Acute Myeloid Leukemia

Effective Date: July 2019

SUMMARY OF RECOMMENDATIONS

1) All patients being considered for therapy should undergo a bone marrow aspiration and biopsy as well as peripheral blood films to establish a diagnosis and prognosis.
    a. Immunophenotyping by flow cytometry should be performed for diagnosis and to determine a leukemia-associated immunophenotype (LAIP) if possible.
    b. Samples should also be sent for cytogenetics, including fluorescence in-situ hybridization (FISH) where appropriate.
    c. Molecular analysis should be sent.
2) Ancillary Tests:
    a. Organ function should be assessed including liver, kidneys, coagulation and cardiac function.
    b. Blood group and human leukocyte antigen (HLA) typing of patient and family should be done as soon as possible in transplant eligible patients.
3) A lumbar puncture, with the installation of intrathecal chemotherapy, should be performed if worrisome unexplained neurological symptoms are present without a mass lesion by imaging.
    a. Consider a screening lumbar puncture in cases of myelomonocytic or monocytic acute myeloid leukemia (AML) or in those with a presenting white cell count of >40 x 10^9/L.
4) AML classification and risk stratification and transplant eligibility should be ascertained for all patients using age, performance status, World Health Organization (WHO) classification, cytogenetic and molecular risk group, as well response to therapy including minimal residual disease when possible. In the appropriate situations, establishing whether a genetic change is germline should be pursued.
5) Supportive care:
    a. In patients undergoing intensive chemotherapy a central venous catheter ideally should be placed.
    b. Red blood cell transfusions for symptomatic anemia.
    c. Platelets should be transfused at a threshold of 10 x 10^9/L if there is no evidence of bleeding or to keep a platelet level of around 50 x 10^9/L if there is active bleeding.
    d. Tumor lysis prophylaxis should be initiated in all patients.
    e. Antifungal prophylaxis should be considered during all phases of chemotherapy.
    f. Therapy of febrile neutropenia should include empiric broad spectrum antibiotics according to IDSA guideline.
    g. The use of growth factor support should be individualized.
    h. Steroid eye drops are recommended during the administration of intermediate to high dose cytarabine. These patients should also be screened for cerebellar toxicities before each dose of cytarabine.
    i. Sperm preservation should be discussed with male patients and a serum pregnancy test should be performed in female patients.
6) In transplant eligible patients treatment consists of induction and consolidation chemotherapy along with a FLT3 inhibitor in FLT3 positive cases
    a. Induction chemotherapy should consist of standard-dose cytarabine with an anthracycline
    b. Consolidation can consist of further cycles of chemotherapy alone or in association with a hematopoietic stem cell transplant depending on risk of relapse.
        i. Good risk – chemotherapy alone.
        ii. Intermediate risk – consider transplantation.
        iii. High risk – transplantation.
7) In transplant ineligible patients treatment options consist of palliation, low dose cytarabine, azacitidine or induction chemotherapy, depending on performance status and risk stratification. Strong consideration should be given to enrollment into a clinical trial.
8) In the instance of relapse re-induction chemotherapy can be considered depending on performance status, otherwise palliation should be instituted.

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team 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.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

BACKGROUND

Acute myeloid leukemia (AML) is a group of infrequent neoplasms responsible for a significant number of cancer-related deaths. Its incidence has been relatively stable over the last years at about 3.7 per 100 000 persons per year in the western world. It is primarily a disease of later adulthood with an increasing incidence with age. The median age at diagnosis is 65 years with a slight male preponderance. Outcome varies greatly according to age at diagnosis due to disease and patient features. Untreated AML is a uniformly fatal disease with a median survival of 11-20 weeks[1].

The etiology of AML in most cases is unclear. Known risk factors include exposure to chemotherapeutic agents particularly alkylating agents, topoisomerase-II inhibitors and anthracyclines as well as both therapeutic and nontherapeutic radiation. A higher than average incidence is seen in individuals with Down's syndrome, Klinfelter's syndrome, Ataxia telangectasia, Kostmann syndrome, neurofibromatosis or Fanconi anemia. Exposure to benzenes, pesticides, herbicides and cigarette smoking may also play a role in its development. There is also a greater incidence of AML in individuals with pre-existing hematologic disorders such as the myelodysplastic syndromes or myeloproliferative disorders.

GUIDELINE GOALS AND OBJECTIVES

- To delineate the diagnostic criteria for acute myeloid leukemias
- To delineate the prognostic markers in acute myeloid leukemias
- To identify the management options for acute myeloid leukemias in adults including chemotherapy, hematopoietic stem cell transplantation, and palliation

GUIDELINE QUESTIONS

- What is the optimal management of the acute myeloid leukemias in Alberta at the present time?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of the Alberta Provincial Hematology Tumour Team include hematologists, medical oncologists, radiation oncologists, nurses, hematopathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2008. This guideline was revised in 2015, 2017, 2018 and 2019.

SEARCH STRATEGY

The original guideline (2008) was generated using systematic literature searches of the Pubmed and Medlinedatabases, ASCO abstracts and proceedings, and ASH abstracts and proceedings databases. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and clinical trials. The 2015, 2017, 2018 and 2019 updates involved review of the Pubmed and Medline

databases for relevant information on a topic-by-topic basis. The ASH, ASCO and EHA abstracts and proceedings databases were also screened.

TARGET POPULATION

The following guidelines apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

DISCUSSION

Diagnosis

AML describes a heterogeneous group of clonal hematopoietic progenitor cell disorders with a spectrum of morphologic, immunophenotypic, cytogenetic and molecular characteristics. For a diagnosis of AML, a marrow blast count of ≥ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia.

Diagnostic Tests:
The diagnosis is often suspected and can at times be confirmed from the peripheral blood. However, all patients being considered for therapy should undergo a bone marrow aspiration and biopsy. Samples should be sent for morphology, flow cytometry, cytogenetics and molecular analysis. Immunophenotyping by flow cytometry confirms myeloid lineage and stage of differentiation of the malignant cell. It may have a prognostic role by establishing a unique phenotype for minimal residual disease monitoring, the leukemia associated immunophenotyped (LAIP). A full karyotype will be determined at diagnosis in all cases. Fluorescence in-situ hybridization (FISH) will also be carried out in cases morphologically suspicious for specific subsets. Molecular analysis will be carried out in cases suspicious for promyelocytic leukemia looking for the PML/RARα, in the core binding factor leukemias looking for c-KIT mutations, as well as in cases with normal karyotypes looking for FLT3, NPM1 and CEBPA mutations. Information regarding FLT3-ITD allelic burden should also be provided. Next generation sequencing (NGS) should be performed at diagnosis, particularly in patients being treated with curative intent, with a panel that includes these genes as well as RUNX1, TP53, KIT and ASXL1 (see below). If there is no aspirate sample obtained the ancillary studies should be attempted on a peripheral blood sample. NGS is also available on a case by case basis in relapsed or elderly patients. Results of FLT3 testing must be available by day 8 of initiation of induction chemotherapy (allelic burden can be provided later).

Diagnostic Criteria:
The threshold number of immature clonal cells, typically blasts, required to make the diagnosis of AML is 20% of total nucleated cells in the bone marrow by morphology. Exceptions include AML with t(8;21), inv(16), t(16;16) or t(15;17), in which the diagnosis of AML is made regardless of the percentage of bone marrow blasts[2]. *De novo* AML and acute erythroid leukemia should refer to patients with no clinical history of prior myelodysplastic syndrome, myeloproliferative disorder or exposure to potentially leukemogenic therapies or agents. Secondary AML should refer to patients with prior hematologic disease. Therapy related (t-AML) is a well-recognized clinical syndrome occurring as a late complication following cytotoxic therapy or radiotherapy for a primary neoplasm or a non-neoplastic disorder.

Epidemiological Distribution at Presentation:

There are four main groups of AML recognized by the WHO classification system: AML with recurrent genetic abnormalities (11% of cases), AML with myelodysplasia-related features (6% of cases), Therapy-related AML (2% of cases) and AML, not otherwise specified (81% of cases)[3,4]. AML can occur in people of all ages; however, it is most common in elderly patients. In rare circumstances AML can be caused by exposure to ionizing radiation and/or drugs that damage DNA. Anthracyclines and epipodophylloxtoxins which target topoisomerase II can lead to rapidly proliferative disease with monocytic histology and cytogenetic abnormalities at the MLL gene (11q23) months to 2 years after treatment[5]. Exposure to alkylating agents may lead to alkylator agent-induced disease, usually 5 to 6 years after exposure and characterized deletions in chromosomes 5 and 7 and by a myelodysplastic prodrome with complex karyotypes[6].

