagulation is not feasible then line removal is indicated.
• Anticoagulation should be continued at least for the duration of line placement if removal is not feasible.
• Anticoagulation duration is controversial and CVC catheter-related thrombosis should be treated as per established guidelines for DVT.
• Catheter-related thrombosis should be treated as a provoked thrombosis and treated with anticoagulation for 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 with low molecular weight heparin until complete remission has been achieved.
• Tinzaparin 175 IU/kg once daily 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. Caution should also be used with direct oral anticoagulants (DOAC) due to drug interactions.
Background

Multiple 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 Recipients:**
- For autologous transplantation, a rigid line is needed for apheresis/stem cell collection. The current recommended catheter used prior to apheresis is the Cook 12.5Fr triple lumen silicone tunneled catheter (Product Code: G13490 – lumen diameter: red 2.5x1.2mm, blue 2.5x1.2mm, white 0.5mm), and is to remain in place until after autologous transplant.
- High dose heparin (5,000u/ml) is instilled in all lumens of the CVC for the 4 days prior to apheresis, if platelets are >50. High dose heparin shall be aspirated before line use.
- If a patient has had a previously installed portacath, it need not be removed prior to transplant but a triple lumen catheter will also be placed.
- If apheresis is not necessary a flexible double or triple (preferred) lumen catheter is acceptable for transplant (same as for allogeneic transplantation).
- If a peripherally inserted central catheter (PICC) line will be used for transplant instead of a tunneled central line a Bard Groshong silicone PICC line should be used instead of a Power PICC Solo polyurethane catheter. ABMTP (Alberta Bone Marrow Transplant Program) has experience infusing dimethyl sulfoxide through a silicone line but not a polyurethane line.

**Allogeneic Transplant Recipients:**
- In allogeneic transplantation, a large bore, triple lumen catheter is required for transfusions and medication administration.
- The current recommended catheter used for allogeneic transplantation is the Bard 12.5Fr Triple Lumen Hickman silicone tunneled catheter (Product Code: #0600650 – lumen diameter red 1.5mm, blue 1.0mm, white 1.0mm).
- Non-rigid 12.5F catheters are preferred for patient comfort (i.e. Raff, Bard)
- If a PICC line needs to be inserted pre transplant or while a patient is on IVPB cyclosporine a Bard Groshong silicone line should be used instead of a Power PICC Solo polyurethane catheter. ABMTP has experience infusing DMSO, busulfan, cyclosporine through a silicone line but not a polyurethane line.

**Healthy 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 Quinton Mahurkars (8 or 12 French diameter), length 15 cm, is inserted the day of collection to facilitate apheresis and then removed the same day post apheresis.
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, reversal of anticoagulation (i.e. heparin from line, PT and PTT must be checked), clotting factors if necessary, tranexamic acid, gelfoam.
- 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 CVC – 1.6/1000
- PICC – 2.1/1000
- Temporary non cuffed CVC – 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 defences 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* (31%)**
- **Gram negative organisms (21%)**
  - Increasing third generation cephalosporin resistance in *E.coli* and *Klebsiella*, increasing imipenem and ceftazidime resistance among *Pseudomonas aeruginosa*
- ***Staphylococcus aureus* (20%)**
  - Increasing MRSA frequency
- ***Enterococci* (9%)**
  - Increasing VRE frequency at FMC (Foothills Medical Center)
- ***Candida species* (9%)**
  - Increasing fluconazole resistance

**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 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
- If the infection occurred within 48 hours after insertion initiate “FMC DI/IP&C/BMT/Hematology Cluster Investigation Form for CVC Insertion Related Infections”.

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BMT Standard Practice Manual
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www.ahs.ca/guru
Prevention of CVC Infections (Adapted from IDSA Guidelines)²

- Rigorous attention to hand hygiene and aseptic technique is essential before inserting, removing, or manipulating the CVC.
- Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before CVC 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 CVC if intraluminal catheter thrombosis cannot be corrected
- Promptly remove CVC lines that are no longer being used, non-functional or bulging.

Treatment of CVC 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.

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 CVC infections. Based largely on published guidelines, the following empiric therapy is suggested⁷:

- 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 CRBSI (catheter-related bloodstream infection)
  - Covers *Staph. aureus*, coagulase negative *Staph.* and *Enterococci*
Gram negative bacilli coverage (including *Pseudomonas*) in neutropenic/markedly immunocompromised or severely ill patients
  - Third or fourth generation antipseudomonal penicillin (i.e., cefipime, ceftazidime)
  - Alternatives could include meropenem or tazocin

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:

- 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 (CVC) or a port (P)-related bloodstream infection.
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 CVC 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).  

Two weeks of antibiotic lock therapy can be considered in CVC 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.

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).  
- Non-tunneled catheters should be removed.
- Tunneled catheters should be removed if possible, 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 CVC should be removed.  
- 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 CVC-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**

**Thrombotic occlusions:**
- Occluded CVCs 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 1.8mL sterile water by a certified RN. As much as possible up to 2mg is instilled into the blocked CVC 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 CVCs 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. A small series in bone marrow transplant patients showed an incidence as high as 50% although the majority were asymptomatic. Risk factors include malplacement of the catheter, >1 insertion attempt, a previous CVC, 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 CVC-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). 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.

Treatment of CVC-related Thrombosis and Deep Venous Thrombosis
- There is insufficient evidence to recommend routine removal of clinically-necessary, functional and non-infected central lines in the setting of catheter-related 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.
  o Catheter-related thrombosis should be treated as a provoked thrombosis and treated with anticoagulation for a total of 3 months.
  o 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 with low molecular weight heparin until complete remission has been achieved.
- Tinzaparin 175 IU/kg once daily 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.

**Catheter Care**

Patients should be educated about their own catheter care in preparation for outpatient therapy. Written instructions for catheter care should be given to patients prior to discharge as per nursing policy and procedures.

**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 line removed if they are eating/drinking well and not requiring transfusions or IV medications. A new line should be inserted if it is again 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.
References


Additional Resources

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)

- 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.
- VOD/SOS should be suspected in the patient with weight gain, hyperbilirubinemia and 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 rental perfusion and elimination of hepatotoxic medications. Defibrotide 25 mg/kg/day should be considered for patients with severe VOD/SOS or in the presence of organ dysfunction.
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. 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. 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. 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. 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. 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.
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.

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. 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. 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.
Table 1. Hepatitis B Serology and BMT (adapted from Strasser et al.)

<table>
<thead>
<tr>
<th>Patient Result</th>
<th>Donor Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HBs</td>
<td>Anti-HBs</td>
<td>Exposed or vaccinated.</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Anti-HBc</td>
<td>Exposed. Risk of reactivation present if anti-HBs negative.</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>HBsAg positive</td>
<td>Active infection: Liver biopsy and start treatment if HBV DNA +</td>
</tr>
<tr>
<td>HBc</td>
<td>Exposed. Negligible risk of transmission if HBV DNA negative.</td>
<td></td>
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</table>

Transient Elastograpy (i.e. FibroScan™)

Transient elastography is a non-invasive test of liver stiffness which uses a vibrating ultrasound probe to transmit a sheer wave into the liver. The rate at which the vibrating pulse returns to the probe from the liver is directly proportional to the stiffness of the liver; stiffness in this context correlates to the degree of fibrosis. A liver stiffness of less than 11 kPa makes cirrhosis unlikely. Transient elastography is of limited utility in morbidly obese patients and patients with ascites. Liver biopsy may still be required to clarify the degree of fibrosis.

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. 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.

In BMT, lamivudine has been reportedly used in three Japanese autologous peripheral blood stem cell transplant recipients. 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.15,16

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.17 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.18 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.19 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.20 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\textsuperscript{21}.

**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 55\% for myeloablative transplants. The table below describes the patient, disease, and transplant factors associated with SOS.

**Table 2.** Patient, disease, and transplant factors associated with SOS

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Disease Factors</th>
<th>Transplant Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior liver disease</td>
<td>Advanced disease</td>
<td>Ablative conditioning</td>
</tr>
<tr>
<td>Age &gt; 20 years</td>
<td>Prior SCT</td>
<td>Busulfan-based</td>
</tr>
<tr>
<td>Prior fungal infection</td>
<td>Malignant disease</td>
<td>High Busulfan AUC</td>
</tr>
<tr>
<td>Hepatitis C infection</td>
<td>Abdominal radiation</td>
<td>Unrelated or mismatched donor</td>
</tr>
<tr>
<td>Iron overload</td>
<td>Gemtuzumab or inotuzumab ozogamicin</td>
<td>Sirolimus GVHD prophylaxis</td>
</tr>
<tr>
<td>HFE C282Y genotype</td>
<td>Prior chemotherapy</td>
<td>Norethistrone use</td>
</tr>
</tbody>
</table>

Diagnosis of SOS can occur using either the Seattle Criteria or the Baltimore Criteria, outlined in the table below.\textsuperscript{20,21} 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.

**Table 3. Comparison of Seattle and Baltimore Diagnostic Criteria for SOS**

<table>
<thead>
<tr>
<th>Seattle Criteria\textsuperscript{20}</th>
<th>Baltimore Criteria\textsuperscript{21}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of 2 of the following within 20 days of transplant:</td>
<td>Hyperbilirubinemia (&gt; 34 micromolar) within 21 days of transplant and 2 of the following:</td>
</tr>
<tr>
<td>• Hyperbilirubinemia (&gt; 34 micromolar)</td>
<td>• Ascites</td>
</tr>
<tr>
<td>• Tender hepatomegaly</td>
<td>• Hepatomegaly (may be painful)</td>
</tr>
<tr>
<td>• Weight gain (&gt; 2%)</td>
<td>• Weight gain (&gt; 5%)</td>
</tr>
</tbody>
</table>

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). 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. 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.

**Treatment of SOS**

Results of a randomized controlled trial of ursodiol for SOS prophylaxis were reported by Essell et al. 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 =0.03). 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. 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. 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.

Defibrotide is a single-stranded polydeoxyribonucleotide that has anti-inflammatory and antithrombotic properties, and has been suggested for use in cases of severe SOS. Richardson et al. reported on the use of defibrotide in 88 patients who developed severe SOS and multisystem organ failure after stem cell transplantation. 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. 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)30. Similarly, a systematic review of 17 defibrotide studies in the treatment of VOD/SOS demonstrated that among those treated with 15 mg/kg/day dosing the Day+100 survival rate was 56%, higher in patients without MOD at 71% vs. 44% with MOD (Richardson et al. BMT 2019 Feb 25 [EPub ahead of print])31

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)32. 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 osteopetrosis33. The HARMONY clinical trial (NCT02851407) to compare efficacy and safety of defibrotide versus best supportive care in the prevention of VOD/SOS in pediatric and adult patients is continuing to recruit patients. 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.

Management of SOS

• Careful management of fluid balance to limit third-space fluid and maintain renal perfusion.
• Limit hepatotoxic medications.
• Transjugular intrahepatic portosystemic shunt (TIPS) may improve fluid balance. Hyperbilirubinemia responds poorly, and survival is not improved.
• Thrombolytic therapy has been given with limited success and a high rate of fatal bleeding.

Summary of Recommendations for Treatment of SOS

• The diagnosis of SOS should be made based on established criteria with support of ultrasound or liver biopsy if possible
• Ursodeoxycholic acid prophylaxis should be given for the first 80 days after transplant
• Standard management of SOS includes supportive care, careful attention to fluid balance and renal perfusion, and elimination of unnecessary hepatotoxic medications
The use of defibrotide should be considered in patients with severe SOS or SOS with dysfunction of extrahepatic organs.
References


Reproductive System Complications Post-Transplant
Presented by: Michelle Geddes

Summary

- All patients should be advised prior to transplantation of a high rate of infertility post transplantation, especially if age >30 or TBI
- Prior to transplant, specialist referral should be made as early as possible to discuss fertility options if desired.
- Men should be counseled and offered sperm banking if further fertility desired.
- Patient fertility status (FSH, E2, anti-mullerian hormone) should be assessed at repeat time intervals post transplant if fertility desired, or to assess uncertain menopausal status in conjunction with menstrual history (lack of menses >1 year suggestive of postmenopausal state)
- Suppression of menstruation in menstruating women on chemotherapy, if needed, can be done with estrogen replacement or in patients with intolerance to estrogens use of GnRH analogues can be used.

- All patients should be educated regarding estrogen deficiency syndromes and genital tract GVHD prior to transplant. Baseline assessment by a gynecologist pretransplant should be carried out for female patients who are premenopausal, require consultation re: fertility preservation, and who have had a hysterectomy but ovarian function remains intact. Patients who are postmenopausal and have had a hysterectomy and bilateral oophorectomy do not need a pre transplant gynecologic assessment.
- All female patients should receive assessment by a gynecologist 6 months after transplantation and then ongoing assessment by gynecology or a family physician as appropriate. Routine follow-up care for these patients should include review of hormone therapy, sexual function and vaginal self-surveillance, and Pap smears with cytology as per age-appropriate guidelines for cancer screening.

- Flushing may respond to hormone replacement therapy or agents such as SSRIs.
- Systemic hormone replacement should be discussed with women experiencing premature menopause to reduce osteoporosis risk until the normal age of menopause.
- Women with genital tract lesions suspicious for vaginal graft-versus-host disease should be swabbed for herpes simplex virus and evaluated by a gynecologist with experience in care of patients with graft-versus-host disease.
- Topical therapies including steroids and calcineurin inhibitors, and sometimes systemic therapies are effective treatments for vaginal graft-versus-host disease and should be used in conjunction with a skilled gynecologist. Vaginal dilatation or surgery may be recommended for women with vaginal narrowing.

- Sexual dysfunction should initially be addressed by reviewing medications for contributing factors and assessing gonadal function.
Low libido in men and male erectile dysfunction may respond to testosterone replacement therapy. Men with ED may also respond to sildenafil or related drugs.

Topical estrogens i.e. Vagifem are recommended in the absence of contraindications to prevent tissue atrophy. Water soluble vaginal lubricants may be helpful to relieve vaginal dryness and dyspareunia (Replens, Nae or vitamin E oil from a punctured vitamin E capsule can be useful) at least twice weekly.

Referral to sexual function clinic is appropriate for patients experiencing difficulty with sexuality or sexual function post transplant, and referral for sexual or relationship counseling may help improve sexual function and satisfaction.

**Infertility**

**Female Infertility**

In women, chemotherapy has a greater effect on follicle development than on the resting oocytes. Some women may have recurrence of menopause and ovulation months or years post chemotherapy or possibly post transplantation. The degree of impact is dependent on patient age; women given daily cyclophosphamamide at an average dose of 100 mg/day have been shown to reach amenorrhea at a mean of 9.5g for patients under 40 years and 5.3g if older than 40 years.\(^1\)

Radiation is more toxic to oocytes and can sometimes cause transient amenorrhea in young women which resolves after recruitment and development of a new cohort of primary follicles. A single high dose of radiation causes ovarian failure in all women (>6 Gy in all women > 40 years). The predicted radiation to cause immediate and permanent infertility in 97.5% of patients decreases with age: 20.3 Gy at birth, 18.4 Gy at age 10 years, 16.5 Gy at age 20 years, and 14.3 Gy at age 30 years.\(^2\) In addition, pelvic radiation is known to alter uterine vasculature and blood flow, with restricted uterine growth in young girls (mean age 12.5 years) undergoing HCT with cyclophosphamamide and total body irradiation (TBI) at a dose of 8.5 to 11.7 Gy.\(^3\) There is an associated increased risk of miscarriage, mid-trimester pregnancy loss, preterm birth, and low birth weight post-HCT with high dose TBI.

The rate of infertility with FLUBUP and TBI is unclear; pregnancies have occurred following this regimen. In a retrospective review of 619 women and partners of men treated in the BMT registry with auto- (n=241) or allo-HCT (n=378) and transplanted at age 21-45 years (median 33.3 years), Carter et al. reported 54 pregnancies in 34 patients (26 males, 40 pregnancies; 8 females, 14 pregnancies) and 46 live births.\(^4\) Factors associated with no conception included age >30 years at HCT (OR=4.8), female sex (OR=3.0), and TBI (OR=3.3). Survivors were not more likely than siblings to report miscarriage or stillbirth (OR=0.7).

Options for preventing infertility after HCT in females include:

1. Ovulation induction, oocyte retrieval, IVF followed by cryopreservation of embryos
   - proven to be successful, but requires a partner or sperm donor
   - may take several weeks to develop and retrieve oocytes
2. Unfertilized oocyte cryopreservation
   - Does not require a partner or donor sperm
   - Timeframe of weeks required for oocyte stimulation

3. Ovarian tissue cryopreservation
   - Ovarian tissue is obtained and later re-implanted, can be combined with ovarian stimulation after tissue removal
   - Delay to stimulate the ovary, less commonly used or reliable than oocyte storage.
   - Unknown risk of contamination of tissue by malignant cells (i.e., leukemia cells) therefore guidelines do not recommend use in leukemia patients (case report of Hodgkins cells in preserved ovarian tissue)

4. GnRH analogues
   - For patients receiving standard chemotherapy, administration of GnRH analogues may be useful to preserve fertility. Three meta-analyses in have supported use; Use of GnRHa during chemotherapy associated with fertility preservation in 93% on cyclophosphamide for autoimmune disease or combination chemotherapy for hematologic malignancy maintained ovarian function compared to 48% of those not on GnRHa therapy (RR=1.68, 95% CI 1.34-2.1) with 22% achieving pregnancy compared to 14% (CI 1.03-2.6, RR=1.65). This may be useful to preserve fertility with chemotherapy prior to transplantation or for non-myeloablative transplants such as for aplastic anemia but is not well studied in this population.
   - Initial gonadotropin release followed by hypogonadism therefore need to start GnRHa therapy at least 1 week before starting chemotherapy, continue at least 1-2 weeks after last chemotherapy cycle.

Male Infertility
Radiation damage to gonads and disruption of endocrine production results in increased LH and FSH levels with azoospermia, testicular atrophy and infertility in many patients post-HCT. In pediatric patients who undergo TBI, gonadal shielding has been shown to preserve testosterone production, but fertility rates are still low in these patients.

Leydig cells are relatively resistant to chemotherapy or radiotherapy, and testosterone usually remains in the normal range with some decrease in total and free testosterone, especially in males over age 45. Again, azoospermia and infertility is dependent on age at transplant, radiation and chemotherapy doses, and type of chemotherapy especially alkylators.

Sperm cryopreservation is a simple and low risk procedure for males prior to HCT. Schmidt et al. reported the results of a retrospective series involving 67 couples in which the male patient had received chemotherapy for lymphoma or germ cell tumours (8 with BMT). 151 cycles of in vitro fertilization with fresh or cryopreserved (58%) sperm were performed, and per cycle pregnancy rates
were: 14.8% after intrauterine insemination, 38.6% after intracytoplasmic sperm injection (ICSI), and 25% after ICSI-frozen embryo replacement. Live births were achieved in 11.1, 30.5 and 21% of the cases, respectively.

In general, most studies show an approximate 40% success rate per cycle. Intracytoplasmic sperm injection is an option for men with low sperm quality. Epididymal sperm aspiration or testicular sperm extraction are also options.

**Recommendations**

- All patients should be advised of a high rate of infertility post transplantation, especially if they are over the age of 30 or have received TBI.
- Prior to transplant, specialist referral should be made as early as possible for women to discuss fertility options if desired. While this is costly, some funding options available for select cancer patients may be pursued.
- Men should be counseled and offered sperm banking if further fertility is desired, ideally with several donations 2-3 days apart if time permits.
- Patients’ fertility status should be assessed at repeat time intervals post transplant if fertility is desired.
- Suppression of menstruation in menstruating women while cytopenic is routinely done with hormone replacement and in patients with intolerance to estrogens use of GnRH analogues is preferred.

**Premature Menopause Symptoms**

Following HCT, menopause is rapid rather than gradual as in natural menopause. Symptoms include hot flashes, night sweats, insomnia, mood swings, irritability, depression, vaginal dryness, vaginal atrophy and fibrosis, pruritis, and urogenital symptoms. In a series of 15 women already menopausal pre transplant, 53% experienced hot flashes, 40% poor libido, and 53% painful intercourse. Post-HCT, commonly prescribed doses of hormone replacement therapy (HRT) have been associated with low estradiol levels and often ongoing symptoms; therefore the optimal hormone dose is unclear. Syrjala et al. reported that at 3 years posttransplant, although 76% of women were taking HRT, 52% still reported problems with lubrication and arousal, 33% reported dyspareunia, and 46% had difficulties with orgasm.

**Recommendations - Pretransplant**

- All patients should be educated regarding estrogen deficiency syndromes and genital tract GVHD prior to transplant.
- Referral to gynecologist for assessment and education pretransplant.
Recommendations – Three Months Posttransplant

- Encourage self-surveillance
- Systemic or topical estrogens can be used
  - 0.1% estriol vaginal cream or vagifem should be used in all patients without a contraindication (i.e. history of hormone receptor positive breast cancer) for prophylaxis
- A decision regarding systemic hormones until the age of natural menopause should be discussed with the gynecologist or family physician due to 50-60% rate of bone loss post due to hormone deficiencies, chronic steroids and other mechanisms.\textsuperscript{18}

Recommendations – Subsequent Care

- Regular gynecologic follow-up at a frequency determined by gynecology service. In patients without ongoing issues surveillance may be most appropriate through their family physician.
- Review of hormone therapy, sexual function and vaginal self-surveillance.
- Annual Pap smears with cytology.
- Consider androgen replacement if indicated.

Vaginal Graft Host Disease

Symptoms of vaginal graft versus host disease (GVHD) include vaginal dryness, pain, discomfort, and vaginal scarring with strictures and dyspareunia. Often the vaginal mucosa is excoriated, ulcerated and thickened with a narrowed or obliterated introitus from scar tissue. Synechiae most commonly obliterate the upper vaginal canal or are circumferential around the introitus. Milder cases have open, flat sores, erythematous and excoriated mucosa which is tender and friable. These changes do not improve with estrogen therapy.

In one series of 11 patients, Spiryda \textit{et al.} reported that symptoms developed at a mean of 10 months posttransplant, when all but one patient was receiving systemic steroids.\textsuperscript{13} Excoriated mucosa and moderately thickened mucosa successfully treated with topical cyclosporine with response taking 2 weeks, while synechiae and obliteration of the vaginal canal required surgical lysis and postoperative topical cyclosporine with dilators in 7 of the 11 patients. These patients found intercourse possible in 6-12 weeks. However, 2 of the 11 developed persistent high grade squamous intraepithelial lesions.\textsuperscript{13}

Zantomio \textit{et al.} reported the results of a series of 61 patients with a median follow up of 24 months (range 6-60 months).\textsuperscript{14} 29 of these patients developed GVHD (36% at 1 year, 49% at 2 years), and 90% had chronic GVHD of other organs.\textsuperscript{14} Stem cell source was the only variable that was found to be a risk factor for genital tract GVHD; peripheral blood progenitor cells (PBPCs) were associated with a higher risk than bone marrow-harvested cells (HR=3.07, \textit{p}=.017). One third of the cases of GVHD were mild, one third were moderate, and one third were rated as severe. All were treated with topical estrogens and all but 2 with systemic hormones; 7 patients required additional topical cyclosporine and dilators were used in 9 patients. No patient required surgery and 15 of 28 had
complete resolution of their vaginal GVHD, with a median time to CR of 12 months and median treatment time of 15 months. Twenty-two of 28 were able to resume sexual activity, while six reported dyspareunia.

**Signs and Symptoms of Vaginal GVHD:**
- Vaginal dryness and dyspareunia: most often occurs in patients with other cutaneous or mucosal manifestations of cGHVD; 50% are grade I at diagnosis, 50% grade II or III
- Lichen planus-like disease – hyperkeratosis, hypergranulosis, acanthosis, saw-tooth rete, interface dermatitis, dyskeratotic keratinocytes, periadnexal inflammation
- Vaginal sclerosis – epidermal atrophy with edema and homogenization of collagen in superficial dermis
- Erosions

**If Suspicious of Vaginal Graft versus Host Disease**
- Swab for herpes simplex virus
- Check hormone levels (LH, FSH, estrogen) if menopausal status is unclear
- Refer patient to a gynecologist experienced in the care of vaginal GVHD
- Biopsy of the affected site to confirm diagnosis is recommended if there is no response to initial steroids

**Treatment Options for Graft versus Host Disease of the Vagina/Vulva**
- Ensure topical estrogen replacement is adequate and vaginal moisturizers (ie Replens, Mae or vitamin E oil) and water or silicone based lubricants are helpful to maintain comfort and tissue health.
- Topical immunosuppression can be used with the guidance of gynecology:
  - Steroids
    - introital/vulvar lesions: high dose steroid ointment (Ultravate or Celestoderm), betamethasone dipropionate augmented gel (vagina) or ointment (vulva).\(^{17}\)
    - mid-vaginal lesions: betnesol douche (rectal enema preparation) or steroid foam (hydrocortisone acetate 100mg/g mucoadherent rectal foam 1g daily x 4-6 weeks, then taper)
    - high vaginal lesions (associated with dyspareunia, stenosis): steroid ointment applied to vaginal dilator and used 2x/day
  - Calcineurin inhibitors
    - Can be used if steroids alone are ineffective
    - Cyclosporine A:
      - 200 mg oral suspension compounded with evaporation of the alcohol and mixed into 5g anhydrous ointment base
      - Twice daily for 4 weeks, then taper over 2 months
- Alternative regimen is 100 mg/mL solution 1 mL in 20 mL normal saline; high vaginal installation 15 min/day for 4-6 weeks, then taper
  - Topical tacrolimus ointment 0.1% can be used

- Mechanical methods
  - Vaginal Dilators (or intercourse) 2 times/week for prophylaxis, 1-2 times daily dilators for established narrowing
  - Surgery – can be used for stenosis if severe

**Sexuality Posttransplant**

The diagnosis of cancer, malignancy, pretransplant therapy, preparatory regimen, complications and treatment affect feelings of sexuality and the sexual response cycle, which consists of desire, arousal, orgasm and resolution. This can have an impact on relationships and quality of life posttransplant.

In the UK MRC-AML10 trial conducted by Watson *et al.*, 55% of allotransplant and 42% of autotransplant patients reported worsening of their sex life posttransplant, and BMT patients fared worse than chemotherapy patients with decreased interest in sex (48% versus 24%), decreased sexual activity (53% versus 35%), decreased pleasure from sex (36% versus 18%), and decreased ability to have sex (38% versus 18%). In addition, patients with GVHD experienced a higher loss of sexual functioning than patients without GVHD; however, when the patients with GVHD were removed from analysis, the transplant patients still experienced poorer sexual functioning than chemotherapy patients.

Sexual dysfunction is common posttransplantation. In the Syrjala *et al.* study, 102 sexually active allogeneic stem cell transplant survivors were prospectively followed and assessed at 1 and 3 years posttransplant; while they reported equal sexual satisfaction pretransplant, 80% of women and 29% of men reported at least 1 sexual problem posttransplant. Predictors for men included older age, poorer psychological function, unmarried status and lower pretransplant sexual satisfaction. In addition, the group of more dissatisfied women were less likely to have received HRT.

Male sexual dysfunction can result from hormone level abnormalities, peripheral neuropathy from the preparatory regimen, vessel damage from cyclosporine or high doses of radiation, fatigue, and decreased physical stamina. Erectile dysfunction is present in 25 to 38% of cases, arousal problems in 20% of cases, and orgasm difficulties in 6 to 13% of cases.

Female sexual dysfunction can result from amenorrhea, vaginal alterations from chemotherapy or radiotherapy, or GVHD of the vagina or vulva.

**Recommendations – Females**

- Review medications to assess for contributing factors
• HRT can be considered for menopausal symptoms such as hot flashes, vaginal atrophy and lubrication, or changes in the skin or breasts
• Testosterone level testing for patients with low libido
• Antidepressants may be effective in treatment of hot flashes e.g. venlafaxine\textsuperscript{11}
• Topical hormonal therapy is helpful to prevent atrophy and water soluble vaginal lubricants are useful for vaginal dryness and dyspareunia

Referral to sexual function clinic is appropriate for patients experiencing difficulty with sexuality or sexual function post transplant

**Recommendations – Males**

• Review of all medications is indicated to assess for interference in sexual function
• Check total testosterone, sex hormone binding globulin, free androgen index, LH, FSH, and prolactin levels
• Referral to an endocrinologist or urologist for specific testing and therapy
• Testosterone replacement may improve libido and erectile function in men with low testosterone and free androgen index
• Sildenafil and related drugs may improve erectile function
• Referral to sexual function clinic is appropriate for patients experiencing difficulty with sexuality or sexual function post transplant
References

Management of Cytokine Release Syndrome and Neurotoxicity Following Treatment with Immune Effector Cells
Presented by: 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 most common presenting feature of CRS is fever, frequently higher than 40° C. Patients may also complain of myalgia, nausea and malaise. Patients with CRS may also develop fluid-refractory hypotension, cardiomyopathy, liver and/or kidney dysfunction, coagulopathy and features of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).
- A four-grade grading system based on changes in vital signs (temperature, blood pressure and need for supplemental O2 or ventilator support) (ASTCT Consensus Grading) will be used to determine severity of CRS (see below).
- Management of CRS with antipyretics, tocilizumab and/or corticosteroids will be used (see below). Patients in the Intensive Care Unit will be managed concurrently by the ICU team and the Bone Marrow Transplant service. Features of multiorgan dysfunction may persist for days or weeks after resolution of CRS and it is essential to continue support during this time.
- Supportive care is the mainstay of ICANS management. Careful evaluation for possible metabolic, medication-associated and infectious (including neuroimaging and CSF evaluation) causes is essential. The prophylactic administration of anticonvulsant medications should be considered in conjunction with the neurology consult service. The patient who is severely obtunded and unable to protect their airway should be intubated prophylactically.
- Steroids and tocilizumab may be of benefit for patients with ICANS.

Background

The development of chimeric antigen receptor T-cells (CAR T-cells), which began in the 1980’s, has resulted in marketing approval for two commercially-available anti-CD19 products. Furthermore, several CAR T-cell products are in clinical development and are likely to become available through clinical trials at our center. Recent studies have demonstrated that anti-CD19 CAR T-cells can be highly effective in patients with relapsed or refractory CD19+ acute lymphoblastic leukemia, non-hodgkin lymphoma and chronic lymphocytic leukemia (see Table 1). We expect to see the application of this technology broaden to other malignancies and to some non-malignant conditions.

A range of unique toxicities has been observed in patients treated with CAR T-cells. These include on-target, off-tumor effects such as persistent B-cell aplasia in patients treated with CD19 CAR T-
cells. Foreign protein expressed as part of the CAR construct may on rare occasions elicit allergic reactions. 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 2 summarizes the rate of CRS and NT observed in published trials.