Classification

The blast count, lineage commitment, and level of differentiation of the neoplastic cells have long been the basis of AML classification. The WHO classification includes features such as genetic abnormalities at the chromosomal and/or molecular level and history of previous therapy or antecedent hematologic disease. The AML portion of the WHO classification of myeloid neoplasms was updated in 2016[3,7].

Table 1. Acute myeloid leukemia and related precursor neoplasms according to the WHO 2016 classification[3,7].

Categories
Acute Myeloid Leukemia with Recurrent Genetic Abnormalities AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1 AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11 APL with PML-RARA AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A AML with t(6;9)(p23;q34.1);DEK-NUP214 AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1 Provisional entity: AML with BCR-ABL1 AML with mutated NPM1 AML with biallelic mutations of CEBPA Provisional entity: AML with mutated RUNX1
Acute Myeloid Leukemia with Myelodysplasia-Related Changes
Therapy-Related Myeloid Neoplasms
Acute Myeloid Leukemia, Not Otherwise Specified (NOS) AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Pure erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis
Myeloid Sarcoma (syn.: Extramedullary Myeloid Tumor; Granulocytic Sarcoma; Chlorama)
Myeloid Proliferation Related to Down Syndrome Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder) Myeloid leukemia associated with Down syndrome
Blastic Plasmacytoid Dendtritic Cell Neoplasm
Acute Leukemias of Ambiguous Lineage Acute undifferentiated leukemia Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1 MPAL with t(v;11q23.3); KMT2A rearranged MPAL, B/myeloid, NOS MPAL, T/myeloid, NOS

Ancillary Tests

Routine chemistry should be performed to assess liver and kidney parameters (electrolytes, calcium, magnesium, phosphatase, creatinine, ALT (alanine aminotransferase), alkaline phosphatase, total and direct bilirubin and uric acid) as well as a coagulation tests (INR (international normalized ratio), PTT (partial thromboplastin time), Fibrinogen). Bloodwork for tumour lysis (LDH and uric acid) should also be determined. Blood group and human leukocyte (HLA) typing of the patient and the patient's family members should be performed if stem cell transplant is being considered.

Cardiac function should be assessed by echocardiogram, nuclear medicine cardiac scan, or cardiac MRI.

A lumbar puncture, with the installation of intrathecal chemotherapy, should be performed if worrisome unexplained neurological symptoms are present without a mass lesion by imaging. Consider a screening lumbar puncture in cases of myelomonocytic or monocytic AML or in those with a presenting white cell count of greater than 40 x 10^9/L. The lumbar puncture should be done after clearing of peripheral blood blasts with platelet transfusion support as necessary. If done prior to blast clearance and there are blasts in the cerebrospinal fluid (CSF) the Steiherz/Bleyer algorithm should be applied to determine the CNS (central nervous system) status as per in acute lymphoblastic leukemia (ALL)[8].

Definition of CNS Status

Table 2. Percent blasts

	Percent blasts (at least 200 cells counted)
M1	<5%
M2	5 – 25%
M3	>25%

Table 3. Cytology and CSF cell count

	CSF cell count and cytology
CNS1	No blasts on cytology
CNS2	<5/uL WBCs and cytology positive for blasts or Traumatic spinal tap with ≥ 10/µL RBCs, WBC ≥ 5/µL, cytospin positive for blasts but negative by Steinherz/Bleyer algorithm*
CNS3	≥ 5/µl WBCs, cytospin positive for blasts or Traumatic spinal tap with ≥ 10/µL RBCs, cytospin positive for blasts, and positive Steinherz/Bleyer algorithm*

*Steinherz/Bleyer algorithm method of evaluating traumatic lumbar punctures:
If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/µL and blasts, the following algorithm should be used to distinguish between CNS2 and CNS3 disease:

- CSF WBC/RBC > 2X Blood WBC/RBC

If clinically suspicious, consider performing viral serologies (HIV, HSV, VZV, CMV, Hepatitis B and C) or TB testing.

Abbreviations: RBC = red blood cell; WBC = white blood cell; HIV = human immunodeficiency virus; HSV = herpes simplex virus; VZV = varicella zoster virus; CMV = cytomegalovirus; TB = tuberculosis

Response Criteria[9]

- **Minimal residual disease (MRD)** is defined as the persistence of leukemic cells after chemotherapy at numbers below the sensitivity detection level of routine morphology[10]. Typically detected by polymerase chain reaction or flow cytometry.
- **Morphological leukemia-free state** – less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 500 nucleated cells
- **Morphological complete remission (CR)** has been defined using the following criteria developed by an International Working Group[9,11,12].

  - Normal values for absolute neutrophil count (>1000/µl) and platelet count (>100,000/µl), and independence from red cell transfusion
  - A bone marrow biopsy which is free from clusters or collections of blast cells. Extramedullary leukemia (i.e., central nervous system or soft tissue involvement) must be absent
  - A bone marrow aspiration reveals normal maturation of all cellular components (i.e., erythrocytic, granulocytic, and megakaryocytic series). There is no requirement for bone marrow cellularity
  - Less than 5% blast cells are present in the bone marrow, and none can have a leukemic phenotype (i.e., Auer rods). The persistence of dysplasia is worrisome as an indicator of residual AML but has not been validated as a criterion for remission status
  - The absence of a previously detected clonal cytogenetic abnormality (i.e., complete cytogenetic remission, CRc) confirms the morphologic diagnosis of CR but is not currently a required criterion. However, conversion from an abnormal to a normal karyotype at the time of first CR is an important prognostic indicator, supporting the use of CRc as a criterion for CR in AML[10,13,14]
- **Complete remission with incomplete recovery (CR_i)** – All CR criteria are met, however, residual neutropenia (<1.0 x 10^9/L or <1000/µl) or thrombocytopenia (<100 x 10^9/L or <100,000/µl)
- **Cytogenetic complete remission (CR_c)** – this category is recommended primarily for use in clinical research studies but likely to be informative
- **Molecular complete remission** – recognized as a therapeutic objective in acute promyelocytic leukemia but still controversial in other subsets

Treatment Failure

- **Resistant disease (RD)** – Failure to achieve CR or CRi (general practice; phase II/III trials), or failure to achieve CR, CRi or PR (phase I trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
- **Death in aplasia –** Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hydroplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
- **Death from indeterminate cause** – Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
- **Relapse** – a reappearance of leukemic blasts in the peripheral blood or greater than 5% blasts in the bone marrow not attributable to any other cause

Prognosis/Risk Stratification

Several factors influence the ability to achieve and maintain a complete remission in acute myeloid leukemia. The most important of these are **age** and **cytogenetic abnormalities** (see Table 4 and 5). **Molecular findings** (Table 6) are also emerging as having important significance. There is some evidence from a small prospective study which indicates that the presence of minimal residual disease is associated with a significantly elevated risk of recurrence in patients with core binding factor AML[15]. MRD may also have a role in determining whether or not stem cell transplant is appropriate after achieving first remission[16], however, further evidence is required. AML evolving from a myelodysplastic disorder or myeloproliferative disorder is often more resistant to cytotoxic chemotherapy than de novo AML. However,

it may also have a more indolent course. The need for greater than one cycle of induction chemotherapy to achieve a complete remission is also considered a poor prognostic factor.

Age:
Older patients have a higher prevalence of unfavorable cytogenetics and antecedent myelodysplastic/myeloproliferative disorders, higher incidence of multidrug resistance and an increased frequency of comorbid medical conditions that affect the ability to tolerate intensive treatment[17]. Even when standard chemotherapy is given outcomes are generally inferior to those achieved in younger patients[18].Treatment related mortality often exceeds any expected transient response in this group.

Cytogenetics:
Karyotype represents the single most important prognostic factor for predicting remission rate, relapse, and overall survival. Three groups of cytogenetic abnormalities have been defined with respects to these outcomes classified as favorable, intermediate and unfavorable risk. For example, in a retrospective review of 1213 (median age 52 years; 36% over age 60 years) AML patients treated on CALGB (Cancer and Leukemia Group B) protocols up to the year 2000, the 5-year survival rate was 55% for patients with favorable cytogenetics, 24% for patients with intermediate cytogenetics and 5% for those with poor risk cytogenetics[19]. This categorization holds whether the therapy includes stem cell transplantation or consolidation with chemotherapy alone[19-24]. See table 4 for the cytogenetic classification. Cytogenetics at diagnosis retain their independent predictive value in the older AML patient population[25,26].

Table 4. Cytogenetic Abnormalities in Acute Myeloid Leukaemia[27] adapted from [28]. Breakdown of important AML relevant genes with associated independent prognosis. See Table 5 below for important, clinical relevant combinations.

	French, American, and British Morphology	Affected Genes	Typical Average Age (yrs)	Approximate Incidence in de-novo AML	Outlook	Comments
t(8;21)	M2	RUNX1/ RUNX1T1	30	5-7%	Favourable	Auer rods usually present
t(15;17)	M3	PML/ RARA	40	5-8%	Favourable high cure rate with all-transretinoic acid-based therapy	Disseminated intravascular coagulation
t(11;17)	Similar to M3	ZBTB16/ RARA	Unknown	<1%	Poor response to all-trans retinoic acid-based treatment	n/a
abn(16q22)	M4 with eosinophilia	CBFB/ MYH11	35-40	5%	Favourable	High reinduction rate post relapse
abn(11q23)	M5	MLL and many partners	>50	3%	Poor, except t(9;11)	Hyperleucoytosis and extramedullary disease
+8	Varied	n/a	>60	~3% if +8 alone	Poor	Often associated with other chromosomal additions and deletions
del 5, del 7, 5q-, 7q-, or combinations	Varied; common in M6	n/a	>60	15-20%	Poor	Common in patients with secondary acute myeloid leukemia and prior myelodysplastic syndrome
Inv 3	Abnormal Megakaryocytes	RPN1/ MECOM	Unknown	<1%	Poor	Increased platelet count; other abnormalities common (del 5, 7)
abn(p17)	Varied	TP53	Probably <60	5%	Poor	Other abnormalities common; (del 5, 7; complex karyotype)
+13	Varied; sometimes undifferentiated	n/a	Probably >60	About 1-2%	Poor	High frequency of hybrid features
t(6;9)(p2;q34)	M2/M4 with basophilia	DEK/ NUP214	Unknown	<1%	Poor	Prominent basophilia
t(9;22)	Usually M1	BCR/ ABL1	Probably >50	About 1%	Poor (possible transformation of unrecognized CML)	Splenomegaly
t(1;22)	Often M7	RBM15/ MKL1	Infants (0-2 years)	<1%	Poor	Organomegaly
t(8;16)	M4 and M5	KAT6A/ CREBBP	Unknown	<1%	Poor	Erythrophagocytosis

Table 5. Clinically relevant cytogenetic classifications

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

Abbreviations: SWOG – Southwestern Oncology Group; MRC – Medical Research Council; abn - abnormalities

Molecular Abnormalities:
In addition to basic cytogenetic analysis, molecular markers are helping refine prognostic groups. These include FMS-like tyrosine kinase 3 (FLT3), c-KIT, nucleophosmin 1 (NPM1) and CEPBA. The most recent National Comprehensive Cancer Network (NCCN) guidelines recommend testing for these in all patients[29]. Recent European Leukemia Net (ELN) guidelines suggest testing as well for TP53, ASXL1 and RUNX1[30].

FLT3 mutations
The *FLT3* gene encodes an enzyme (*fms*-related tyrosine kinase 3) which belongs to the type III receptor tyrosine kinase family, and is mutated in about 30% of AML patients[31,32]. *FLT3* is expressed on the cellular surface and plays a role in proliferation, survival, and differentiation of hematopoietic progenitor cells[33]. *FLT3* internal tandem duplication (FLT3-ITD) mutations, which are seen in approx. 25% of AML cases, are a strong poor prognostic factor, with higher relapse rates and inferior long-term survival in AML patients, even with high-dose chemotherapy and allogeneic hematopoietic stem cell transplant[31,32,34-39].

The FLT3-ITD allelic burden also has an impact on prognosis; patients with a high allelic burden, as defined by a mutant:wild type ratio of > 0.5, have a very high relapse rate and therefore constitute an adverse prognosis group. In contrast, those with a low allelic burden (mutant:wild type ratio ≤ 0.5) have a relatively more favourable prognosis, particularly in the presence of a co-existing NPM1 mutation, and fall into an intermediate risk category[40-44]. FLT3- tyrosine kinase domain (TKD) point mutations are seen in approx. 5% of cases; the prognostic value of this mutation is less clear, but it does not clearly appear to have a poor prognostic value[45].

The development of *FLT3* inhibitors has been an area of much interest and promise[46-48]. The multikinase inhibitor midostaurin has been shown to increase complete remission rates and overall survival in FLT3 mutated patients when used in combination with 7 + 3 chemotherapy and HiDAC (high dose cytarabine) consolidation starting on day 8 of induction chemotherapy[49]. It has now been approved and is considered standard of care for AML patients with FLT3 mutations undergoing induction chemotherapy. FLT3 mutation analysis must therefore be available to act upon by day 8 after the initiation of induction chemotherapy.

NPM1 mutations
Nucleophosmin 1 also nucleolar phosphoprotein B23 or numatrin is encoded by the *NPM1* gene which is mutated in approximately 45-64% of cytogenetically normal AML patients. *NPM1* mutations lead to abnormal cytoplasmic localization of the protein, which typically functions as a chaperone in the nucleoli and acts in the control and regulation of the ARF-p53 tumor suppressor pathway. The *NPM1* mutation in AML patients is a favourable prognostic factor, associated with overall survival and relapse-free survival of approximately 60%[50-59]. However, this effect is mitigated by the presence of co-existing FLT3-ITD, and possibly by DNMT3A mutations, although there are conflicting data regarding the latter[60,61]. The presence of a co-existing low allelic burden FLT3-ITD lowers the survival to approx. 40%, while a high allelic burden FLT3-ITD lowers survival to 20-30%[40-44,53-55].

c-KIT mutations
c-KIT is a receptor tyrosine kinase which is expressed in 60-80% of myeloblasts[62]. It activates an important signaling pathway mediating cell proliferation and survival. c-KIT mutations are rare in most AML subtypes but are present in approx. 30% of core binding factor (CBF) AML, which includes t(8;21) and inv(16); these cases are associated with a higher relapse rate compared with non-c-KIT mutated CBF[63-65]. Because of this, these patients are frequently referred for allogeneic HSCT in first CR. However, a recent French GRAALL study found that, incorporating MRD testing post-cycle 2 of chemotherapy by qRT-PCR (see below) into a multivariate analysis, c-KIT mutation status was not an independent prognostic factor for relapse[66]. Therefore, if MRD monitoring is available, patients who achieve a >3 log reduction in RUNX1-RUNX1T1 or CBFB-MYH11 transcripts by qRT-PCR at the end of the second chemotherapy cycle could be serially monitored by qRT-PCR, without transplant.

CEBPA mutations
The CCAAT/Enhancer Binding Protein α (CEBPA) gene encodes a transcription factor which is mutated in 10-15% of AML patients, mostly with normal cytogenetics or 9q deletion[67,68]. Three different mutation patterns are typically reported in AML patients: (i) A single mutated allele (single mutation CEBPA, therefore heterozygous with wild type) (CEBPAsm) representing approximately 50% of CEPBA mutated AML cases. (ii) AML with two CEPBA mutations (double-mutated, typically biallelic, no wild type CEBPA expression (CEBPAdm). (iii) AML carrying a homozygous CEBPA mutation due to loss of heterozygosity (no wild type CEPBA expression)[69,70]. Favourable prognosis in CEBPA-mutated AML patients is typically restricted to those cases with biallelic CEBPA in the absence of other cytogenetic aberrations or FLT3-ITD[57,71]. The favourable prognosis associated with biallelic CEBPA mutations is mitigated by FLT3-ITD mutations[71,72,], although it is unclear whether this applies to all such mutations or only those with higher FLT3 allelic burden.