Table 1. Clinical outcomes of CAR T-cell therapy in published trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Product</th>
<th>N=</th>
<th>ORR</th>
<th>CR</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHL/CLL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neelapu et al.²</td>
<td>Axicabtagene</td>
<td>110</td>
<td>82%</td>
<td>54%</td>
<td>52%</td>
<td>42%</td>
</tr>
<tr>
<td>Schuster et al.³</td>
<td>Tisagenlecleucel</td>
<td>81</td>
<td>53%</td>
<td>32%</td>
<td>65% (6 mos)</td>
<td>RFS 74% (6 mos)</td>
</tr>
<tr>
<td>Porter et al.⁴</td>
<td>Tisagenlecleucel</td>
<td>14</td>
<td>8/14 (57%)</td>
<td>4/14% (29%)</td>
<td>71% (18 mos)</td>
<td>CR 40+ (21-53) mos</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maude et al.⁵</td>
<td>Tisagenlecleucel</td>
<td>75</td>
<td>NR</td>
<td>81%</td>
<td>76% (12 mos)</td>
<td>50% (12 mos)</td>
</tr>
<tr>
<td>Turtle et al.⁶</td>
<td>Lisocabtagene</td>
<td>30</td>
<td>NR</td>
<td>86% by FC/PCR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Myeloma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noopur et al.⁷</td>
<td>bb2121</td>
<td>18</td>
<td>NR</td>
<td>10/18 (56%)</td>
<td>NR</td>
<td>71% (9 mos)</td>
</tr>
</tbody>
</table>

Table 2. Frequency of CRS and NT observed in published trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Product</th>
<th>N=</th>
<th>CRS</th>
<th>CRS grade 3-4</th>
<th>CRES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHL/CLL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neelapu et al.²</td>
<td>Axicabtagene</td>
<td>110</td>
<td>93%</td>
<td>13%</td>
<td>28%</td>
</tr>
<tr>
<td>Schuster et al.³</td>
<td>Tisagenlecleucel</td>
<td>81</td>
<td>58%</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Porter et al.⁴</td>
<td>Tisagenlecleucel</td>
<td>14</td>
<td>64%</td>
<td>43%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maude et al.⁵</td>
<td>Tisagenlecleucel</td>
<td>75</td>
<td>77%</td>
<td>47% ICU</td>
<td>40%</td>
</tr>
<tr>
<td>Turtle et al.⁶</td>
<td>Lisocabtagene</td>
<td>30</td>
<td>83%</td>
<td>23%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Myeloma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noopur et al.⁷</td>
<td>bb2121</td>
<td>18</td>
<td>63%</td>
<td>4.6%</td>
<td>33%</td>
</tr>
</tbody>
</table>

* Interstudy comparisons of CRS grade are difficult as there is no universally-accepted grading system for this condition.
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, 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 onset of fever is typically within the first 14 days of administration of the modified T-cells, and is notable for its severity. Fevers are often as high as 40.5°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. The degree of elevation of creatinine, liver enzymes and bilirubin are useful in grading CRS (see below). Patients may develop nausea, vomiting, diarrhea and abdominal pain.

Cytopenias are 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. Patients may 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 keep patients in hospital for at least the first 14 days. 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 carried out by every 8 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. An electrocardiogram should be obtained at least once per day and patients should be considered for telemetry if it is available. 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.

Grading Cytokine Release Syndrome

Several CRS grading systems have been used in the clinical management of CAR T-cell recipients. The ideal grading system would be useful across CAR T-cell platforms, use data easily obtained from a clinical laboratory if it incorporates laboratory results and would correlate with the outcome of CRS. Utility of a grading system to guide management would be of further benefit, as very few centers are likely to obtain enough clinical experience in managing CRS outside of guidelines. The ASTCT grading system described by Lee et al.6 (Table 3) 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 3. Cytokine release syndrome grading (per Lee et al.8).

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever*</td>
<td>Yes, ≥ 38°C</td>
<td>Yes, ≥ 38°C</td>
<td>Yes, ≥ 38°C</td>
<td>Yes, ≥ 38°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring high-flow nasal cannula, facemask, non-rebreather mask or</td>
<td>Requiring positive pressure (CPAP, BiPAP, intubation and mechanical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Venturi mask</td>
<td>ventilation)</td>
</tr>
<tr>
<td>Hypoxia**</td>
<td>None</td>
<td>Requiring low-flow nasal</td>
<td>Requiring high-flow nasal cannula, facemask, non-rebreather mask or</td>
<td>Requiring positive pressure (CPAP, BiPAP, intubation and mechanical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cannula or blow-by</td>
<td>Venturi mask</td>
<td>ventilation)</td>
</tr>
</tbody>
</table>

Organ toxicity may be graded according to CTCAE Version 5.0 (2017)


* 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 titres) 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.
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).

5. Patients with comorbid medical conditions experience a more complicated course with CRS and so early initiation of anticytokine therapy is justifiable in this population.

6. In general the use of tocilizumab and steroids have moved earlier in the course of CRS treatment.

**Figure 1.** General approach to management of CRS after CAR T-cell therapy.
The management of CRS is based on expert opinion. There have been no comparative studies and no formal Phase 2 studies have been published. Most clinical trials provide guidance on how to manage CRS for patients on study and those guidelines should take precedence over these in a clinical trial patient. For patients who are not on a clinical trial, our general approach to CRS is shown in Figure 1. After CAR T-cell infusion clinical (temperature, blood pressure and oxygen saturation) and laboratory (serum CRP, ferritin and coagulation parameters) factors are monitored frequently for early identification and treatment of CRS. At onset of fever, hypoxia or hemodynamic change, infection should be ruled out by cultures and imaging and antibiotics should be started if the patient is neutropenic or suspicion of infection is high. First line treatment for patients with grade 1 CRS is supportive care alone except in the case of CRS arising within 72 hours of CAR T infusion or for patients with comorbid conditions, in which case treatment with tocilizumab is indicated. For all other grades of CRS early treatment with tocilizumab may improve outcomes. Failure to improve after an adequate trial of CRS therapy should lead to escalation of therapy in a stepwise fashion (Figure 1). In this case the definition of an adequate trial is left intentionally vague and may be as little as 12 hours and as long as several days depending on response and the clinical status of the patient.

It has been more difficult to define resolution of CRS. Fever resolves quickly with anticytokine therapy whereas hypotension and hypoxia resolve more slowly. We consider CRS to have resolved only when all manifestations of the syndrome that led to its diagnosis have resolved and as such, even in the absence of fever a hypotensive or hypoxic patient should continue to receive treatment for CRS. Typically any CRS patient whose fever, hypotension and hypoxia have resolved will be considered to have resolved CRS and treatment with steroids and anticytokine therapy may be discontinued.

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
  - May repeat q4-6 hours based on response, up to 3 doses in 24 hours
  - May premedicate with Benadryl or Tylenol if not recently given. NO STEROID PREMEDS.
- **Steroids**
  - If no response to tocilizumab (e.g. CRS grade not improved) trial of dexamethasone 10-20 mg IV q6h
  - If life-threatening, and no response to tocilizumab may give up to MP 1 gm IV daily x 3
- **Other monoclonal antibodies**
  - Anakinra (esp. if overlap with HLH/MAS)
  - 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 CAR T-Cell Reversible Encephalopathy Syndrome (CRES)

Neurological abnormalities are relatively common among recipients of CAR T-cells. Early findings 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\textsuperscript{10,11}. 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\textsuperscript{12}. It is important to note that ICANS may exhibit a biphasic pattern, with symptoms appearing and resolving within the first five days 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 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:

- Correctly identifying the year
- Correctly identifying the month
- Correctly naming the city
- Correctly identifying the hospital
- Correctly naming three objects pointed to in the room (one point each)
- Correctly following a simple command (“show me two fingers” or “close your eyes and stick out your tongue”)
- Correctly writing a sentence
- Correctly counting backwards from 100 by 10's

The system is reproducible and prognostic, and has been integrated into a comprehensive ICANS grading system (Table 4). ICANS management according to grade is outlined in Table 5.
## Table 4. Grading Immune Effector Cell-Associated Neurological Syndrome

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score</td>
<td>7-9 (mild)</td>
<td>3-6 (moderate)</td>
<td>0-2 (severe)</td>
<td>Unable to perform</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens to touch</td>
<td>Unarousable or requires vigorous or repeated stimuli to arouse. Stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>NA</td>
<td>NA</td>
<td>Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizure that resolves with intervention</td>
<td>Life-threatening or prolonged seizure (&gt; 5 minutes) or repetitive clinical or electrical seizures without return to baseline between</td>
</tr>
<tr>
<td>Motor Findings</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/Cerebral edema</td>
<td>NA</td>
<td>NA</td>
<td>Focal/local edema on neuroimaging</td>
<td>Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or CN VI palsy; or papilledema or Cushing’s</td>
</tr>
</tbody>
</table>
### Table 5. Management of CAR T-cell Reversible Encephalopathy Syndrome\(^\text{10}\)

| 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, diagnostic LP with measurement of opening pressure, MR spine for focal neurological deficits  
  • Consider tocilizumab 8 mg/kg IV if ICANS occurs in setting of CRS |
| --- | --- |
| 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 q6h if refractory to anti-IL6 therapy or for CRES without concurrent CRS  
  • Consider ICU transfer if associated with grade > 2 CRS  
  • Consider levetiracetam 500 mg bid prophylactically |
| 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 mg IV q6h if refractory to anti-IL6 therapy or for ICANS without concurrent CRS  
  • 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.  
  • 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  
  • Dexamethasone 10 mg IV q6h continued until improvement to grade 1 ICANS then tapered  
  • 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

Transfusions and Management of Cytopenias Early Post-HSCT
Presented by: Jason Tay & Nicole Prokopishyn

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 x 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.
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 1\(^{st}\) 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Timeline</th>
<th>Red Cell Utilization (units)</th>
<th>Platelet Utilization (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Observational Studies</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Xenocostas 2003</td>
<td>Allo</td>
<td>Day 0 to 60</td>
<td>6.8 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>Sohl 2011</td>
<td>Allo</td>
<td>Day 0 to 60</td>
<td>5.2 (95% CI 3.7-6.7)</td>
<td>12.9 (95% CI 9.4-16.4)</td>
</tr>
<tr>
<td></td>
<td>Cord Allo</td>
<td>Day 0 to 60</td>
<td>7.8 (95% CI 6.7-8.9)</td>
<td>25.2 (95% CI 22.1-28.2)</td>
</tr>
<tr>
<td>Kekre 2012</td>
<td>Auto &amp; Allo</td>
<td>Day 0 to 30</td>
<td>4.7 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Christou 2015</td>
<td>Auto &amp; Allo</td>
<td>Day 0 to 60</td>
<td>7.5 (95% CI 6.7-8.4)</td>
<td></td>
</tr>
<tr>
<td>LeVieillez 2015</td>
<td>Allo</td>
<td>Day 0 to 60</td>
<td>Median 4</td>
<td>Median 4</td>
</tr>
<tr>
<td>Leahy 2017</td>
<td>Induction AML or Allo</td>
<td>Day</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Gastecki 2019</td>
<td>Allo</td>
<td>Day</td>
<td>Median 19</td>
<td></td>
</tr>
<tr>
<td>Konuma 2019</td>
<td>Cord Allo only</td>
<td>Day 0 to 30</td>
<td>Median 12 (range 4-66)</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wandt 2012</td>
<td>Induction AML or Auto</td>
<td>Day 0 to 30</td>
<td>2.85 (95% CI 2.58-3.12) in St. Arm</td>
<td>2.44 (95%CI 2.22-2.67) in St. arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.14 (95% CI 2.81-3.46) in Exp arm</td>
<td>1.63 (95% CI 1.42-1.83) in Exp arm</td>
</tr>
<tr>
<td>Stansworth 2013</td>
<td>Chemotherapy or HCT</td>
<td>Day 0 to 30</td>
<td>3.0 ±3.4 in St. arm</td>
<td>1.7 ± 2.6 in St. arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.8 ±3.1 in St. arm</td>
<td>3.0 ±3.2 in exp. arm</td>
</tr>
<tr>
<td>Tay 2020</td>
<td>Auto &amp; Allo</td>
<td>Day 0 to 100</td>
<td>5.02 ± 6.13 in St. arm</td>
<td>2.73 ± 4.81 in exp. arm</td>
</tr>
</tbody>
</table>

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 malignancy12. 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)\textsuperscript{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)\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 group18.

**Number of Red Cell Units per Transfusion:**
With the advent of the Choosing Wisely initiatives18, 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 units20-22 although the results are inconsistent23. 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 lesion24. However, numerous randomized studies in a varied clinical settings, summarized by systematic reviews have found no convincing evidence that the age of red blood cells have an adverse effect on patient outcomes25-29. Moreover, retrospective reviews in the general cancer30 and HCT31 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

<table>
<thead>
<tr>
<th>RCT</th>
<th>Setting</th>
<th>Patients (N)</th>
<th>Interventions</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heckman 1997</td>
<td>Induction therapy for acute leukemia</td>
<td>78</td>
<td>&lt;10 vs. &lt;20</td>
<td>1. &lt;10 group received more platelet transfusions for bleeding.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. &lt;20 group arm received more platelet transfusions for prophylactic indications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. No difference in RBC transfusion requirements, febrile days, days hospitalized, days thrombocytopenic, need for HLA-matched platelets, remission rate, or death.</td>
</tr>
<tr>
<td>Rebulla 1997</td>
<td>Induction for acute myeloid leukemia</td>
<td>255</td>
<td>&lt;10 vs. &lt;20</td>
<td>1. &lt;10 group had 21.5 percent fewer platelet transfusions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. No difference in risk of major bleeding.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. No difference in survival, absence of major bleeding or length of stay</td>
</tr>
<tr>
<td>Zumberg 2002</td>
<td>Autologous or Allogeneic HCT</td>
<td>159</td>
<td>&lt;10 vs. &lt;20</td>
<td>1. No differences in bleeding incidence or severity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. More transfusions were given above the assigned transfusion threshold.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. No difference in transfusion utilization.</td>
</tr>
<tr>
<td>Diedrich 2005</td>
<td>Allogeneic HCT</td>
<td>166</td>
<td>&lt;10 vs. &lt;30</td>
<td>4. &lt;10 group had fewer platelet transfusions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5. No difference in bleeding, bacteremia, engraftment, GVHD, hospital stay, death, and survival.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6. No difference in RBC transfusions.</td>
</tr>
</tbody>
</table>

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 (1.1x10^11, 2.2x10^11, or 4.4x10^11) 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

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transfusions given. At doses between $1.1 \times 10^{11}$ and $4.4 \times 10^{11}$ 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\textsuperscript{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\textsuperscript{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\textsuperscript{45,46}. There has been interest in the use of prophylactic TXA to prevent bleeding in patients with chemotherapy-related hypoproliferative thrombocytopenia\textsuperscript{47,48}. This includes 3 ongoing RCTs, with 2 examining the addition of prophylactic TXA to prophylactic platelet transfusions in patients with hematological malignancies with severe thrombocytopenia (NCT03136445\textsuperscript{49} and NCT02578901) and another examining prophylactic tranexamic acid with prophylactic platelets in patients undergoing autologous HCT (NCT04448184)\textsuperscript{50}.

**Platelet Transfusion-Summary:**
Taken together, the clinical evidence supports the use of $< 10 \times 10^9$/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\(^5\). There have been various formulae that have been proposed to determine platelet refractoriness\(^5\). 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\(^6\). The following table summarizes some potential causes for platelet refractoriness:

Table 3: Potential causes for platelet refactoriness

<table>
<thead>
<tr>
<th>Immune</th>
<th>Non-Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet alloantibodies: HLA, ABO, human platelet antigen (HPA, rare)</td>
<td>Infection</td>
</tr>
<tr>
<td>Other antibodies: Platelet autoantibodies, Drug dependent antibodies</td>
<td>Fever</td>
</tr>
<tr>
<td>Immune complexes</td>
<td>Anti-microbials (vancomycin, fluoroquinolones, Ampho B)</td>
</tr>
<tr>
<td></td>
<td>Graft versus host Disease</td>
</tr>
<tr>
<td></td>
<td>Veno-occlusive Disease</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Disseminated Intravascular Coagulation</td>
</tr>
</tbody>
</table>

While universal leukoreduction has decreased the incidence of platelet refractoriness from HLA antibodies\(^5\), 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). 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. Blood products from the Canadian Blood Services are universally leukodepleted, a practice that is supported by randomized trial data. However, leukodepletion may not be fully protective. 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. 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.

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. 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.

Prevention of CMV Transmission

Cytomegalovirus (CMV) infection continues to be a serious complication following HSCT. 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. 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\textsuperscript{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)\textsuperscript{74,75}.