Other mutations
RUNX1 and AXSL1 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[73-76]. Similarly, TP53 and splicing factor mutations (e.g. SRSF2) have also been associated with independently adverse prognosis[77]. 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 favourable risk disease[30]. 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.

Germline mutations
It is now recognized that patients with certain inherited mutations carry a higher risk of developing AML and other myeloid neoplasms; some of these can be detected in standard myeloid panels. These include RUNX1, GATA2 and CEBPA[78]. Detection of one of these mutations in a younger patient should prompt germline mutation testing, using non-hematopoietic tissues such as buccal swabs or cultured fibroblasts. If a germline mutation is detected, any potential sibling donor should be tested, as this would present a theoretical risk of the donor marrow developing leukemia. TP53 mutations (as seen in Li-Fraumeni syndrome) predispose patients to the early development of a number of solid tumour malignancies; these patients are also at higher risk of developing AML or MDS with exposure to chemotherapy or radiation[78]. Therefore, detection of a TP53 mutation in patients with such a history should also prompt consideration of germline mutation testing.

Table 6. Molecular markers in acute myeloid leukemia, adapted from[79]

Gene	Function	Prevalence %	Prognosis
ASXL1	Chromatin modification	5–7	Poorer in NK
BCOR	Transcription factor	1–2	ND
biCEBPA	Transcription factors	5–10	Favorable especially in NK
CBL	Activated signaling	1–3	controversial
DNMT3A	DNA methylation	20–25	Adverse
EZH2	Chromatin regulation	1	Poor
FLT3-ITD	Activated signaling	25–30	Poor in NK
FLT3-TKD	Activated signaling	5–10	Variable according to study
IDH1	DNA methylation	5–7	Poorer in FLT3-ITD - neg AML
IDH2-R140	DNA methylation	7	Controversial
IDH2-R172	DNA methylation	2	Controversial
KIT	Activated signaling	4	Poorer outcome in CBF AML
KRAS	Activated signaling	5	Controversial
MLL-PTD	Chromatin modification	5	Adverse
NF1	Activated signaling	4	ND
NPM1	Transcription factor	30–35	Favorable in absence of FLT3-ITD and mutant DNMT3A
NRAS	Activated signaling	5–10	Neutral
PHF6	Transcription factor	3	ND
PTPN11	Activated signaling	5	ND
RUNX1	Transcription factor	5	Controversial
SF3B1	Spliceosome machinery	3	Favorable in secondary AML
SRSF2	Spliceosome machinery	2	Poor
TET2	DNA methylation	8–10	Poorer in normal karyotype
TP53	Tumor suppressor	5–10	Adverse
U2AF1	Spliceosome machinery	2	Poor
WT1	Tumor suppressor	5–9	Poor in NK
ZRSR2	Spliceosome machinery	<1	ND
Gene fusions			
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1		7	Favorable
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11		5	Favorable
AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A		1	Intermediate
AML with t(6;9)(p23;q34.1); DEK-NUP214		1	Poor
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM		1	Poor
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1		<0.5	Poor
Provisional entity: AML with BCR-ABL1		1	Poor

Abbreviations: AML= acute myeloid leukaemia; CN AML=cytogenetically normal acute myeloid leukaemia, ITD= internal tandem duplication. TKD= tyrosine kinase domain; APL= acute promyelocytic leukaemia; CBF AML = core binding factors acute myeloid leukaemia; NK = natural killer; ND = not determined

Myeloid neoplasms with germline predisposition

Although the majority of cases of MDS and AML are believed to arise de novo, there is currently increasing awareness of germline abnormalities predisposing to the development of myeloid malignancies (REF). The WHO classification has addressed these predisposing conditions in its recent revision, with a proposed approach to classification[80]. The myeloid neoplasms with germline predisposition are organized into (I) entities *without* an associated known disorder or organ dysfunction (with emphasis on germline *CEPBA* and *DDX41* mutations); (II) entities *with a preceding platelet disorder* (with emphasis on germline *RUNX1*, *ANKRD26* and *ETV6*); and (III) entities *with other associated/preceding organ dysfunction* (including germline mutations of *GATA2*)[80]. Of note, this rubric places the historical entities known to be associated with predisposition to myeloid malignancies, such as the bone marrow failure syndromes (e.g. Fanconi anemia, Dyskeratosis Congenita, etc.), and other inherited disorders (e.g. Down Syndrome, Noonan Syndrome, etc.), in subgroup (III).

(I) Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction
Acute myeloid leukemia with germline *CEBPA* mutation
Myeloid neoplasms with germline *DDX41* mutation
(II) Myeloid neoplasms with germline predisposition and pre-existing platelet disorders
Myeloid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid neoplasms with germline *ETV6* mutation
(III) Myeloid neoplasms with germline predisposition and other organ dysfunction
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms associated with bone marrow failure syndromes, including: • Fanconi anemia • Severe congenital neutropenia • Shwachman-Diamond syndrome • Diamond-Blackfan anemia • Telomere biology disorders (including dyskeratosis congenita and related syndromes)
Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome

Modified from [80]

The true prevalence of myeloid neoplasms with germline predisposition is uncertain, based largely on a lack of available population data; the WHO nevertheless describes these as relatively rare[80]. Despite the likely low prevalence of predisposing mutations in the general population, recent next-generation sequencing data suggest that germline mutations may be found in as many as 8.4–11.6% of AMLs and 12.9% of MPNs[81], which would equate to one in every 5-10 patients with a new diagnosis. There is vast variation in germline mutation prevalence by subgroup, however; Down syndrome associated AML, for example, accounts for up to 14% of pediatric cases of AML[82], whereas *DDX41* germline mutations are observed in an estimated 1.4%[83]. There are also notable differences in malignancy penetrance by germline event: the relative risk of development of a myeloid malignancy in patients with germline *CEBPA* mutations is estimated to be near complete, for example, whereas the risk of AML in patients with Dyskeratosis Congenita is far lower[80,84]. Finally, variable age of onset of disease may be seen across the

entities: patients with bone marrow failure syndromes may develop malignancies in early adulthood, whereas the mean age of onset of disease in patients with germline *DDX41* mutations is the seventh decade[80].

Population-based screening for germline mutations associated with increased risk of myeloid malignancies is not currently feasible, however advanced molecular testing might be considered in certain settings. Clinical suspicion for a myeloid neoplasm with germline predisposition may arise by way of specific clinical features:

Personal history of multiple cancers
Thrombocytopenia, bleeding propensity or macrocytosis preceding the diagnosis of a myeloid neoplasm by several years
A first or second degree relative with a hematological neoplasm
A first or second degree relative with a solid tumor suggestive of germline predisposition (e.g. early-onset breast cancer)
Physical exam features compatible with an inherited condition
Failure of a potential stem cell donor to mobilize using standard protocols

Modified from[80,85]

The possibility of germline predisposition might also arise in cases of myeloid neoplasia with specific mutational profiles, and some genetic changes cannot be discerned reliably as somatic or germline without confirmatory germline testing[86]. Variants in some genes established as germline predisposing factors may be acquired in the somatic context[86]. In the absence of tumor-normal paired testing (which is typical in hematologic neoplasms), germline variants tend to demonstrate heterozygous range variant burdens that remain fixed over time (and despite changes in tumor burden), tend not to be of high frequency in somatic mutation databases (with the potential for emphasis in germline variant databases), and tend to have specific functional implications[86]. Guidelines published by the American College of Medical Geneticists may be employed to assist in the assessment of a putative germline variant[87].

Patients considered high risk, either by clinical assessment or tumor-only variant profiling, should have confirmatory testing. In Alberta, comprehensive testing for myeloid neoplasms with germline predisposition is largely unavailable, and therefore the approach to confirmatory testing is mainly dictated by the putative gene or condition under consideration. If a patient is presenting with a possible bone marrow failure syndrome or aplastic anemia, recommended testing approaches are elaborated in a separate CKCM document (https://extranet.ahsnet.ca/teams/policydocuments/1/klink/et-klink-ckv-aplastic-anemia-adult-cancer-inpatient.pdf). These conditions require chromosomal breakage or telomere length studies (the latter performed in British Columbia). Confirmatory testing by next-generation sequencing for possible Fanconi Anemia is available through AHS Genetics & Genomics, however the common genetic variants associated with Dyskeratosis Congenita are not available as part of the AHS Genetics & Genomics comprehensive germline testing panel. Similarly, this panel can provide testing for *CEBPA*, *GATA2* and *RUNX1*, however the panel does not include test features for *DDX41*, *ANKRD26*, or *ETV6*. Testing using the AHS Genetics & Genomics comprehensive germline testing panel requires a specific requisition (https://www.albertahealthservices.ca/frm-20897.pdf). Send out testing to address the above genes not interrogable in Alberta must be organized through AHS Genetics & Genomics (https://www.albertahealthservices.ca/frm-18176.pdf); the University of Chicago offers a comprehensive familial myelodysplastic syndrome/acute leukemia panel

(https://dnatesting.uchicago.edu/tests/comprehensive-familial-myelodysplastic-syndromeacute-leukemia-panel)

Patients with an established familial germline predisposition syndrome should not be worked-up using comprehensive panels. Instead, testing tailored to the specific variant of interest should be organized through AHS Genetics & Genomics.

Determining if a genetic abnormality is germline or if a predisposing condition exits is important for genetic counselling with respects to other family members. It becomes particularly important if a hematopoietic stem cell transplant is being considered and donors are being sought within the family. In some rare instances such as Faconi anemia and Li Fraumeni syndrome (germline TP53 mutation) conditioning for the transplant would need to be altered to avoid excessive toxicity.

Minimal (measurable) residual disease
Early response to therapy is one of the most important prognostic factors in acute leukemia. Evaluation of minimal or measurable residual disease (MRD) is critical to identify patients at elevated risk of relapse which influences clinical decision-making. The leukemia associated immunophenotype (LAIP) of each patient should be established at diagnosis by multiparameter flow cytometry (MPFC), particularly if there is not a molecular abnormality to follow. Analysis of MRD by a properly validated technique performed locally is then recommended to be followed regularly by bone marrow aspirate until negative or the patient proceeds to transplantation.

A study in *de novo* (n=126) AML evaluated the utility of MRD in predicting relapse. Patients were segregated by their detectable levels of cells with LAIP at the remission determination bone marrow. The patients were split into very low risk (n=8), defined as having fewer than 10^{-4} LAP cells per sample, low risk (n=37), defined as having 10^{-4} to 10^{-3} LAP cells per sample, intermediate risk (n=64), defined as having fewer than 10^{-3} to 10^{-2} LAP cells per sample, and high risk (n=17), defined as having greater than 10^{-2} LAP cells per sample. No patients from the very low risk category relapsed during the time observed, whereas 14%, 50% and 84% of patients in the low, intermediate and high-risk group relapsed after 3 years, respectively (p=0.0001). Additionally, there were significant differences in overall survival (OS) between groups, with 100%, 90%, 62% and 29% rates after 3 years of follow-up (p= 0.003)[88].

Another study, by Perea and colleagues, evaluated the prognostic value of MRD amongst AML patients with favorable cytogenetics (t(8;21) and inv(16)) (n=55). MRD was evaluated by tandem RT-PCR (reverse transcription polymerase chain reaction) and flow cytometry. The group found that the mean amount of MRD detected by flow cytometry at the end of treatment in relapsed vs non-relapsed patients was significantly different (0.3% vs 0.08%, respectively; p=0.002)[89].

In a prospective, blinded study of pediatric patients (n=252) with *de novo* AML employing a multivariate analysis controlling for allogeneic marrow transplantation, age, sex, white blood count at diagnosis, presence of splenomegaly or hepatomegaly, and presence of more than 15% blasts in the marrow after the first course of induction (by flow cytometry), showed that patients with MRD, defined as ≥0.5% blasts, after one induction and one consolidation were 4.8-fold more likely to relapse (p<0.001) and 3.1-fold more likely to die (p< 0.001) when compared to MRD-negative patients[90].

A large multi-center prospective study (n=471) was designed to determine cut-off points for MRD in determining relapse rates. MRD was tested after induction cycle 1, cycle 2, and consolidation treatment in age <60 years patients with AML (Dutch-Belgian HOVON-SAKK study)[91]. The study demonstrated that in

patients with MRD (reported as % LAIP-positive cells) of >0.1% after induction cycle 1 and after two cycles of chemotherapy, there was a significant increases in relapse rates compared to those with lower or undetectable MRD levels. On multivariate analysis, MRD positivity after cycle 2 remained an independent prognostic factor for relapse[91].

Another prospective study (n=892) reporting findings from the United Kingdom National Cancer Research Institute AML 16 Trial evaluated the prognostic utility of MRD in elderly patients. MRD negativity amongst patients who achieved CR, was reported in 51% (n=286) of patients after first treatment, and 64% (n= 279) of patients after the second treatment, which was associated with a significantly better 3-year survival ($p < 0.001$ for both) and a significantly lower relapse rate ($p< 0.001$ for both) when compared to MRD-positive patients. Higher risk of early relapse was also reported amongst MRD-positive patients (median time to relapse 17.1 vs 8.5 months in MRD-negative patients)[92].

A retrospective study sought to investigate the prognostic utility of MRD in pre-hematopoietic cell transplant (HCT) patients. The study consecutively enrolled patients (n=99) receiving myeloablative HCT for AML in first morphologic remission. MRD was defined as any detectable level of residual disease. Two-year overall survival was 30.2% amongst MRD-positive patients versus 76.6% in MRD-negative patients and two-year relapse rates were 64.9% amongst MRD-positive patients versus 17.6% in MRD-negative patients. After adjustment for all or a subset of cytogenetic risk, secondary disease, incomplete blood count recovery, and abnormal karyotype pre-HCT, MRD-positive HCT was associated with increased overall mortality (HR 4.05, 95% CI: 1.90 to 8.62; $p <0.001$) and relapse (HR 8.49, 95% CI 3.67 to 19.65; $p <0.001$) when compared to MRD-negative HCT[93]. A subsequent report confirmed the poor prognosis and high relapse rate of patients with MRD detectable disease by MPFC just prior to transplant[160].

Molecular studies by quantitative RT-PCR can also be used for detection of MRD, with a sensitivity of 1 in 10^{-4}cells. The value of RT-PCR in core binding factor AML has already been discussed. NPM1 mutations can also be monitored by this technique[94,95]. A study by the UK NRCI found that persistence of detectable NPM1 transcripts after the second cycle of chemotherapy was associated with a higher risk of relapse (82% vs. 30%; hazard ratio, 4.80, $P<0.001$) and a lower OS (24% vs. 75%; hazard ratio for death, 4.38, $P<0.001$). This effect was seen even in patients with a co-existing FLT3-ITD mutation[73].

ELN guidelines have now been published[96], recommending that CR_{MRD} be included as a response designation. These guidelines also recommend that qRT-PCR be available for assessment of response for PML-RARA, RUNX1-RUNX1T1, CBFB-MYH11, and NPM1. For other AML patients, MRD assessment by multiparameter flow cytometry (MPFC) is recommended. Patients that fail to achieve a 3-log reduction in RUNX1-RUNX1T1 or CBFB-MYH11 transcripts, have detectable NPM1 transcripts or have $\geq$ 0.1% detectable disease by MPFC, following the second cycle of intensive chemotherapy (e.g. one induction and one consolidation) have high relapse rates. In these cases, consideration should be made to altering therapy. It was also recommended that serial monitoring by qRT-PCR be considered for those patients with RUNX1-RUNX1T1, CBFB-MYH11 or NPM1 who are not proceeding to transplant.

Not all of these tests are currently routinely available or uniformly reported in Alberta; our goal is to work toward implementing standardized MRD testing, based on these guidelines.

A recent study found that mutational profiling by NGS can also be used for MRD detection post-chemotherapy, and can be predictive of relapse[97], however, this is not currently recommended for MRD assessment outside of clinical trials.