However, this practice has been challenged\textsuperscript{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\textsuperscript{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**


**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\textsuperscript{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\textsuperscript{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\textsuperscript{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 principal 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\(^9\). 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\(^5\). 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\(^6\). 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\(^7\).
Table 4: 6 RCTs evaluating the use of erythropoietin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of Publication</th>
<th>Sample Size</th>
<th>EPO treatment arm</th>
<th>Control arm</th>
<th>Hb level</th>
<th>Bleeding</th>
<th>Days to PLT engraftment</th>
<th>Days to neutrophil engraftment</th>
<th>RBC utilization</th>
<th>PLT utilization</th>
<th>GVHD</th>
<th>Infection</th>
<th>Transfusion reaction</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steegmann et al.</td>
<td>1992</td>
<td>27</td>
<td>100 U/kg/day IV Day 0-Day 7 then 150 U/kg/day IV Day 7-Day 30</td>
<td>No injection</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
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</tr>
<tr>
<td>Link et al.</td>
<td>1994</td>
<td>329</td>
<td>150 U/kg/day IV continuous infusion Day 0-Day 42 or transfusion independence</td>
<td>Placebo</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>Klaesson et al.</td>
<td>1994</td>
<td>50</td>
<td>200 U/kg/day IV continuous infusion day 0-Day 28, then 2X/week IV Day 29-Day 48</td>
<td>Placebo</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>Biggs et al.</td>
<td>1995</td>
<td>91</td>
<td>300 U/kg/day IV Day 0-Day 28, then 2X/week Day 0-Day 42</td>
<td>No injection</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
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</tr>
<tr>
<td>Vanstraalen et al.</td>
<td>2006</td>
<td>60</td>
<td>500 U/kg/day SC weekly starting at Day 0 or Day 30</td>
<td>No injection</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Jaspers et al.</td>
<td>2014</td>
<td>131</td>
<td>500 U/kg SC weekly starting at Day 0 or Day 28</td>
<td>No injection</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
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<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

* 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 populations97,98.

**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 utilization99,100. 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 $\leq 20 \times 10^9/\text{L}$) with neutropenia (absolute neutrophil count ANC $\leq 0.5 \times 10^9/\text{L}$) and/or hemoglobin $< 7 \text{ g/dL}$ 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 $< 20 \times 10^9/\text{L}$ for 7 consecutive days or requiring transfusion support after achieving a sustained platelet count $\geq 50 \times 10^9/\text{L}$ without transfusion for 7 consecutive days after HCT\textsuperscript{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\textsuperscript{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\textsuperscript{103}. Invariably, these observations and experiences have led to the use of TPOs in patients with either persistent thrombocytopenia or general hypoplasia post-HCT\textsuperscript{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\textsuperscript{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.
References


Other Topics
Transplantation Eligibility Assessment: Patient Factors
Presented by: Jason Tay and Sara Beattie

Summary

1. We recommend the routine documentation and use of the Hematopoietic cell transplantation specific comorbidity index (HCT-CI) and its components as part of the pre-transplant evaluative process.

2. We suggest a Geriatric Assessment of activities of daily living (ADL) in patients >65 years of age who are considered for HCT to better aid decision making.

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 UNL
   g. Uncontrolled infection, including dental

4. The following are absolute contraindications for HSCT.
   a. Active second malignancy
   b. Cirrhosis of the liver
   c. Pregnancy
   d. HCT-CI ≥3 plus one abnormal ADL

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), HSCT may be deferred in order to prioritize stabilization of psychosocial concerns.

6. The ultimate decision to proceed to HSCT is an interdisciplinary team-based decision paying attention to recipient characteristics and their perceived “trade-offs” with disease and donor characteristics.

Background

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for a variety of malignant and nonmalignant hematological disorders. The decision to recommend and proceed with HSCT is complex and multi-faceted. Prior to recommendation a thorough 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 HSCT 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 HSCT technology and supportive care would suggest the relative contributions would be “fluid”. The ultimate decision to proceed to HSCT 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-HSCT outcomes, there is no clear and/or consistent evidence that modification of these characteristics clearly attenuates post-HSCT outcomes. This review focuses on Patient characteristics and draws attention to assessments and variables that might influence the decision to proceed with a HSCT.

Physical Assessment(s)

A detailed history, physical examination complemented with investigative diagnostics is a crucial 1st step in documenting and assessing comorbidities. A modified table in Appendix 1 as presented by Hamadini et.al serves as a reasonable guide. The rationale is presented in the following sections:

Age
An ideal HSCT candidate should be in excellent physical and physiologic health at the time of HSCT. There is a movement to consider physiologic age over chronologic age in the determination of HSCT eligibility. However, the chronologic age could be considered a simple variable that embraces a multitude of patient characteristics.

Data on the impact of age on outcomes post-auto HSCT is predominantly in myeloma setting, based on retrospective observational studies. There are fewer studies examining its impact in the lymphoma setting. In brief, biologic age should not be key criteria used to determine eligibility for autologous HSCT. Rather, one may need to consider attenuating the dosing of the conditioning regimen.

In the allogeneic setting, CIBMTR registry data suggests that the median age of HSCT has increased to up to 75 years over the last few decades. 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). 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. 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\textsuperscript{15}.

There is increasing interest in utilizing biomarkers of physiologic age\textsuperscript{16}. There are numerous candidate markers including: p16\textsuperscript{INK4A}, Leukocyte telomere length, DNA methylation, miRNA, Immunosenesence, SASP, Anemia, IL-6, CRP, NT-proBNP, Albumin, D-dimer, TNF and sICAM-1. Further, various geriatric assessment scales have also been used\textsuperscript{17,18}. In brief, it appears that p16\textsuperscript{INK4A} may be a leading biomarker candidate – a molecular maker of cellular senescence\textsuperscript{19-21}.

Observational health outcomes research evaluating age is confounded by indication - suggesting a more conservative approach. Taken together, it is reasonable to consider a HSCT up to the age of 65. In individuals who are >65 years of age, the case will be discussed at an individual basis.

**Performance Status and Geriatric Assessments**

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\textsuperscript{22}, a geriatric assessment (GA) has its proponents in older patients\textsuperscript{23,24}. There are many variants of GAs with different domains. However, the comprehensive geriatric assessment (CGA) include domains of functional status, cognitive function, comorbidities & geriatric syndromes, polypharmacy, psychological status, social support and nutritional status\textsuperscript{25} and is suggested in the practice guidelines developed by the National Comprehensive Cancer Network. The use of GA was able to identify older patients with inferior survival undergoing allogeneic HSCT\textsuperscript{26}. 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 if the presence of one abnormal Activity of Daily Living (ADL) and a HCT-CI score of ≥3 (see Section 3.4 for discussion on HCT-CI).

*We suggest that it is reasonable to proceed with HSCT if the KPS score >60 and consider utilizing CGA in individuals who are >65 years of age to better guide decision making. We suggest that a HSCT be deferred in the presence of a HCT-CI score of ≥3 and one abnormal ADL.*

**Pulmonary Evaluation**

Post-HSCT 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-HSCT pulmonary complications with up to 3% and 24% of autologous and allogeneic HSCT patients developing severe pulmonary complications requiring mechanical ventilation\textsuperscript{27}. Indeed, an abnormal PFT pre-HSCT is associated with poorer post-transplant outcomes\textsuperscript{28-31}. Further, smoking pre-HSCT is independently associated with poor outcomes\textsuperscript{32}.

The proposed cutoff for eligibility in HSCT 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\textsuperscript{33}. In the allogeneic setting, a higher threshold of DLCO$>60\%$ has been used. Moreover, the PAM score (described in Section 3.2) uses a DLCO cutoff of $60\%$\textsuperscript{34}. The correlation between FEV\textsubscript{1} and DLCO pretransplant is poor, with pre-HSCT FEV\textsubscript{1} independently predictive of early respiratory failure\textsuperscript{35,36}.

\textit{Taken together, it is optimal to consider a HSCT in an individual with a DLCO $>60\%$ and a FEV\textsubscript{1} $>60\%$. In all other scenarios, the case will 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 HSCT\textsuperscript{37}. Overall, the rate of major or life threatening cardiac events post-HSCT has been estimated to be $<1\%$\textsuperscript{38}.

Cardiac injury can occur post HSCT, 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\textsuperscript{39,40}. Separately, there is also an association between prolonged QT and QT dispersion noted on routine EKG with post-HSCT morbidity from heart failure\textsuperscript{41,42}. Further, it would be important to optimize cardiac risk factors prior to HSCT\textsuperscript{43}.

\textit{Taken together, it is optimal to consider a HSCT in an individual with a LVEF $>45\%$ with a normal EKG. In all other scenarios, the case will be discussed at an individual basis.}

**Hepatic and Nutritional Evaluation**

Baseline elevations of serum transaminases and alkaline phosphatase are associated with an increased risk of sinusoidal obstruction syndrome (SOS) post-HSCT in the allogeneic setting\textsuperscript{44}. Further, serum hyperferritinemia is also associated with increased risk of SOS, disease free and overall survival\textsuperscript{45-49}. It may be reasonable to consider chelation therapy for iron overload prior to HSCT, in particular patients with multiple red cell transfusion supports.

\textit{Overall, it is reasonable to proceed with HSCT 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 HSCT, 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-HSCT and non-relapse mortality\textsuperscript{50-52}. The use of Transient Elastography (Fibroscan) is suggested if there is clinical concern of cirrhosis.

*In general, it is reasonable to exclude patients with frank cirrhosis from HSCT.*

There is a paucity of evidence to suggest a specific nutritional state that would preclude HSCT. However, it is notable that patients with high BMI have similar post- autologous HSCT outcomes as patients with a normal BMI \textsuperscript{53-56}. Interestingly, obesity is associated with higher non-relapse mortality but a lower relapse rate, resulting in similar overall survival in the allogeneic setting\textsuperscript{57}.

**Renal Function Evaluation**
Renal dysfunction is associated with a higher morbidity and mortality in patients undergoing autologous HSCT for myeloma\textsuperscript{58-60}. 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 HSCT\textsuperscript{61}. Further, there is some evidence to support an increased risk of non-relapsed mortality in patients with renal impairment pre-HSCT\textsuperscript{62}. Indeed, long-term follow-up data suggests that the more severe the acute renal injury peri-HSCT, the higher the likelihood of chronic kidney disease\textsuperscript{63}. Interestingly, the risk of acute renal injury could be anticipated using the HCT-CI (see Section 3.4)\textsuperscript{64}.

*Overall, it is reasonable to proceed with HSCT where the Creatinine is < 177micromol/L and are < 2 times upper limit of the normal reference range. All other scenarios will be discussed on an individual basis.*

**Dental Evaluation**
The goal of pre-HSCT dental assessments is to identify potential sources of infection during the peri-HSCT period \textsuperscript{65,66}. 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-HSCT \textsuperscript{67,68}.

**Active Infections Section**
HSCT will be deferred and/or excluded if there is active systemic infection or infection(s) that are not responding to therapy.
Comorbidity Indices

There are multiple standardized co-morbidity indices in clinical use that aims to aid pre-HSCT assessments\(^6\). 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**
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 ($P = .001$)\(^7\).

**Pretransplant 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\(^3\). This score is useful for predicting the risk for death within the first 2 years after hematopoietic cell transplantation.

The authors re-evaluated the PAM score using a contemporary cohort (2003-2009) to update and recalibrate its predictive capability\(^7\) and the score was also validated in non-Caucasians\(^7\). 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. The following is a link to an online calculator: [http://pamscore.org/](http://pamscore.org/)

However, there is also literature to support an assertion that the PAM score may not be useful in all allogeneic\(^7\) or autologous\(^7\) settings.

**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 \(^7\). 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\(^7\). Similarly, the EBMT score has utility in the autologous setting\(^7\).
Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI)
Using the Charlson Comorbidity Index\textsuperscript{79} as a template, Sorror et al. re-developed this tool as a prognostic tool to better gauge post-allogeneic transplant survival outcomes – HCT-CI\textsuperscript{80}. 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\textsuperscript{81-85}. Further, modifications of the HCT-CI have been used in the autologous setting\textsuperscript{86-88}.

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 HSCT in patients with acute myeloid leukemia\textsuperscript{89}. 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\textsuperscript{90}.

The PAM score was compared with the HCT CI at a single institution and suggests the HCT-CI was more predictive of overall survival\textsuperscript{91} but the conclusions are inconsistent\textsuperscript{92}.

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. \textit{It is the author’s opinion that the HCT-CI is the most widely used tool for pre-transplant 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. Taken together, we recommend the routine use of the HCT-CI as an evaluative standard of care.}

Psychosocial Assessment
Psychosocial assessment(s) forms an important piece in pre-HSCT evaluation, performed by different clinicians – physicians, psychologists, social workers and nurses. A dedicated programme and staff is preferred to ensure consistency and expertise.
The observations in Sections 4.2 to 4.7 could suggest that measures (complex interventions) that broadly support and improve psychosocial health may lead to improve post-transplant psychosocial, patient reported outcomes as well as traditional medical post-HSCT outcomes (e.g. survival).

**Psychosocial Uncertainties**

Foster et al. performed a survey of HSCT 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 HSCT. 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.

Interestingly, a follow-up survey of 62 chairpersons of the hospital ethics committees (HEC) with an accredited HSCT program elicited whether they would recommend HSCT in the 6 scenarios (as above) where the majority HSCT 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).

**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, but may not be specific to the HSCT population.

Garcia et al. developed a psychosocial structured interview to assess candidates for hematopoietic stem cell transplantation with the interview averaging 50 minutes to complete.

Separately, the Psychosocial assessment of candidates for transplantation (PACT) 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. This scale was originally developed for clinical decision-making in psychosocial screening of organ transplant (heart and liver) candidates. 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 graft-versus-host disease, or relapse.

In a small randomized study, 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).

**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 HSCT using different scales (validated and unvalidated). Consequently, it is challenging to given firm conclusions on its association with post-HSCT outcomes.

Cancer and treatment specific distress pre-allogeneic HSCT is associated with Post-traumatic Stress Disorder (PTSD). Specifically, uncertainty, appearance and sexuality as well as health burden were concepts associated with PTSD103. Pre-transplant psychological distress as measured with an unvalidated Likert-like scale was unrelated to survival in a single centered study104.

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-transplant 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 HSCT but conclusions remain tentative in light of methodological limitations and risk of bias in their included studies105.

**Depression**
Pre-transplant clinical depression is associated with lower overall survival and higher acute GVHD among allogeneic transplant recipients106. 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 – the assumption (not proven) is that it would result in superior post-transplant outcomes.

**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 advice107. The prevalence on non-compliance is unknown in the HSCT population108. Moreover, there is a paucity of research that evaluates the consequences of noncompliance in adult HSCT 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 HSCT patients suggests 80% of patients were deemed non-compliant with an aspect of the transplant on ≥1 day\textsuperscript{109}. 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 HSCT patients did not identify compliance as predictive of post-HSCT outcomes\textsuperscript{110}.

It has been suggested that the following considerations may improve compliance\textsuperscript{108}: 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 HSCT.

Substance Abuse
Lifetime substance abuse appears to be associated with adverse outcomes post HSCT\textsuperscript{111}. 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, pretransplant conditioning regimen, and age. Survival analysis demonstrated reduced survival times for patients with substance abuse (p = .0022)\textsuperscript{112} with 15 of 17 patients dying within the first year. Interestingly, a follow-up study did show this association\textsuperscript{113}.

Due to the paucity of data, substance abuse should not be an absolute contraindication to HSCT.

Other Psychological Functioning and Coping Styles
Data on other aspects of psychological functioning/coping style is sparse and have not been clearly evaluated precluding discussion.

Financial/Socioeconomic Status
The socioeconomic status (SES) of the recipient is associated with poor-HSCT outcomes due to multiple interrelated factors\textsuperscript{114,115}. 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), lack of employment before transplantation was associated with worse physical functioning (P < .01)\textsuperscript{116}. 
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\(^\text{117}\). Similar results were noted by Silla et al\(^\text{118}\).

Interestingly, Knight et al. suggests that low SES effects are modulated through upregulation of conserved transcriptional response to adversity (CTRA)\(^\text{119}\). From a psychologic perspective, it has been suggested that the effects of “objective” SES is modulated through the individual’s “subjective” SES\(^\text{120}\).

The influence of SES is less clear in the autologous setting\(^\text{121,122}\) and it is likely that other patient and/or disease factors are more important in this setting.

**Caregiver Considerations**
The consistent presence of a caregiver is independently associated with superior post-allogeneic HSCT overall survival\(^\text{99,110,123}\). The optimal caregiver(s) and the qualities of the caregiver remains unclear, however there is evidence to suggest the quality of the caregiver may matter more than caregiver consistent presence\(^\text{124}\). Interestingly, patient’s perception of over-benefiting within a dyadic relationship was associated with patient distress, but not the patient’s self-perceived burden\(^\text{125}\).