Risk Groups as per Cytogenetic and Molecular Status

Table 7. Summary of AML Risk Groups (Adapted from European LeukemiaNet[30])

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD$^{low(c)}$ Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD$^{high(c)}$ Wild type NPM1 without FLT3-ITD or with FLT3-ITD$^{low(c)}$ (w/o adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A[d] Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[e] monosomal karyotype[f] Wild type NPM1 and FLT3-ITD$^{high(c)}$ Mutated RUNX1[g] Mutated ASXL1[g] Mutated TP53[h]

a. Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.
b. Prognostic impact of a marker is treatment-dependent and may change with new therapies.
c. Low, low allelic ratio (<0.5); high, high allelic ratio (>0.5); semi-quantitative assessment of FLT3-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve (AUC) "FLT3-ITD" divided by AUC "FLT3-wild type"; recent studies indicate that acute myeloid leukemia with NPM1 mutation and FLT3-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic hematopoietic-cell transplantation.
d. The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
e. Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, i.e., t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.
f. Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
g. These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
h. TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Treatment[29,98,99]

The initial goal of therapy for AML is to achieve a complete remission, given that a complete remission with currently available therapy is requisite, although not sufficient for a cure. It is the sole outcome currently associated with improved survival. Chemotherapy is the mainstay of treatment. Poor performance status and comorbid medical conditions, in addition to age, are factors which influence the ability of an individual to tolerate induction therapy.

In patients undergoing intensive chemotherapy a central venous catheter ideally should be placed.

Supportive care in all patients includes red blood cell transfusions for symptomatic anemia. Platelets should be transfused at a threshold of 10×10^9/L if there is no evidence of bleeding or to keep a platelet level of around 50×10^9/L if there is active bleeding.

Tumor lysis prophylaxis with allopurinol should be initiated in all patients. Monitoring for electrolyte abnormalities and renal function should be ongoing during the first few days of induction chemotherapy particularly in patients with significantly elevated white blood cell count. Rasburicase should be considered in those at high risk of significant tumor lysis.

Antifungal prophylaxis should be considered during all phases of chemotherapy depending on local incidence of invasive fungal infections[29,98]. In a large randomized trial in AML patients receiving induction and post-remission chemotherapy, posaconazole prophylaxis was associated with a lower incidence of invasive Aspergillosis and lower mortality compared with fluconazole or itraconazole[100]. Therapy of febrile neutropenia should include empiric broad spectrum antibiotics according to IDSA guidelines[101].

The use of growth factor support should be individualized and should be considered in those with documented life-threatening infections. Recent use of G-CSF can increase the blast count in a bone marrow specimen obtained to determine remission status, however immunophentoyping may be useful in this situation if the leukemic cells are known to have an abnormal phenotype. Pegylated growth factors have not been studied in this setting.

Steroid eye drops are recommended during the administration of intermediate to high dose cytarabine to prevent conjunctivitis. These patients should also be screened for cerebellar toxicities before each dose of cytarabine.

Sperm preservation should be discussed with male patients and a serum pregnancy test should be performed in female patients. Women should be given their options regarding fertility preservation.

Rare patients who present with extramedullary disease should be treated with systemic therapy. Local therapy (surgery/radiotherapy may be useful for residual disease).

Transplant Eligible Patients:

Table 8. Prognosis by European LeukemiaNet Risk group in Younger patients (<60 years of age)[102]

Risk	N	CR (%)	DFS (%)	OS (%)	Median DFS (years)	Median OS (years)
Favourable*	339	95	55	66	5.5	11.5
Intermediate I**	144	76	23	28	0.8	1.2
Intermediate II***	156	79	34	45	1.2	2.1
Adverse******	179	50	10	12	0.6	0.8

N=number of patients, CR=complete remission, DFS= disease free survival, OS=overall survival
* t(8;21)(q22;q22); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11, Mutated NPM1 without FLT3-ITD (normal karyotype), Mutated CEBPA (normal karyotype)
**Mutated NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 without FLT3-ITD (normal karyotype)
***t(9;11)(p22;q23); MLLT3-MLL, Cytogenetic abnormalities not classified as favorable or adverse
****inv(3)/(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, t(6;9)(p23;q34); DEK-NUP214, t(v;11)(v;q23); MLL rearranged, -5 or del(5q), -7, abnl(17p), Complex karyotype (three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions).

Induction

Chemotherapy should consist of standard-dose cytarabine with an anthracycline, so called 7&3 chemotherapy (see appendix A for regimens). Studies looking at higher doses of cytarabine in induction have not shown an increased CR rate but have demonstrated an increased treatment related mortality[103-105]. At count recovery or about day 28-35 from the start of chemotherapy a bone marrow aspirate should be done to determine remission status. The likelihood of establishing a CR with one cycle of induction chemotherapy varies amongst prognostic groups but overall is in the order of 60-70%. Consider repeating cytogenetic analysis if initially abnormal as part of the remission documentation[29].Other regimens such as FLAG (fludarabine + high-dose cytarabine + G-CSF) or NOVE (mitoxantrone + etoposide) may need to be considered in the case of significant left ventricular dysfunction.

Re-induction

If CR is not achieved after one cycle of induction chemotherapy another attempt is appropriate. This may consistent of a repeat of 7&3 chemotherapy or alternatively a different regimen such as NOVE, NOVE-HiDAC[80], FLAG-Ida (FLAG + idarubicin), or high dose cytarabine (HiDAC) (see appendix A for regimens) may be tried. A bone marrow aspirate and biopsy should be done at count recovery or day 30-35 to document remission status. The likelihood of a second regimen being successful is in the order of 50%. If no remission is achieved after 2 cycles of induction chemotherapy palliation may become the goal of care.

Consolidation

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. HiDAC is the mainstay of consolidation chemotherapy as there has been shown to be a dose intensity effect to cytarabine suggesting that HiDAC is beneficial in induction or consolidation[103,104]. 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.

- **Good 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[106-109].Our recommendation is 3-4 cycles of HiDAC post induction chemotherapy. A recent retrospective study from Edmonton and Vancouver found similar outcomes with 2 cycles of consolidation compared with 3[110], but this requires confirmation in a prospective study. There is also evidence that the addition of gemtuzumab ozogamicin (GO) may produce better outcomes when combined with chemotherapy[111]; however, this agent is not yet approved in Canada.

- **Intermediate risk patients**: HiDAC has been shown to be preferable over lower dose cytarabine in this cytogenetic group as well[26,107] 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[109,112-114]. The transplant related mortality gap between matched related and unrelated donors has been shown to be significantly reduced in recent years[115,116]. A suitable hematopoietic stem cell donor should be sought. If a matched sibling donor is found a related myeloablative stem cell transplant should proceed as soon as possible, ideally after one dose of HiDAC. If there are no suitable family donors, the patient should proceed through 3-4 cycles of HiDAC consolidation while a match unrelated donor is sought. If one is found before the third cycle of consolidation chemotherapy, consider matched unrelated donor stem cell transplantation.

- **High risk patients:** All efforts should be undertaken to find a matched donor, related or unrelated for eligible 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. If no fully matched donor is available consideration should be given to a haploidentical related transplant if a suitable donor is available. Finally, unrelated cord blood transplantation is also an option in selected situations.

FLT3 Mutation Positive Patients:
If not enrolled on a clinical trial with a FLT3 inhibitor, midostaurin should be added for these patients on day 8 of each induction and consolidation treatment cycle, as per the RATIFY clinical trial protocol (midostaurin and standard induction/consolidation chemotherapy). The Phase III RATIFY (CALGB 10603) trial randomized 717 AML patients with FLT3 mutation to receive standard induction and consolidation chemotherapy +/- midostaurin. After a median follow-up of 57 months, patients in the midostaurin arm had a significant improvement in median overall survival vs. placebo (74.7 months vs. 26 months, respectively; p=0.007), representing a 23% reduction in the risk for death[49]. It has now been approved by Health Canada for this indication.

Relapse:
- **Re-induction:** An attempt at achieving a second CR should be attempted. If the remission was greater than one year 7&3 chemotherapy can be used again. Otherwise other regimens such as FLAG-Ida, NOVE, NOVE-HiDAC, or HiDAC are appropriate. Participation in a clinical trial is encouraged.

- **Hematopoietic stem cell transplantation:** If a stem cell transplant was not done in first CR it should be undertaken once a second CR has been achieved. The ideal donor would be an allogeneic matched related or unrelated donor, or if necessary a related haploidentical donor or cord blood unit.

Palliation
If comorbid conditions affect the ability to proceed with optimal aggressive therapy, treatment with either low-dose cytarabine (LDAC) or azacitidine (VIDAZA®) is recommended as these have been shown to increase overall survival compared to supportive care alone[117,118]. Azacitidine is recommended for patients with 20-30% marrow blasts with dysplasia and for patients with adverse risk cytogenetics, based on two Phase III randomized trials[119,120]. For patients with >30% blasts and intermediate risk cytogenetics, LDAC and azacitidine have similar survivals[121]; LDAC has the advantage of lower cost and the potential for at-home administration.

The recommended dose of azacitidine is 75 mg/m^2/day subcutaneously for 7 days, every 28 days, for at least six cycles[122]. This is also an appropriate approach in the setting of primary induction failure not eligible for further intensive therapy, or relapse, particularly after allogeneic stem cell transplantation. It may also be considered in patients in CR after induction where aggressive chemotherapy for consolidation is no longer indicated. The most commonly used dosing for LDAC is 20 mg subcutaneously twice daily for 10 days[117], repeated every 4-5 weeks; 40 mg once daily may be used for home care administration. At least 4 cycles should be used, unless there is clear evidence of progression earlier. In patients not responding to LDAC, azacitidine may be utilized; however, LDAC does not appear to be effective in azacitidine failures.

For patients not able or willing to receive these treatments, or not responding to these, supportive care alone is appropriate, with hydroxyurea to control circulating blast counts.

Transplant Ineligible Patients:
Table 9. Prognosis by European LeukemiaNet Risk factor in Elderly patients (≥60 years of age)[102]

Risk	N	CR (%)	DFS (%)	OS (%)	Median DFS (years)	Median OS (years)
Favourable*	145	83	24	33	1.1	1.6
Intermediate I**	136	61	10	11	0.6	0.9
Intermediate II***	229	63	11	16	0.7	0.9
Adverse ******	229	39	6	3	0.5	0.5

N=number of patients, CR=complete remission, DFS= disease free survival, OS=overall survival
* t(8;21)(q22;q22); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11, Mutated NPM1 without FLT3-ITD (normal karyotype), Mutated CEBPA (normal karyotype)
**Mutated NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 without FLT3-ITD (normal karyotype)
***t(9;11)(p22;q23); MLLT3-MLL, Cytogenetic abnormalities not classified as favorable or adverse
****inv(3)/(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, t(6;9)(p23;q34); DEK-NUP214, t(v;11)(v;q23); MLL rearranged, -5 or del(5q), -7, abnl(17p), Complex karyotype (three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions).

In patients with a normal karyotype, the remission rate on older patients is 50-60% with cytarabine combined with idarubicin, daunorubicin or mitoxantrone. In those with adverse risk cytogenetics the chance of achieving a remission is approximately 25%, with median OS of approximately 6 months[25,26,123]. Attempts to modify this by adjusting the chemotherapy regimens, adding growth factors or multidrug resistance protein regulators have not been successful[17,124-126]. Due to the poor outcomes in this group, clinical trials are particularly important. However, if none are available, azacitidine would be appropriate therapy in older patients with high-risk cytogenetics who are not considered candidates for allogeneic HSCT. In other elderly non-fit patients, low-dose cytarabine would also be appropriate

Induction
In patients with an ECOG performance status of 2 or less and no prohibitive comorbid conditions, standard 7&3 induction chemotherapy is appropriate[127], particularly in patients with core-binding factor leukemias. If consideration is being given to consolidation therapy or re-induction in the case of primary induction failure, a bone marrow aspirate should be performed to document remission. If no further therapy is planned this can be omitted.

Consolidation
Consolidation chemotherapy in this group of patients is controversial. There is evidence to suggest that low-dose, prolonged ambulatory treatment should be preferred to intensive chemotherapy[123]; however intermediate dose cytarabine can be considered if the patient maintains a good performance status, normal renal function, and has a good or normal karyotype. Consolidation has not been shown to prolong survival in patients with high risk karyotypes. There is limited retrospective data which suggests azacitidine may be appropriate in this setting, although prior cytotoxic therapy was associated with a decreased marrow response rate, azacitidine treatment still prolonged overall survival[128]. LDAC may also be considered in patients in CR who are not suitable candidates for further intensive chemotherapy.

Relapse
In this age group, if acute leukemia recurs palliation with best supportive care or azacitidine is indicated if there are no available clinical trials.

Mixed-Phenotype Acute Leukemia:
Mixed-phenotype acute leukemia (MPAL) is rare, accounting for less than 5% of acute leukemia cases[7]. Treatment approaches to MPAL vary, as there is no standard therapy for patients. Typical, treatment may include AML-type induction therapy, ALL-type induction therapy, or a hybrid combination of AML/ALL-type induction regimen[129]. An early allogeneic hematopoietic cell transplant should be considered for these patients. It should be noted that data regarding the treatment of MPAL is largely retrospective in nature, with limited studies available for review.

One international retrospective study of 100 children and adults with MPAL defined by the 2008 WHO classification reported a 5-year survival rate of 37% (median survival 1.5 years)[130]. Treatment was selected by the managing physician and information regarding the treatment choice by age group was not presented. Age >15, Philadelphia chromosome positive leukemia, and AML-type induction treatment approaches were associated with significantly reduced median survival. Data from this study is summarized below.

Table 10. Treatment Approaches and Outcomes for Mixed-Phenotype Acute Leukemia (Retrospective data, both children and adults)[130]

Treatment Approach	Patients	CR (%)	Treatment-Related Deaths	Median Survival (months)
ALL-type induction	27	85	0	139
AML-type induction	34	41	3	11
AML/ALL hybrid induction	5	60	2	N/A

CNS Prophylaxis/ Disease Treatment[131]:
Involvement of the central nervous system at the time of AML diagnosis is rare (occurring in approximately 3% of cases), and routine evaluation is not recommended in asymptomatic patients. Development of CNS involvement during treatment is also rare. CNS involvement may be more common in AML patients with a prominent monocytic component, acute promyelocytic leukemia in systemic relapse, AML with inv(16) or chromosome 11 abnormality, in those with hyperleukocytosis (WBC > 40), or an elevated lactate dehydrogenase[132-134], however, it remains unclear whether all of these risk factors still apply to patients treated with modern induction regimens.

Symptoms of increased intracranial pressure, cranial nerve palsies, symptoms of CNS hemorrhage, symptoms of spinal cord compression and/or visual changes indicate potential CNS involvement. Mass lesions are uncommon, although reported at a higher frequency in inv(16) patients[132]. Diagnosis of CNS leukemia is typically confirmed by the identification of leukemic blasts on cytocentrifuge preparations of cerebrospinal fluid after lumber puncture.

No prospective studies comparing intrathecal chemotherapy, systemic chemotherapy and/or cranial radiation have been reported to guide treatment in patients with CNS leukemia. Intrathecal chemotherapy with methotrexate (12 to 15 mg/dose) or cytarabine (50-70 mg/dose) is a common approach. Systemic high dose methotrexate or cytarabine in combination with diaziquone has been shown to achieve clearance of the CNS tumour load[135], however, even after successful therapy, treatment in this setting is associated with high relapse rates[136]. Patients with cranial nerve involvement or a tumour mass that impinges on important structures may require initial radiation therapy (18 to 25 Gy for the brain) followed by intrathecal chemotherapy[136,137].

In patients with neurological symptoms imaging should be done to rule out a mass or bleed. If neither of these is present a lumbar puncture should be done and sent for morphology as well as flow cytometry. If this is negative for leukemic cells initially it should be repeated if the symptoms persist. If it is positive, as per the diagnostic criteria in section 3, intrathecal chemotherapy should be administered twice a week concurrently with induction chemotherapy until the cerebrospinal fluid is no longer positive by morphology and flow cytometry. An additional 2 intrathecal treatments should then be administered. Intrathecal chemotherapy should consist of alternating single agent cytarabine and methotrexate or “triple therapy” with cytarabine, methotrexate and hydrocortisone.

In patients with myelomonocytic or monocytic leukemia as well as those with a presenting blast count of greater than 40 $x10^9$/L consider a screening lumbar puncture at diagnosis with intrathecal chemotherapy administered at the same time. If the cerebrospinal fluid is positive for leukemic cells the patient should be treated as above.