Separately, there is evidence to suggest that unmarried status is associated with worse sleep in the allogeneic setting\(^\text{116}\). Overall, there is a paucity of evidence to guide practice as summarized by a systematic review\(^\text{126}\).

**Psychosocial Assessment Summary**
Due to lack of definitive evidence, none of the psychosocial factors discussed above represent absolute contraindications to HSCT. 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 HSCT, 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).
References


58. Sweiss K, Patel S, Culos K, Oh A, Rondelli D, Patel P. Melphalan 200 mg/m2 in patients with renal impairment is associated with increased short-term toxicity but improved response and longer treatment-free survival. Bone Marrow Transplant. 2016;51(10):1337-1341.


Appendix A. Optimal Physiologic Parameters for Transplant Eligibility

<table>
<thead>
<tr>
<th>Age and Performance Status</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
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</thead>
<tbody>
<tr>
<td>Maximum age limit (years)</td>
<td>≤65</td>
<td>≤65</td>
</tr>
<tr>
<td>KPS</td>
<td>&gt;60</td>
<td>&gt;60</td>
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</table>

**Pulmonary**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
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</thead>
<tbody>
<tr>
<td>FEV₁ (% of predicted value)</td>
<td>&gt;60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>DLCO (% of predicted value)</td>
<td>&gt;60</td>
<td>&gt;60</td>
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**Cardiac**

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<tr>
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<th>Allogeneic SCT</th>
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<td>LVEF (%)</td>
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<td>&gt;45</td>
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<td>Heart rhythm</td>
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**Hepatic**

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<tr>
<th>Parameter</th>
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<th>Allogeneic SCT</th>
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</thead>
<tbody>
<tr>
<td>Serum Bilirubin</td>
<td>&lt;2 x normal</td>
<td>&lt;2 x normal</td>
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<tr>
<td>ALT/AST/ALP</td>
<td>&lt;2 x normal</td>
<td>&lt;2 x normal</td>
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**Renal**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
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</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>&lt;2 x normal</td>
<td>&lt;2 x normal</td>
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</tbody>
</table>

**Second active malignancy**

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<tr>
<th>Parameter</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
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</thead>
<tbody>
<tr>
<td>Must be absent</td>
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<td></td>
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</table>

**Pregnancy test**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
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</thead>
<tbody>
<tr>
<td>Must be absent</td>
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</tbody>
</table>

**Uncontrolled Infections including dental**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must be absent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
### Appendix B. Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI)\(^80\)

#### Co-morbidity  
**Definition/compartments**
- Atrial fibrillation*
- Atrial flutter*
- Sick sinus syndrome*
- Ventricular arrhythmia*

#### 1. Arrhythmia

#### 2. Cardiovascular
- Coronary artery disease*
- Congestive heart failure*
- Myocardial infarction*
- Ejection fraction ≤50%§

#### 3. Inflammatory bowel disease
- Crohn’s disease*
- Ulcerative colitis*

#### 4. Diabetes
- Treated with insulin or oral hypoglycemic drugs§

#### 5. Cerebro-vascular
- Transient ischemic attacks*
- Cerebro-vascular ischemic or hemorrhagic stroke*

#### 6. Depression/anxiety
- Requiring psychological consultation and/or specific treatments§

#### 7. Hepatic - mild
- Chronic hepatitis§
- Bilirubin >ULN 1.5 X ULN§
- AST/ALT >ULN 2.5 X ULN§

#### 8. Obesity
- Body mass index >35 (adults)§
- Body mass index-for-age ≥95% percentile (children)§

#### 9. Infection
- Requiring anti-microbial treatment before, during, and after the start of conditioning§

#### 10. Rheumatologic
- Requiring Treatment*

#### 11. Peptic ulcer
- Confirmed by endoscopy and requiring treatment*

#### 12. Renal
- Serum creatinine >2mg/dl (or >177μmol/L)§
- On dialysis§
- Prior renal transplantation*

#### 13. Pulmonary - Moderate
- DLco corrected for hemoglobin 66-80% of predicted§
- FEV1 66-80% of predicted§
- Dyspnea on slight activity§

#### 14. Pulmonary - Severe
- DLco corrected for hemoglobin ≤65% of predicted§
- FEV1 ≤65% of predicted§
- Dyspnea at rest or requiring oxygen therapy§

#### 15. Heart valve disease
- Except asymptomatic mitral valve prolapse§

#### 16. Prior solid malignancy
- Treated with surgery, chemotherapy, and/or radiotherapy, excluding non-melanoma skin cancer*

#### 17. Hepatic - moderate/severe
- Liver cirrhosis§
- Bilirubin > 1.5 X ULN§
- AST/ALT > 2.5 X ULN§

#### 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, aspartate aminotransferase; and ALT, alanine aminotransferase
The HCT-CI is able to classify allo-HCT patients into three risk groups:

<table>
<thead>
<tr>
<th>Score</th>
<th>Non-Relapse Mortality</th>
<th>Overall Survival</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>2-year %</td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td>14</td>
</tr>
<tr>
<td>1 - 2</td>
<td>1.42 (0.8-2.7)</td>
<td>21</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3.54 (2.0-6.3)</td>
<td>41</td>
</tr>
</tbody>
</table>
Appendix C. Psychosocial Assessment Interview of Candidates for Hematopoietic Stem Cell Transplantation (PAIC-HSCT)

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. COPE 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) 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 checked by the term that best describes the patient's present condition.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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</thead>
<tbody>
<tr>
<td>Somatic concern</td>
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<tr>
<td>Emotional Withdrawal</td>
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<td>Hostility</td>
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<td>Suspiciousness</td>
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<td>Uncooperativeness</td>
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<td>Blunted affect</td>
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<td>Excitement</td>
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<td>Disorientation</td>
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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 ☐
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. urgency of transplant, cytomegalovirus (CMV) serostatus, age of donor) and is summarized in Figures 1-3.
- Syngeneic donors may be preferred for aplastic anemia and other non-malignant conditions, and disorders with minimal reliance on graft-versus-tumour effect.
- For recipients with potential HLA-mismatched donors, graft failure has been reported in patients with donor-specific HLA antibodies, thus careful 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. This is located on ABMTP Sharepoint.

Introduction to HLA Antigens and Testing

HLA antigens are peptides that present antigens to the T-cell receptor (TCR) to stimulate an immune response against endogenous (Class I HLA presenting to CD8+ T-cells) or exogenous (Class II HLA presenting to CD4+ T-cells) antigen. Class I antigens considered in HLA matching hematopoietic stem cell donors consist of HLA-A, HLA-B, and HLA-C antigens, and Class II antigens include HLA-DR, HLA-DQ, and HLA-DP. HLA antigens are encoded in the Major Histocompatibility Complex (MHC) on chromosome six and are inherited in a Mendelian fashion.

Linkage disequilibrium exists and therefore some gene combinations are found together more frequently than is explained by chance alone; some combinations of genes are found together more frequently in populations with different ethnic origins. This can greatly increase or decrease the likelihood of finding a full allelic match. In addition, minor histocompatibility antigens are found outside of the MHC complex that may impact engraftment and graft-versus-host disease (GVHD).

In the past, serologic typing defined antigen groups on lymphocytes using antisera to different antigens in the presence of complement to induce cell death. More recently, DNA technology has changed the face of HLA typing, with >1000 alleles detected. Difficulties arise in knowing which antigens/alleles mediate graft rejection and GVHD, and as testing becomes more specific, the pool of available donors for each patient becomes smaller.

HLA typing of siblings and potential donors will be by next generation sequencing.
Nomenclature

Terminology is standardized through the WHO nomenclature committee:¹
The identifier starts with a hyphen, followed by the name of the gene (for example, A, B, C), an asterisk and at least a four sets of digits separated by colons (i.e. HLA-A*XX:XX:XX:XX). The first set of digits corresponds to the allele group and the second set of digits defines a specific HLA protein. Thus, HLA alleles that differ in these first four digits will differ in the amino acid sequence of the HLA protein. The third set of digits corresponds to differences in the coding sequence that do not lead to a different amino acid sequence (i.e., a synonymous substitution in the coding sequence). The fourth set of digits corresponds to differences in non-coding regions.

Low resolution typing uses probes or a primer that detect all the alleles of an HLA gene to identify a gene group. Intermediate resolution typing identifies multiple but limited alleles, and high resolution provides accurate typing at the allele level.

If the recipient and donor are homozygous at a mismatched locus, this is considered a two-locus mismatch. In addition, if a recipient is homozygous at a locus and the donor is mismatched at that locus, this is considered a mismatch in the rejection direction.

Selecting an Allogenic 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 centres.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

Selection of Alternative Donors

Importantly, ABMTP data suggests that 7/8 unrelated donor HCT in Alberta is associated with similar overall survival as compared to 8/8 unrelated donor HCT (Ousia & Storek, manuscript in preparation), thus 7/8 unrelated donors are acceptable alternative donor sources when a matched sibling or 8/8 unrelated donor are unavailable. Alternatively, 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.4 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.5

• 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).\(^6\)

Selection of donors for haploidentical HCT has recently been reviewed by the EBMT along with the publication of consensus recommendations.\(^7\) 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:\(^7\)

- Younger donor age (particularly less than 40 y.o.).
- Sibling or offspring donor as opposed to parent donor.
- 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:\(^7\)

- 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:\(^7\)

- CMV serostatus matching
- Degree of HLA mismatch.

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.

**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).\(^8\) 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.
Role of Non-HLA Factors

A retrospective review by the NMDP of 6978 unrelated bone marrow transplants from 1987 to 1999 assessed the impact of donor age, sex, parity, CMV status, ABO incompatibility, and ethnicity on transplant outcomes. Only increasing donor age was associated with decreasing 5-year overall survival, and increased acute grade ≥3 and chronic GVHD. Overall survival at 5 years was 33% with donors 18-30 years old, 29% with donors 31-45 years old, and 25% if donors were >45 years old (p=0.0002). Multiparous female donors were associated with a higher likelihood of GVHD than male donors (54 versus 44%, p<0.0001) but there was no impact on overall survival.

Two 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. 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.

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, but this is generally based on studies in which GVHD prophylaxis did not include rabbit ATG (anti-thymocyte globulin). Kalra et al. recently 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. 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 appears to be limited to those with lymphoid malignancies (Ousia & Storek, manuscript in preparation). Thus, CMV matching may only need 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, and avoidance of HLA-DPB1 non-permissive mismatching; other less important factors (eg, gender, ABO compatibility, donor size, in no particular order) can be considered.

**Donor Eligibility**

Please refer to the ABMTP Donor Eligibility and Suitability Standard Operating Procedures for allogeneic and cord blood donations. This is located on ABMTP Sharepoint:


An exceptional release may be requested in cases of urgent medical need.

WMDA Donor Medical Suitability Wiki can be used as a resource regarding suitability issues. This can be found on WMDA’s website at:

https://share.wmda.info/display/DMSR/WMDA+Donor+Medical+Suitability+Recommendations+Main+page
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

*Physician choice to proceed with CMV mismatched sib vs. await unrelated donor search/recruitment

†Physician choice to proceed with CMV mismatched unrelated vs. alternative donor

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.

In no particular order:
- Match HLA-DQB1
- Donor size
- ABO compatibility
- Male or nulliparous female donor
- Multiparous female donor

>1 MUD

Select Youngest

>1 youngest (within 2 years)

Avoid Non-permissive HLA-DPB1 Mismatch

>1
Figure 3. Algorithm for Selection of an Alternative Donor

- Screen for donor-specific antibodies
- Physician Directed
  - 7/8 Unrelated Donor*
    - Prefer HLA-C 03:03/03:04 Mismatch
    - Younger Donor
      - >1
      - >1 young (within 2 years) in no particular order:
        - Minimize mismatches at HLA-DQ, -DP, -DRB3/4/5
        - Donor size
        - ABO compatibility
        - CMV serostatus match
        - Male or nulliparous female donor > multiparous female
  - Haploidentical Donor
    - Younger Donor (Prefer <40)
      - >1
    - Sibling or Offspring over Parent Donor
      - If Bone Marrow Graft: Avoid Major ABO Incompat.
        - >1
        - In no particular order:
          - Male donor for male recipient
          - If using a parent, father preferred over mother
          - CMV serostatus match

*CMV matched if recipient seropositive & lymphoid malignancy

Note:
- For haploidentical donors, consider family hx of malignancy and testing donor for germine mutations if indicated and after discussion with donor.
References

Stem Cell Mobilization
Presented by: Mona Shafey

Summary

Autologous Stem Cell Collections
- For autologous stem cell collection, mobilization options include growth factors alone (for patients who have not had prior chemo- or radio-therapy) or combined chemotherapy and growth factor mobilization (for those who have had prior chemo- or radio-therapy).
- Filgrastim is the pharmaceutical analog of G-CSF used for stem cell mobilization. Biosimilars may be used for autologous stem cell collection.
- Plerixafor is indicated for patients who are at risk for poor mobilization, those who have failed a previous mobilization attempt, and for salvage during a suboptimal mobilization attempt.
- Peripheral blood is the recommended source of stem cells for autologous transplantation. Bone marrow harvests are not recommended.
- Ex-vivo purging of autologous stem cell products is not recommended.

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.
- Neupogen is the only brand of filgrastim approved by the World Marrow Donor Association (WMDA) for use in allogeneic donors; biosimilars are not to be used at this time.
- 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.
- 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 OneMatch 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.

Autologous Stem Cell Mobilization Options.

Stem Cell Source for Autologous HCT, and Purging
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
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.

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. 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. Because of these facts, routine ex-vivo autograft purging is not recommended.

**Option 1. Granulocyte Colony Stimulating Factor (G-CSF) Only**

**Indications:** Mobilization of peripheral blood stem cells for autologous stem cell transplant patients who have not had prior chemotherapy or radiotherapy.

**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).

**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
- Germ cell tumours
- Lymphoma with largest tumour mass less than 5 cm and negative marrow biopsies
- Most other miscellaneous cancers

**Standard intensity regimens include:**
- Cyclophosphamide 2.5 g/m² day 1 OR standard dose regimen such as DHAP, ESHAP, ICE, 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/m²/day x 3 days
  - Etoposide 350 mg/m²/day x 3 days
  - Cisplatin 35 mg/m²/day x 3 days
- Add Rituximab 375mg/m² 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**

<table>
<thead>
<tr>
<th>Donor Weight (kg)</th>
<th>G-CSF Dose (μg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60kg</td>
<td>300</td>
</tr>
<tr>
<td>60 - 75</td>
<td>480</td>
</tr>
<tr>
<td>75.1 – 100</td>
<td>600</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>780</td>
</tr>
</tbody>
</table>

*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 10⁹/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 $>5 \times 10^9$/L and CD34 count is $>5$ but $<30 \times 10^6$/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.

**Plerixafor dosing:** The recommended dose of Plerixafor is 0.24 mg/kg body weight by subcutaneous injection, given the day before apheresis is expected to occur, 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 $30 \times 10^9$/L and hemoglobin $>80$ g/L
  - CD34+ count greater than $20 \times 10^6$/L
- Plan for large volume apheresis ($\geq 3$ 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: $2 \times 10^6$ CD34+ cells/kg/transplant
  - Ideal target 5 to $10 \times 10^6$ CD34+ cells/kg/transplant (preferred)

**Allogeneic Stem Cell Transplant Donors**

**Indications:** Mobilization of peripheral blood stem cells in allogeneic blood stem cell 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

<table>
<thead>
<tr>
<th>Donor Weight (kg)</th>
<th>G-CSF Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48</td>
<td>300</td>
</tr>
<tr>
<td>48-60</td>
<td>480</td>
</tr>
<tr>
<td>60.1-78</td>
<td>600</td>
</tr>
<tr>
<td>78.1-100</td>
<td>780</td>
</tr>
<tr>
<td>100.1-120</td>
<td>960</td>
</tr>
</tbody>
</table>
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 $3 \times 10^6$ CD34+ cells/kg were collected in the first apheresis session.

Apheresis:
- Plan large volume apheresis ($\geq 3$ 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.
- Minimum of 8L apheresis.
- Target CD34+ Collection: $5 - 10 \times 10^6$/kg recipient weight.
- Minimum target: $3 \times 10^6$ 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. In the case of unrelated donors, early notification of the transplant center is essential; the CBS Stem Cell Registry has advised that plerixafor should not be administered to unrelated donors.

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. 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 transplant 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”

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. Grastofil), 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. 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. 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.

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, OneMatch has recommended against the use of biosimilar G-CSFs in healthy donors at this time.
References

Stem Cell Graft
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.

Mobilization


Purging


G-CSF Stimulated Marrow

Biosimilars


Chimerism and Its Uses
Presented by: Jan Storek

Summary

- Chimerism of **blood** T cells (CD3+) and blood malignancy lineage cells (e.g., CD13/33+ cells in case of myeloid leukemia or CD19+ cells in case of B cell malignancy) is routinely determined in all allotransplant recipients at 3 months. This is to document engraftment, and to generate baseline values for potential later chimerism testing (when rejection or relapse is suspected). Results are interpreted as shown in Appendix 1. No anti-relapse therapy should be given based on the 3 month or post-3 month chimerism result, as blood chimerism has limited positive and negative predictive values for relapse.
- Chimerism of **marrow** cells enriched for malignancy lineage/phenotype cells is useful for distinguishing relapse from benign conditions resembling relapse (e.g., increased percentage of marrow blasts due to “regeneration”). This should be ordered by hematopathologist.

Techniques for Chimerism Determination

Chimerism (% cells of donor versus recipient origin)\(^1\) can be determined using one of the techniques described in the table below (courtesy of F. Khan).

**Table 1. Techniques to determine chimerism (courtesy of F. Khan).**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity (%)</th>
<th>Quantitation Accuracy</th>
<th>Informativeness (likelihood of finding alleles different between donor &amp; recipient)</th>
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</thead>
<tbody>
<tr>
<td>Fluorescent dye-labeled STR, multiplex, capillary electrophoresis</td>
<td>1-5</td>
<td>Very High</td>
<td>High</td>
</tr>
<tr>
<td>(^{32})P-labeled STR/VNTR, multiplex, gel electrophoresis</td>
<td>1-5</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>XY Cytogenetics</td>
<td>10-20</td>
<td>Low</td>
<td>Sex-mismatched only</td>
</tr>
<tr>
<td>XY FISH</td>
<td>0.1-0.2</td>
<td>Very High</td>
<td>Sex-mismatched only, potential origin of sex-mismatched cells from transfusion, mother or offspring</td>
</tr>
<tr>
<td>RFLP</td>
<td>5-20</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Real time PCR using ‘indels’ (insertion/deletion polymorphism)</td>
<td>0.001-0.1</td>
<td>Moderate</td>
<td>Moderate-High</td>
</tr>
</tbody>
</table>

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.

Clinical Utility

**Chimerism of blood cells can be used for:**
1. **Detection of graft rejection**
   - Rejection is defined as <5% donor cells among T cells.
2. **Detection of relapse**
   - The sensitivity and specificity of relapse detection is increased when chimerism is determined in FACS-sorted leukemia lineage cells (and, for comparison, in FACS-sorted T cells). The specificity is further increased if comparison to a baseline result is possible. Therefore, in Alberta, we routinely determine chimerism of sorted blood malignancy lineage cells and T cells at 3 months post-transplant (baseline), and subsequently when and if rejection or relapse is suspected. However, it needs to be emphasized that the blood chimerism even among sorted leukemia lineage cells has only limited positive predictive value (~75% per our October 2014 analysis of patients undergoing HCT in 2010-2013), and limited negative predictive value (~93%), so if relapse is suspected strongly, more sensitive and specific tests (e.g., bone marrow morphology, flow cytometry and cytogenetics/nucleic acid tests) should be used. For interpretation of blood chimerism, see the table in Appendix 1 below. The recommended algorithm is:
   - if at >3 months post-transplant there is a weak suspicion for relapse, and it is desired to avoid an invasive test like marrow aspiration → order chimerism
     - if >95% leukemia lineage cells and >95% CD3 cells are donor → routine follow up
     - if ≤95% leukemia lineage and ≤ 95% CD3 cells are donor →
       - if stable chimerism → routine follow up
- if decreasing donor chimerism → close follow up for relapse and rejection
  ▪ if ≤95% or decreasing percent of leukemia lineage cells and >95% CD3 cells are donor → close follow up for relapse
  o if there is a strong suspicion for relapse, do a definitive diagnostic test (e.g., marrow aspiration), particularly if treatment would change if relapse was known.

3. Prediction of rejection
   • This is primarily useful in the setting of nonmyeloablative transplants or transplants using alemtuzumab during conditioning, as in these settings low donor chimerism (risk factor for rejection) can be converted to full donor chimerism by donor lymphocyte infusion (DLI), which appears to prevent rejection. This is not applicable to routine Albertan patients (conditioning with fludarabine + busulfan + TBI + ATG).

4. Prediction of relapse
   • To achieve a useful sensitivity, serial testing may be required, probably every 1-2 months for 2 years; however, this is costly. Moreover, there is no conclusive data on whether impeding relapse can be safely and effectively treated (e.g., with DLI or discontinuation of pharmacologic immunosuppression). Thus, routine serial chimerism testing is currently not recommended. In Alberta, patients should be encouraged to enter the trial “Predictors of Relapse”.

BMT Standard Practice Manual
Last Revised: January 18, 2018
Effective: January 18, 2018
www.ahs.ca/guru
References


Appendix A. Interpretation of Blood Chimerism Results

Table 1. Interpretation of blood chimerism results.

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Donor Among Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD3 Cells</td>
</tr>
<tr>
<td>Normal</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>Benign mixed chimerism</td>
<td>5 – 95%,* stable or increasing</td>
</tr>
<tr>
<td>Impeding rejection (per other centers' experience)</td>
<td>5 – 95%,* decreasing</td>
</tr>
<tr>
<td>Rejection</td>
<td>&lt;5%*</td>
</tr>
<tr>
<td>Impeding relapse or bonified relapse**</td>
<td>&gt;95% or stable/increasing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Leukemic Lineage Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>Benign mixed chimerism</td>
<td>5 – 95%, stable or increasing</td>
</tr>
<tr>
<td>Impeding rejection (per other centers' experience)</td>
<td>variable, typically decreasing</td>
</tr>
<tr>
<td>Rejection</td>
<td>variable, typically &lt;5%</td>
</tr>
<tr>
<td>Impeding relapse or bonified relapse**</td>
<td>decreasing</td>
</tr>
</tbody>
</table>

* Per preliminary analysis of Albertan patients transplanted in 2010-2013 (performed in October 2014), ~20% HCT recipients are incomplete chimeras (<95% donor) among T cells at 3 months posttransplant. This incomplete chimerism among T cells does NOT predispose to relapse, as long as it is associated with complete chimerism among leukemia lineage cells. Moreover, <5% donor T cells with >95% donor leukemic lineage cells at 3 months does not appear associated with rejection or relapse, as 2/2 such patients are alive and well >3 years posttransplant, without any therapy for rejection or relapse.

** Per the same preliminary analysis, <95% or declining % donor among leukemic lineage cells at >3 months posttransplant (with >95% or stable/increasing % donor among T cells) appears to have a positive predictive value (PPV) of 75% and a negative predictive value (NPV) of 93% for relapse.
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. For an abbreviated version of the adult schedule, see Appendix 1.

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.
• 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.
  o 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
  o Haemophilus influenzae type b
- Neisseria meningitidis
- Diptheria
- 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
  - 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
  - Eg, for pneumococcal conjugate vaccine, responses are elicited already starting at 3 mo, but higher Ab levels are achieved with a later start, so it may be prudent to start vaccination around the end prophylaxis with sulfamethoxazole-trimethoprim
- 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)

  o Probably safe as early as 1 year posttransplant, so could be used during outbreak

GVHD status consideration
  o 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 or pneumococcal disease. Given that protection against influenza 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
  o 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
  o Patients on post-transplant maintenance therapies may receive non-live and 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 a contraindication 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
    o Pneumococcal Conjugate Vaccine and Influenza Vaccine
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
- 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 and 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. Currently, there is no public funding in Alberta for this indication.

- There are no safety or efficacy data in allo-HCT recipients.
- Allo and auto-HCT recipients late (≥3 years) post-transplant 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
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.


Appendix. Adult Immunization Schedule per 2020 Public Health Guidelines.

For details, see https://open.alberta.ca/dataset/aip/resource/c74197ab-4f13-4052-9dce-73ab84c3314f/download/AIP-Adult-HSCT.pdf

<table>
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<tr>
<th></th>
<th>6 mo</th>
<th>7 mo</th>
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<th>14 mo</th>
<th>24 mo</th>
<th>27 mo</th>
<th>36 mo</th>
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<td>X</td>
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<td>X</td>
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<td>Hepatitis B</td>
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<td>Booster if measles Ab low####</td>
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<td>MMR</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Annual administration starting pretransplant, typically in the fall. Use non-live (intramuscular) vaccine; live (intranasal) vaccine is relatively contraindicated.

**For adults age 18-24 years of age inclusive or laboratory workers routinely exposed to N.meningitidis.

***For adults age 18-26 years of age inclusive.

**** Live attenuated varicella vaccine (Varivax or Varilrix), 5 not live attenuated zoster vaccine (Zostavax), which contains more virus particles than varicella vaccine and thus may be less safe. A non-live vaccine has been licensed (adjuvanted, recombinant, glycoprotein E vaccine (Shingrix)). Shingrix is safe & effective in autologous-HCT recipients, but as of yet unfunded in the province for this indication. The efficacy and safety of Shingrix in allogeneic-HCT recipients is unknown. For further discussion, see above.

# At 14 and 24 mo posttransplant, use Conjugate vaccine (13-valent polysaccharide-protein conjugate) if patient is on systemic immunosuppressive drug(s), and use Polysaccharide vaccine (23-valent polysaccharide vaccine) if patient is off of systemic immunosuppressive drugs.

## If tetanus antibody (tetanus antitoxin, TAT) is low, booster with a multivalent vaccine containing tetanus, diphtheria, pertussis, H.influenzae and poliomyelitis antigens.

### If HBsAb is low, consider a new series of HepB vaccination only for high risk patients (eg, health care worker).

#### If rubella antibody is low, consider a booster only if a woman of childbearing potential. If measles IgG is negative or indeterminate, do not booster. Instead, consider the patient as non-immune to measles, i.e., give IgG prophylaxis if exposed.
Umbilical Cord Blood Transplantation (UCBT)
Presented by: Mona Shafey

Summary

- For children, cord blood as a stem cell source appears to be as useful as bone marrow.
- For adults, data supports cord blood as a stem cell source when no HLA-matched donor is available.
  - Whether cord blood or haploidentical donor results in better HCT outcome is not known
  - In Alberta, we prefer haploidentical donor
- 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:
  - For 5/6 or 6/6 HLA match, TNC at freezing must be ≥2.5 x10^7/kg
  - For 4/6 HLA match, TNC at freezing must be ≥3.5 x10^7/kg
  - HLA-A or –B mismatch is preferable over DRB1 mismatch
  - Absence of donor specific antibodies
  - Other factors to consider if multiple units available – high-resolution HLA-matching, accreditation of cord blood bank and location, RBC-depleted units
- For non-malignant conditions, higher TNC doses are required and HLA-antibodies seem to be more important in these conditions to avoid graft failure.
- Double unit cord blood transplantation is feasible if no adequate single unit available.
  - two best available cord blood units, each with minimum TNC dose of 2.0 x10^7/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
- GVHD prophylaxis after UBCT is with cyclosporine to day 84 and mycophenolate mofetil (~15 mg/kg bid to day 35). Methotrexate is not used as it has been associated with delayed engraftment/graft failure. ATG is not used as it has been associated with too many posttransplant infections.
- 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 1998, 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. It is estimated that >25,000 patients to date have undergone UCBT for
malignant and non-malignant conditions. In Canada, in the year 2007, 68% of all unrelated pediatric stem cell transplants, and 9% of unrelated adult stem cell transplants were performed with umbilical cord blood stem cells.

When selecting a donor source for hematopoietic stem cell transplantation, consider the impact of the donor source on transplant outcomes, in particular engraftment, graft-versus-host disease, treatment-related mortality, and survival. Urgency of transplantation is an important factor as well. A 10/10 human leukocyte antigen (HLA)-matched unrelated donor graft is first choice for the 70% of patients who must look outside their families for donors. Unfortunately, unrelated volunteer registries are limited in ability to provide a prompt source of hematopoietic stem cells for many patients, particularly ethnic minorities. 60% of Caucasians and only 20-25% of ethnic minorities will be matched to an unrelated donor on a registry, thus a simultaneous cord blood search should be performed, especially if transplantation is urgent. Other alternative donor options to consider include HLA-mismatched unrelated donor or related haplo-identical donor.

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 are no randomized clinical trial data comparing transplantation of umbilical cord blood vs. related or unrelated marrow or peripheral blood stem cell donors. The best data available comes from retrospective, comparative registry data available for both children and adults.
Umbilical cord blood transplantation using related donors is performed almost exclusively in children. A Eurocord and IBMTR (International Bone Marrow Transplant Registry) joint study compared children who received umbilical cord blood from HLA-identical siblings (n=113) to children who received marrow from HLA-identical siblings (n=2052). Umbilical cord blood recipients had slower engraftment and lower risk of GVHD compared to those who received marrow, and there was no difference in relapse-related deaths, 100-day mortality, and overall survival (3-yr overall survival (OS) 86% vs. 84% for non-malignant conditions, 46% vs. 53% for malignant). Factors influencing outcomes after related HLA-identical UCBT in children were found to be cell dose, GVHD prophylaxis not including methotrexate, and disease status at transplantation. When UCBT was compared to unrelated marrow donors in children with acute leukemia, there were lower rates of acute GVHD in the HLA-matched umbilical cord blood group compared to HLA-matched bone marrow (RR 0.45, p=0.0387), similar survival outcomes between bone marrow and 1-2 antigen mismatched cord blood, and improved survival with HLA-matched cord blood compared to bone marrow. Thus, it appears that umbilical cord blood as a stem cell source is as useful as bone marrow for children requiring allogeneic hematopoietic stem cell transplantation.

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. When compared to 7-8/8 allele-matched peripheral blood or marrow transplantation, umbilical cord blood transplantation had comparable leukemia-free survival, higher transplant-related mortality, and lower rates of graft-vs-host disease. The authors concluded that data support umbilical cord blood transplantation for adults with acute leukemia when no HLA-matched donor is available for urgent transplants.

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 an analysis of 1061 recipients of single-unit myeloblastic UCBT for the treatment of hematological malignancies, the best transplantation outcomes were in recipients of 6/6 units regardless of pre-cryopreservation TNC (total nucleated cell) dose (though median dose was 4.0x10^7/kg). Recipients of 4/6 HLA-matched units required a TNC ≥5.0x10^7/kg to achieve comparable TRM (treatment-related mortality) and DFS (disease-free survival) to that of recipients of 5/6 units with a TNC of ≥2.5x10^7/kg. This study shows that the greater the HLA mismatch, the higher the required TNC dose to ensure transplantation survival; conversely, the better the HLA match, the less important the TNC dose.

Other studies consistently demonstrate cell dose to be the most important factor on survival outcomes, and Eurocord has previously recommended using >3x10^7 total nucleated cells/kg at collection for patients with malignant disease, and >4.9x10^7 nucleated cells/kg for those with non-malignant disease. An increasing number of HLA mismatches is associated with delayed
engraftment, higher treatment-related mortality, higher rates of chronic GVHD, and decreased relapse rates\(^7\). The Memorial Sloan-Kettering Cancer Center (MSKCC) has similar guidelines for single UCBT, suggesting a minimum nucleated cell dose of 2.5x10\(^7\) 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.

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 DRB1\(^14\). 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 an UCB unit matched ≥6/8 or <6/8, respectively (p=0.01). In fact, on multivariate analysis, a 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-relapsed mortality in 1568 single umbilical cord blood transplantations for hematological malignancy was recently published\(^15\). 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.

**Donor Specific Antibodies (DSA)**

Since most UCBT are performed with HLA-mismatched CB 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 and 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%) vs. 32% in patients without antibodies (p=0.06), and lower engraftment (44% vs. 81%, p=0.006)\(^18\). 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:

- It is desirable to obtain cord blood units from FACT-accredited banks and those that are closer in location
- CD34+ cell count can be considered when choosing between multiple cord units that are otherwise similar from the same bank
- 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 a significant amount of 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 the majority of adults do not have access to a single cord blood unit with the recommended TNC dose. 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 single unit 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.

Preliminary data support the use of this procedure to overcome the cell dose barrier in adults. In one study with 177 patients who underwent myeloblastic UCBT, there was lower risk of relapse in double unit recipients (19%) vs. single unit (34%) at 5-years, primarily due to higher rates of GVHD (acute GVHD 48% vs. 29%, chronic GVHD 18% vs. 10%), and leukemia-free survival was 51% for double UCBT vs. 40% for single UCBT\(^{20}\). 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. How to trade off cell dose versus HLA match in this setting is unknown. It is important to note, however, that there is no relationship between unit-unit HLA match and the likelihood of sustained donor engraftment\(^{19}\). In 84 recipients of double unit UCBT, there was no difference in the distributions of the unit-unit HLA match in the 79 patients with sustained engraftment and the 5 patients with graft failure when analyzed at HLA-A, -B antigen, -DRB1 allele, or 10 HLA-allele match, and there was also no association between unit-unit HLA match and the 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. At the MSKCC, for double-unit UCBT, each unit must have >2.0x10\(^7\) and preference to HLA match above this threshold is given, and HLA match of units to each other is not considered.\(^{13}\)
Whether double UCBT is preferable to single unit UCBT when the cell dose in one unit is acceptable is unknown in the adult setting. 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 x10^7/kg, respectively. The results of this study showed no survival advantage after double unit UCBT compared to single unit UCBT 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.

### Schema for Unrelated Cord Blood Unit Selection

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Evaluate search reports for units 4-6/6 HLA-matched with TNC ≥2.5 x 10^7/kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Review information and bank of origin for each unit. Obtain missing unit information. Prepare cord blood search summary report.</td>
</tr>
<tr>
<td>Step 3</td>
<td>Rank units according to HLA-A, -B antigen, -DRB1 allele match. List highest to lowest TNC within each HLA-match grade.</td>
</tr>
<tr>
<td></td>
<td>1st choice: 6/6 HLA match with largest TNC</td>
</tr>
<tr>
<td></td>
<td>2nd choice: 5/6 HLA match with largest TNC</td>
</tr>
<tr>
<td></td>
<td>3rd choice: 4/6 HLA match with largest TNC, minimum 3.5 x10^7/kg</td>
</tr>
<tr>
<td>Step 4</td>
<td>If suitable cord unit available, proceed with single unit UCBT. If no suitable cord unit available, proceed with double unit UCBT using two best available units each with minimum TNC 2.0 x10^7/kg</td>
</tr>
</tbody>
</table>

### 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
   - Red Cell Replete units are thawed and washed for Adult Recipients
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.

GVHD Prophylaxis
Use of ATG has been associated with decreased survival primarily due to infections. Use of methotrexate has been associated with delayed engraftment and graft failure. The most frequent GVHD prophylaxis after CBT in recent literature is CSA+MMF, including in the US BMT CTN study 1101, which is the prophylaxis we will use (CSA to day 84, MMF to day 35). It is thought but not proven that the likelihood of delayed engraftment/graft failure is lower with MMF than with methotrexate.

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


Summary

Immunosuppression is required for allogeneic transplant patients to prevent the residual immune system from destroying the infused donor cells while preventing the donor cells from causing graft-versus-host disease (GVHD). Pharmacological agents used to prevent and treat GVHD have previously been discussed in sections of the BMT Standard Practice Manual including Acute GVHD: Prevention and Treatment and Management of Chronic Graft versus Host Disease. Please refer to these sections for their place in therapy.

Therapeutic drug monitoring of blood concentrations is required for cyclosporine, tacrolimus and sirolimus due to their narrow therapeutic range and pharmacokinetic variability. Subtherapeutic concentrations may result in increased risk of GVHD, whereas supratherapeutic concentrations result in undesired toxicity.

Cyclosporine, tacrolimus and sirolimus are all metabolized primarily by the hepatic CYP450 system. The addition or discontinuation of drugs that inhibit or induce CYP3A4 may cause changes in blood concentrations. Additional monitoring needs to be considered with potential drug interactions.

Calcineurin Inhibitors

Cyclosporine and tacrolimus act by competitively binding and inhibiting the activity of a protein phosphatase, calcineurin. Inhibition of calcineurin is thought to mediate immunosuppressive activity by suppressing the T lymphocyte activation.

Cyclosporine

The activity of cyclosporine is mediated through inhibition of T-cell function, with minimal activity against B-cells. It inhibits production and release of interleukin-2 (IL-2) and other cytokines including interferon-gamma. This results in an inhibition of the early events of T-cell activation, sensitization and proliferation.

Cyclosporine is a first line drug for immunosuppression in the prevention of GVHD. It may also be used during the treatment of acute and chronic GVHD.

Recommended initial doses are 2.5mg/kg IV q12h or 6.25mg/kg po q12h. Conversion of IV to oral requires a 2.5 to 3 fold increase in dosage. Cyclosporine (Neoral ®) is available as a soft gelatin capsule (10mg, 25mg, 50mg, 100mg) and an oral solution (100mg/ml). Cyclosporine (Sandimmune ®) is available as a concentrate for solution for IV infusion (50mg/ml).
Dosing in renal impairment and hepatic impairment should be reviewed with the transplant physician. Doses may still be adjusted to achieve therapeutic levels, however targeting the lower therapeutic range should be considered. Clinical status and trough levels should be monitored closely.

Cyclosporine trough level target for GVHD prophylaxis is 200-400 ug/L until taper (day 56-84), providing there is no evidence of GVHD. For non-malignant indications (e.g., aplastic anemia), cyclosporine taper is initiated on day 180. Trough level targets are the same during treatment of GVHD or at the physician’s discretion based on clinical response.

Upon initiation of cyclosporine and for the duration of stay in hospital, trough levels are drawn three times a week. If infused intravenously, cyclosporine blood specimen should not be drawn from the same line used for administration. Cyclosporine trough levels are to be drawn within 60 minutes of next scheduled dose. When patients are transferred to the outpatient clinic, levels are then drawn weekly, at a minimum. Consider repeating levels within 2-4 doses after a dose adjustment or the initiation/discontinuation of an interacting medication. Once maintenance dose is established for patients on long term cyclosporine for cGVHD, frequency of trough level collection may decreased to a monthly or as needed basis. Levels should no longer be collected upon initiation of a taper. In addition to monitoring drug levels, regular monitoring should also include blood pressure, CBC, serum electrolytes (Mg, K), renal function and hepatic function.

The following algorithms can be utilized in guiding dose adjustment:

<table>
<thead>
<tr>
<th>CSA level</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 ug/L</td>
<td>Increase by 25%</td>
</tr>
<tr>
<td>200-400 ug/L</td>
<td>No change</td>
</tr>
<tr>
<td>350-400 ug/L</td>
<td>Consider decreasing by 25% if level trending upwards</td>
</tr>
<tr>
<td>400-450 ug/L</td>
<td>Decrease by 25%</td>
</tr>
<tr>
<td>&gt;450 ug/L</td>
<td>Hold 1-2 doses, decrease by 25-50%</td>
</tr>
</tbody>
</table>

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

Cyclosporine is a substrate and inhibitor of CYP3A4 and p-glycoprotein. Drug interactions should be considered when initially dosing cyclosporine. Additional monitoring and dose adjustment may be required when starting or stopping drugs that inhibit or induce CYP3A4 while maintained on cyclosporine. Renal function should be closely monitored with co-administration of drugs that might exhibit additive/synergistic nephrotoxicity with cyclosporine.
Patients are reminded to take cyclosporine 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 cyclosporine’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.

Side effects of cyclosporine may include but are not limited to nausea, vomiting, diarrhea, hypertension, dyslipidemia, tremor, headache, paresthesia, dizziness, encephalopathy, nephrotoxicity, hepatotoxicity, hypomagnesemia, thrombotic microangiopathy and increased risk of infection. Some side effects may be dose related and resolved with a reduction in dose. Discontinuation may be warranted for severe side effects.

**Tacrolimus**

The activity of tacrolimus is similar to that of cyclosporine. Tacrolimus inhibits the production of IL-2, IL-3, IL-4, interferon-gamma, TNF and granulocyte-macrophage colony-stimulating factor (GM-CSF). It has variable effect on B-cell response and has anti-inflammatory effects.

Tacrolimus can be used as an alternative to cyclosporine for GVHD prophylaxis. It is used first line as part of the haploidentical transplant protocol for prevention of GVHD. It is more commonly used in the treatment of cGVHD.

Recommended initial doses are 0.03mg/kg IV as a continuous infusion or 0.12-0.15mg/kg/day po divided q12h. Conversion of IV to oral requires a 3-4 fold increase in dosage. If switching from cyclosporine to tacrolimus, cyclosporine should be discontinued for at least 24 hours prior to initiating Tacrolimus to avoid excess nephrotoxicity. Tacrolimus (Prograf ®) is available as an immediate release capsule (0.5mg, 1mg or 5mg) or concentration for solution for IV infusion (5mg/ml). A 1mg/ml oral suspension can also be compounded. Advagraf ® extended release capsules are not currently used for prophylaxis or treatment.

Dosing in renal impairment and hepatic impairment should be reviewed with the transplant physician. Doses may still be adjusted to achieve therapeutic levels, however targeting the lower therapeutic range should be considered. Clinical status and trough levels should be monitored closely.

Tacrolimus trough level target for GVHD prophylaxis/treatment is 5-15 ug/L. In the setting of cGVHD, dose may be adjusted by the physician based on clinical response, rather than by targeting therapeutic levels.
Tacrolimus trough levels are to be drawn within 60 minutes of next scheduled dose. If infused intravenously, tacrolimus blood specimens should not be drawn from the same line used for administration. Levels are drawn at least once weekly for outpatients and up to three times a week of inpatients. Consider repeating levels within 3-4 doses after a dose adjustment or the initiation/discontinuation of an interacting medication. Once maintenance dose is established for patients on long term tacrolimus for cGVHD, frequency of trough level collection may decrease to a monthly or as needed basis. Levels should no longer be collected upon initiation of a taper. In addition to monitoring drug levels, regular monitoring should also include blood pressure, blood glucose, CBC, serum electrolytes (Mg, K), renal function and hepatic function.

The following algorithm can be utilized in guiding dose adjustment:

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

Tacrolimus is a substrate of CYP3A4 and p-glycoprotein. Drug interactions should be considered when initially dosing Tacrolimus. Additional monitoring and dose adjustment may be required when starting or stopping drugs that inhibit or induce CYP3A4 while maintained on Tacrolimus. 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.

Side effects of tacrolimus may include but are not limited to nausea, vomiting, diarrhea, hypertension, dyslipidemia, increased blood glucose, tremor, headache, paresthesia, dizziness, nephrotoxicity, hepatotoxicity, hypomagnesemia, alopecia, thrombotic microangiopathy and increased risk of infection.. Some side effects may be dose related and resolved with a reduction in dose. Discontinuation may be warranted for severe side effects.

**m-TOR Inhibitor: Sirolimus**

Sirolimus binds and inhibits the activity of the mammalian target of rapamycin (mTOR), therefore reducing DNA transcription, translation, protein synthesis, and cell cycle arrest in the G1 phase in activated lymphocytes. Sirolimus inhibits T-cell activation by cytokines, such as IL-2.

Sirolimus is used in the treatment of cGVHD. It is also used in the prevention of GVHD in transplants for sickle cell disease.
Recommended initial dose is 2mg po daily targeting a trough level target of 5-15 ug/L. The dose may also be adjusted by the physician based on clinical response, rather than by targeting therapeutic levels. Sirolimus (Rapamune®) is available as a 1mg tablet or 1mg/ml oral suspension.

Sirolimus trough levels are to be drawn within 1-2 hours of the next scheduled dose and 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 tough level collection may decrease to a monthly or as needed basis. Levels should no longer be collected upon initiation of a taper. In addition to monitoring drug levels, regular monitoring should also include blood pressure, lipid panel, CBC, and renal function.

The following algorithm can be utilized in guiding dose adjustment:

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

Dosing in renal impairment and hepatic impairment should be reviewed with the transplant physician. Doses may still be adjusted to achieve therapeutic levels, however targeting the lower therapeutic range. Monitor closely.

Sirolimus is a substrate of CYP3A4 and p-glycoprotein. Drug interactions should be considered when initially dosing sirolimus. Additional monitoring and dose adjustment may be required when starting or stopping drugs that inhibit or induce CYP3A4 while maintained on sirolimus.

Patients are reminded to take sirolimus consistently with or without food to minimize variability. The oral solution should be diluted with 60ml 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.

Side effects of sirolimus may include but are not limited to hypertension, dyslipidemia, proteinurea, edema, acne, rash, stomatitis, anemia, and increased risk of infection. Interstitial pneumonia is a rare but serious side effect associated with sirolimus. Some side effects may be dose related and resolved with a reduction in dose. Discontinuation may be warranted for severe side effects.
References

Neoral and Sandimmune product monograph. Novartis Pharmaceuticals Canada Inc. Date of Revision: January 9, 2015.


ABO Incompatible Graft and Recipient  
Presented by: Nicole Prokopishyn & Jason Tay

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. 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 bidirectional incompatibility is present, as shown in Table 1 below. 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

<table>
<thead>
<tr>
<th>Mismatch Type</th>
<th>ABO Blood Type Recipient</th>
<th>ABO Blood Type Donor</th>
<th>Potential Clinical Consequence</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>O</td>
<td>A,B</td>
<td>-Acute hemolytic episode</td>
<td>-Transfusion of incompatible red blood cells</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td></td>
<td>-Delayed RBC engraftment</td>
<td>-Recipient anti-donor isohemagglutinins</td>
</tr>
<tr>
<td>Major</td>
<td>A</td>
<td>AB</td>
<td>-Pure red blood cell aplasia</td>
<td>-Loss of immature stem cells from processing with ABO antigens expressed on granulocytes and platelets</td>
</tr>
<tr>
<td>Major</td>
<td>B</td>
<td>AB</td>
<td>-Delayed granulocyte and platelet engraftment</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>A</td>
<td>O</td>
<td>-Acute hemolytic episode</td>
<td>-Donor plasma with elevated isohemagglutinin titers/small blood volume recipient</td>
</tr>
<tr>
<td>Minor</td>
<td>B</td>
<td>O</td>
<td>-Delayed hemolysis secondary to passenger lymphocyte syndrome</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>AB</td>
<td>O,A,B</td>
<td></td>
<td>-Passenger lymphocytes producing isohemagglutinins</td>
</tr>
<tr>
<td>Bidirectional</td>
<td>A</td>
<td>B</td>
<td>-Combination of major and minor consequences</td>
<td>-Combination of major and minor etiologies</td>
</tr>
<tr>
<td>Bidirectional</td>
<td>B</td>
<td>A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 reports2,7-9 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, and in almost half of those receiving a high volume (>50mL) of incompatible red cells 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. Isoagglutinins disappear more rapidly following unrelated donor compared to related donor transplants and in those with graft versus host disease, and more slowly following non-myeloablative transplant. 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. 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. 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, but was not observed in several other studies, including a recent large CIBMTR/NMDP evaluation of donor characteristics. 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. Some single center studies have reported both platelet and neutrophil engraftment issues, but the majority of studies find no impact of incompatibility. A significantly higher rate of graft failure was reported in major or bidirectional incompatible transplants (6/83 vs 0/141 compatible transplants), 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.
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 as well as two registry studies, but were not seen in most other reports. Interestingly, 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. 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). 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. 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). 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).

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. By contrast, cohort and registry studies have found an increase in NRM and decrease in overall survival, though these findings were not confirmed by other studies.

More recently, Kollman et al. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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, 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. This approach has been counter-challenged as antibody titering is a laboratory technique shown to be difficult to standardize across institutions. 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. 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 bortezomib⁵⁴ 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.
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References


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/m2): 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/m2 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 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

- 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, genitals, breast exam for females, 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 (in women who have not received TBI), cervical, colorectal and prostate cancer should follow established Albertan/Canadian guidelines (www.screeningforlife.ca & for prostate cancer www.canadiantaskforce.ca).
- For women who have received TBI: screening mammography starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40.
• 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 q.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 per the “Reproductive system complications” section.

**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.

**Background**
Survival after hematopoietic cell transplant (HCT) has improved.¹ 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.² 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.³,⁴ 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 follow-up care is not typically required. Survivors of pediatric HCT are typically followed into adulthood and indefinitely in the Alberta Children’s Hospital long-term follow-up/survivorship clinic.

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. 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.

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. 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. 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.
occurrence of cardiovascular disease after HCT encompass both traditional risk factors in addition to chest irradiation, GVHD, and exposure to anthracycline chemotherapy.6,7 Healthy lifestyle choices such as physical activity and fruit/vegetable intake are associated with a lower risk of cardiovascular disease after HCT.9 Current Canadian guidelines for the general population recommend measurement of a lipid panel and glucose in women and men ≥ age 40 every 5 years.10

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.11 Pre-HCT anthracycline exposure, particularly cumulative dose ≥ 250 mg/m² is the primary driver of CHF risk, although significant modifiers that increase this risk further include younger age at CHF risk, although significant modifiers that increase this risk further include younger age at anthracycline exposure, female sex, chest radiation, hypertension and diabetes.2,6

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/m²): 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/m² 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 for CHF).
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. 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. In a recent study, the prevalence of osteoporosis and osteopenia in patients experiencing moderate-severe cGVHD was 17% and 60%, respectively. 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. At least two studies have revealed a higher risk of fracture after auto-HCT versus allo-HCT. Finally, degree of bone loss after HCT does not seem to directly correlate with risk of fracture, 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.

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:
  o those with established osteoporosis (BMD T-score ≤ -2.5) or history of fragility fracture, and
  o 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. 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. 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. 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. 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 myelodysplastic syndrome and AML). The cumulative incidence of t-MN is about 7% at 15 years post auto-HCT. 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). Unfortunately, outcomes of those who develop t-MN is poor.
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, genitals, breast exam for females, 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 (in women who have not received TBI), cervical, colorectal and prostate cancer should follow established Albertan/Canadian guidelines (www.screeningforlife.ca & for prostate cancer www.canadiantaskforce.ca).
- For women who have received TBI: screening mammography starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40.
- 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. Estimates of the cumulative incidence of CKD in the months and years after HCT vary widely at 7 to 48%. 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. In both the general population and the post-HCT population, 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. 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. These pathologies have been recently reviewed and are summarized from these sources in Table 1.
Table 1. Etiologies of chronic kidney disease after hematopoietic cell transplant

<table>
<thead>
<tr>
<th>Clinicopathologic Entity</th>
<th>Incidence</th>
<th>Risk Factors</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Most patients with CKD post HCT</td>
<td>-AKI after HCT -aGVHD &amp; cGVHD -High dose TBI -Hypertension</td>
<td>-None specific</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>2-21%</td>
<td>-TBI -Calcineurin inhibitor use -aGVHD &amp; cGVHD</td>
<td>-Microangiopathic hemolysis -Acute kidney injury, often with incomplete recovery of renal function leading to CKD</td>
</tr>
<tr>
<td>Nephrotic Syndrome (66% membranous and 19% minimal change)</td>
<td>1%</td>
<td>-cGVHD</td>
<td>-Associated with cGVHD -Proteinuria &gt;3.5g/24 hours -Hypoalbuminemia -Edema -Hyperlipidemia</td>
</tr>
<tr>
<td>BK Nephropathy</td>
<td>Rare</td>
<td>-Immunosuppression</td>
<td>-BK viremia</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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. 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). 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. 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. 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. Finally, it should be noted that several chemotherapeutic agents (such as BCNU, bleomycin, busulfan and methotrexate) may contribute to or cause pulmonary toxicity.

<table>
<thead>
<tr>
<th>Entity</th>
<th>Time of Onset</th>
<th>CT Imaging Features</th>
<th>PFT Features</th>
<th>Clinical Features</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis Obliterans</td>
<td>3 months-2 years post-HCT</td>
<td>-Air trapping -Bronchial thickening -Bronchiectasis -Centrilobular nodules</td>
<td>-Obstructive -Diagnosis per NIH criteria</td>
<td>-Extra-pulmonary cGVHD usually present -Asymptomatic early -Cough, dyspnea, wheezing</td>
<td>-Systemic and topical therapy per cGVHD guidelines</td>
</tr>
<tr>
<td>Organizing Pneumonia</td>
<td>Median 3 months post-HCT</td>
<td>-Diffuse consolidation or ground glass opacity</td>
<td>-Restrictive &gt; Normal &gt; Obstructive &gt; Mixed</td>
<td>-“Non-resolving infectious pneumonia” -Often in the setting of taper of immunosuppression for acute or chronic GVHD</td>
<td>-1 mg/kg prednisone with slow taper</td>
</tr>
</tbody>
</table>
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 nasopharyngngeal (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 q.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. Risk factors include younger age at HCT, radiation (neck, mediastinal or total body) and exposure to busulfan and cyclophosphamide. 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, 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. 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. 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. 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 in the “Reproductive system complications” chapter of these guidelines.

**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 per the “Reproductive system complications” section.

**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.41,42 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.

Acknowledgements

Dr. Emma Billington critically reviewed the bone health section & Dr. Brian Clarke critically reviewed the cardiovascular disease section.
References


Distribution of Microbially- Contaminated or Non-Conforming Cellular Therapy Products
Presented by: Andrew Daly

Summary

Upon notification of a potentially or confirmed microbially-contaminated cellular therapy product the recipient’s transplant physician will:

- Notify the recipient of the non-conformance and ensure the recipient receives follow up care. This will be documented in the recipient’s medical record.
- Notify the donor transplant physician.
- Notify the Program Quality Manager.
- 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 613-296-6147. Registry personnel must notify the transplant centre of the Non-Conformance.

Upon notification of a potentially or confirmed microbially-contaminated 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.

Upon notification of a non-conformance (defined below) the recipient’s transplant physician will:

- Notify the recipient of the non-conformance and any potential management to mitigate risks associated with the non-conforming product. Document this discussion in the medical record.
- Institute treatment to reduce risks associated with the non-conforming product.

A non-conforming product investigation will be initiated by the Cellular Therapy Laboratory according to applicable SOP’s.

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 613-296-6147.

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.
Nutrition Support in Hematopoietic Cell Transplant
Presented by: Caitlin Wallis RD, Edward Walker RD, Rebecca Holmes RD

Summary

- Hematopoietic cell transplant patients are at risk of malnutrition.
- 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/m², except for those patients meeting these criteria during the expected period of stomatitis and for 7-10 days after resolution of stomatitis.

Background/Rationale (for doing things the way you propose)

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, dysguesia, nausea, vomiting, and diarrhea. 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, which is the defined criteria in the literature for inadequate oral intake among cancer patients. Decreased oral intake can lead to subsequent weight loss, which is associated with non-relapse mortality among HCT patients. Body mass index (less than 18.5kg/m², underweight) and weight loss were historically used to identify malnutrition, but are no longer considered effective markers on their own. Assessment and diagnosis of malnutrition is not always straightforward and requires dietitian involvement early in the transplant process. Malnutrition can be divided into categories of mild, moderate and severe. 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 or consume less than 60% of recommended nutritional intake for 2 weeks or more. 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, with considerable muscle loss occurring during a prolonged hospital stay. Malnutrition is associated with lower health-related quality of life, impaired functional ability, higher rates of infection, impaired wound healing, longer hospital length of stay, increased health care costs, and higher mortality.

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. 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). 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. Complications of parenteral nutrition may include refeeding syndrome, infection, thromboembolic events, hyperglycemia, cholestasis, hypertriglyceridemia, metabolic bone disease and acalculous cholecystitis.

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). Naso-enteric feeding tubes can contribute to both physical and psychological discomfort for the patient, due to the constant presence of the tube in the nose and throat, potential to cause irritation from friction and possibly more serious complications of nasopharyngeal lesions, sinuitis or reflux esophagitis, tube dislocation and/or movement within the nares and throat, and the tube presence being a reminder of illness. Additionally, 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.

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 and medication administration. 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. 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. Bolus feeding (gastric feeds only) may contribute to increased risk of aspiration and to increased incidence of diarrhea, depending on rate of formula infusion.

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 prevention of bacterial translocation from the GI lumen to the rest of the body, maintenance of gastrointestinal function and mucosal integrity, fewer infections, decreased length of stay and decreased financial cost. Nasogastric feeding tubes are associated with a lower risk of infection, but are associated with a higher risk of tube dislodgment and a poorer quality of life than percutaneous feeding tubes. Enteral nutrition may be discontinued for a number of reasons including nausea, vomiting, diarrhea, psychological intolerance, tube blockage or displacement.
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. 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. 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.

A paucity of recent studies demonstrated benefits of enteral nutrition over parenteral nutrition among allogeneic HCT patients, although the evidence is mostly from lower-quality observational studies. In a larger randomized controlled trial, Andersen et al. compared enteral nutrition to standard of care among patients receiving allogeneic stem cell transplants (~1/3 myeloablative conditioning chemotherapy, ~2/3 reduced intensity conditioning chemotherapy) and found that 43% of patients receiving myeloablative chemotherapy tolerated enteral nutrition for a median of 8 days and received a median of 73% of goal enteral nutrition calories and protein. The authors suggest that because patients tolerate enteral nutrition, it could be used in place of parenteral nutrition more frequently to the benefit of decreased costs and parenteral nutrition-related complications.

A large retrospective cohort study compared enteral nutrition, parenteral nutrition and inadequate nutrition among allogeneic HCT patients and found that enteral nutrition was associated with reduced non-relapse mortality and lower incidence of acute GVHD GI tract compared to the other two groups. Another retrospective cohort study that compared enteral and parenteral nutrition among allogeneic stem cell transplant patients showed a decreased risk of infection among those receiving enteral nutrition. A separate prospective cohort study compared enteral and parenteral nutrition among allogeneic stem cell transplant patients receiving myeloablative conditioning treatment found an association between enteral nutrition and improved neutrophil and platelet engraftment, protection from grade 3-4 acute graft versus host disease and improved overall survival. In contrast, parenteral nutrition was associated with increased early mortality and delayed platelet engraftment. A systematic review included the two aforementioned cohort studies and concluded that enteral nutrition may be superior to parenteral nutrition based on their results. A second systematic review included these same two observational cohort studies as well as a pilot study and a randomized study that ended prematurely and also 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.

Details of Standard Practice in Alberta

There are currently no standardized practice guidelines for the use of nutrition support in adult HCT patients in Alberta. In the pediatric population at the Alberta Children’s Hospital approximately 80% of HCT patients receive a nasogastric feeding tube for nutrition support during transplant. Of these,
approximately 50% -75% of the high intensity HCTs will also require parenteral nutrition as a supplement and/or as a bridge until the nasogastric tube can be reinserted and/or enteral nutrition reinitiated if the feeding tube remains insitu. Many of the pediatric HCT patients are discharged home on the Home Enteral Nutrition Program and patients unable to tolerate or those who refuse nasogastric feeds have longer hospital admissions.

Additional randomized controlled trials comparing enteral nutrition to oral and/or parenteral nutrition are unlikely to be conducted in this population. Given the possible beneficial effects of enteral nutrition noted in both the literature and practice at the Alberta Children’s Hospital, we propose an algorithm to guide the initiation of nutrition support among adult HCT patients in Alberta (Figure 1). We propose a trial of one year. The nutrition support algorithm should be discussed during the pre-transplant interview so that patients are aware of possible nutrition support during transplant. After one year of standard practice implementation, we will compare the following to the previous year:

- Number/percentage of patients who qualify for enteral nutrition as per algorithm criteria,
- Number/percentage of patients who qualify but decline enteral nutrition,
- Number/percentage of patients who fail enteral nutrition (i.e. vomit up tube),
- Number/percentage of patients receiving enteral nutrition,
- Median percentage of goal enteral nutrition tolerated,
- Day of treatment that enteral nutrition starts (i.e. day +5),
- Day of treatment that enteral nutrition ends (i.e. day +20),
- Length of time receiving enteral nutrition,
- Median weight loss,
- Percentage of patients needing top-up parenteral nutrition/no top-up,
- Time (in days) to platelet and neutrophil engraftment,
- Length of hospital stay (LOS),
- Number of infections during the first 100 days post-transplant (i.e. Clostridium difficile, bacteremias),
- Incidence of acute graft versus host disease,
- Day 100 overall survival,
- Patient-reported outcomes as measured by the Putting Patient’s First (PPF) scale.
Figure 1. Nutrition support algorithm for hematopoietic cell transplant (HCT) patients in Calgary, AB. Adapted from Beckerson et. al.\textsuperscript{35} and Andersen et al.\textsuperscript{42}

plt = platelets
References

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Additional Information
Abbreviations

- 2-CDA, 2-chlorodeoxyadenosine
- AAPI, 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)
- ACTH, adrenocorticotropic hormone
- ADL, activities of daily living
- aPML, acute promyelocytic leukemia
- ARR, annual relapse rate
- ASBMT, American Society for Blood and Marrow Transplantation
- ASCO, American Society of Clinical Oncology
- ASCT, autologous stem cell transplantation
- ATG, antithymocyte globulin
- AUC, area under the curve
- autoSCT, autologous stem cell transplant
- BAL, bronchoalveolar lavage
- BCC, bone cell transplantation
- BM, busulfan + melphalan
- BMA, bone marrow aspirations
- BMD, bone marrow 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 CyR or CCR, complete cytogenetic response
- CDC, Centers for Disease Control and Prevention
- CBEB or CBV, cyclophosphamide + etoposide + carbustine
- CGVHD, chronic graft-versus-host disease
- CHF, congestive heart failure
- CMML, chronic myelomonocytic leukemia
- CML, chronic myeloid leukemia
- CMV, cytomegalovirus
- CN, cyogenetically normal
- CNI, calcineurin inhibitor
- CNS, central nervous system
- CR, complete remission/response
- CR1, 1st complete remission
- CR2, second complete response
- CRBSI, catheter-related bloodstream infection
- CRe, early complete remission
- CReI, intracytoplasmic sperm injection
- CREST, calcinosiis of skin
- Csa, calcineurin
- CTC, computerized tomography
- CTMIV, cyclophosphamide + vincristine + doxorubicin + methylprednisolone
- CVS, central venous catheter
- Cy, cyclophosphamide
- CyARA-C, cytosine arabinoside + cytarabine
- Cy-ATG, cyclosporine + antithymocyte globulin
- CyR, cytogenetic response
- DEXA, dual energy X-ray absorptiometry
- DFS, disease-free survival
- DFU, donor lymphocytic infusion
- DLI, donor lymphocytic infusion
- DLT, donor lymphocytic transplantation
- DMF, disease modifying therapy
- EBER, EBV-encoded RNA
- EBMT, European Group for Blood and Marrow Transplantation
- ECOG, Eastern Cooperative Oncology Group
- ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis
- ELD, early diagnosis
- EMA, European Medicines Agency
- EORTC, European Organization for Research and Treatment of Cancer
- EPOP, extracorporeal photopheresis
- ESR, erythrocyte sedimentation rate
- ESRT, extracorporeal shock wave therapy
- FAP, accelerated phase
- FFD, failure-free survival
- FISH, fluorescence in situ hybridization
- FLC, free light chain
- FL, follicular lymphoma
- FLIP, follicular lymphoma international prognostic index
- FLU, fludarabine
- FNA, fine needle aspiration
- FSG, fibrous septal glomerulonephritis
- FVL, florid vascular lesion
- GCT, germ cell tumor
- GCSF, granulocyte colony stimulating factor
- GCTT, genetic counseling team
- GEL, genetic expression library
- GEM, gemcitabine
- GEMTAC, gemcitabine + etoposide + cyclophosphamide + thiopeta
- GIV, gram-negative infection
- GJ, gastrojejunal
- GIST, gastrointestinal stromal tumor
- GIV, gram-negative infection
- GIST, gastrointestinal stromal tumor
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.

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Conflict of Interest Statements
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## Revision History

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