Follow Up

Once all therapy is completed no further bone marrow aspirates are indicated unless there is concern of relapse or loss of graft in transplanted patients. Regular complete blood counts should be performed every month for the first few years then every 3 months until 5 years. The risk of recurrence after 5 years is very low and hematological follow up can be stopped at that point. Patients should be reminded of the signs and symptoms of leukemia including those of anemia, thrombocytopenia and infection and instructed to seek medical attention at any point if these develop. If there is concern of a relapse at any point, a bone marrow aspirate and biopsy should be performed and the patient should be sent for all the appropriate diagnostic tests.

New Therapies

Gemtuzumab ozogamicin (GO) the anti-CD33 antibody carrying a toxic calicheamicin-γ_1 derivative, which after intracellular hydrolytic release, induces DNA strand breaks, apoptosis, and cell death was the first anti-cancer immunoconjugate to obtain regulatory approval in the United States. It was subsequently withdrawn from the US by Pfizer after results from the S0106 trial demonstrated no overall survival benefit, while reporting an increased rate of early mortality in the GO arm of patients 18-60 years old with *de novo* AML receiving 2 cycles of induction chemotherapy with daunorubicin/cytarabine with or without GO (6 mg/m^2)[105]. However, emerging data from other well controlled studies did report benefits from the addition of GO to chemotherapy, particularly when used in smaller fractionated doses[138-141]. A recent metanalysis of 5 randomized trials found an overall survival benefit for GO when added to intensive chemotherapy, most strikingly seen in patients with favourable risk cytogenetics, while those with adverse risk karyotypes did not benefit[111]. In September 2017 GO was approved by the FDA for this indication. It is currently under review by Health Canada (February 2019) and available via compassionate access.

CPX-351 (Vyxeos^R) is a nanoparticle formulation containing a fixed molar ratio of daunorubicin and cytarabine. A phase III randomized trial in previously untreated AML patients with secondary AML age 60-75 found that this agent was superior to standard 3+7 induction therapy[142], while no benefit was seen in another study in de novo[143]. It has now been FDA approved for the treatment of secondary AML as of August 2017; approval in Canada is pending however it is available on a compassionate basis.

The development of more potent second generation FLT3 inhibitors remains an area of active investigation. The second-generation inhibitors (quizartinib, gilteritinib, crenolanib) have produced CR rates in the 40% range as single agents in relapsed AML[144,145], but remain investigational. These agents are being actively investigated in combination with chemotherapy, both in the frontline and relapsed setting. Gilteritinib is now available by compassionate access.

Approximately 15-20% of AML patients have IDH1 or IDH2 mutations, which result in aberrant production of an oncoprotein, 5HG, which induces a block in cell differentiation. Enasidenib (AG221) is a selective oral IDH2 inhibitor that inhibits 5HG production and restores normal cell differentiation. Treatment with this agent in relapsed/refractory AML patients with IDH2 mutations has produced CR in approximately 30% of cases; responses may take up to 6 months to be seen[146]. This agent has now been approved by the FDA and Health Canada for this indication but not yet publically funded. It is available on a compassionate basis. Ivosidenib is a selective IDH1 inhibitor which has shown activity in IDH1 mutated disease in early clinical trials[147].

Another promising agent is venetoclax, a selective oral small molecule BCL-2 inhibitor. Although it has limited activity as a single agent, it has been found to synergize with chemotherapy agents in preclinical models. In a study by Wei et al, venetoclax 600 mg daily was given in combination with low dose cytarabine to patients with newly diagnosed AML not eligible to receive intensive induction chemotherapy[148]. Of the 82 patients evaluable, 44 (54%) achieved CR or CR with incomplete count recovery (CRi), demonstrating that this is an active combination in patients with newly diagnosed AML. Venetoclax in combination with azacitdiine or decitabine was evaluated in older patients with AML unfit to receive intensive chemotherapy. Of the 145 patients enrolled, 67%of patients achieved CR/CRi. The median duration of response was 11.3 months[149].

These regimens are now under evaluation in Phase III randomized clinical trials. Phase I studies are also ongoing adding it to intensive remission inducing chemotherapy. It has been approved by the FDA in patients over the age of 75 with de novo AML in combination with low dose cytarabine or hypomethylating agents as of November 2018.

Many other novel agents are currently in clinical trials in AML, including agents that target MDM2 (inhibition of which results in upregulation of p53, inducing apoptosis)[150], DOT1L (associated with MLL overexpression/rearrangements)[151], Polo-like kinase-1[152,153], and CXCR4[152,153]. A number of novel immunocongugates are also in clinical trials, targeting antigens expressed on AML stem cells such as CD123 and CLL1. CAR-T (chimeric antigen receptor) cell therapy is a novel form of immunotherapy which has produced remissions in many patients with chemotherapy-refractory ALL and lymphoma; early trials in AML are in progress.

Enrollment in trials with novel agents is strongly encouraged. It is our goal to have a clinical trial, investigating new agents or new combinations, applicable to every patient.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
abn	Abnormalities
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase (liver enzyme)
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
AUC	Area under the curve
CALGB	Cancer and Leukemia Group B
CBF AML	Core binding factor acute myeloid leukemia
CEBPA	CCAAT/Enhancer binding protein α
CEBPAdm	Double mutated CEBPA
CEBPAsm	Single mutation CEBPA
CMV	Cytomegalovirus
CN AML	Cytogenically normal acute myeloid leukemia
CNS	Central nervous system
CR	Complete remission
CR_c	Complete cytogenic remission
CR_i	Complete remission with incomplete recovery
CSF	Cerebrospinal fluid
DFS	Disease free survival
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
FISH	Fluorescence in-situ hybridization
FLAG	Fludarabine + cytarabine + G-CSF
FLAG-Ida	Fludarabine + cytarabine + G-CSF + idarubicin
FLT3	FMS-like tyrosine kinase 3 (molecular marker)
G-CSF	Granulocyte colony stimulating factor
GO	Gemtuzumab ozogamicin
HDAC	Histone deacetylases
HiDAC	High-dose cytarabine
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
IDSA	Infectious Diseases Society of America
INR	International normalized ratio
ITD	Internal tandem duplication
LAIP	Leukemia-associated immunophenotype
LAP	Leukocyte-associated phenotype
LDAC	Low-dose cytarabine
MDL	Myelodysplastic syndrome
MPAL	Mixed-phenotype acute leukemia
MRC	Medical Research Council
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network

ND	Not determined
NK	Natural killer
NOVE	Mitoxantrone + etoposide
NPM1	Nucleophosmin 1 (molecular marker)
OS	Overall survival
PML	Promyelocytic leukemia
PTT	Partial thromboplastin time
RARα	Retinoic acid receptor, alpha
RATIFY	Randomized AML trial in FLT3 in patients less than 60 years old
RBC	Red blood cell
RD	Resistant disease
RT-PCR	Reverse transcription polymerase chain reaction
SWOG	Southwestern Oncology Group
TB	Tuberculosis
TKD	Tyrosine kinase domain
VDRL	Venereal Disease Research Laboratory test
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organization

DISSEMINATION/IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

MAINTENANCE

A formal review will be conducted in 2019, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

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APPENDIX A: CHEMOTHERAPY REGIMENS

7&3

- Cytarabine 200 mg/m^2/dcontinuous infusion days 1-7(consider 100 mg/m^2/d if age ≥60)
- Idarubicin 12 mg/m^2/ or daunorubicin 60 mg/m^2/d days 1-3

NOVE

- Mitoxantrone 10 mg/m^2/d days 1-5
- Etoposide 100 mg/m^2/d days 1-5

NOVE-HiDAC

- Mitoxantrone 10 mg/m^2/d days 1-5
- Etoposide 100 mg/m^2/d days 1-5
- Cytarabine 1.5 g/m^2(1.0 g/m^2 if ≥age 60) every 12 hours on days 6-7.

FLAG-Ida

- Fludarabine 30 mg/m^2/d days 1-5
- Cytarabine 2 g/m^2/d days 1-5
- Idarubicin 8 mg/m^2/d days 1-3
- G-CSF 300 µm s/c od starting day 7

HiDAC

- Cytarabine 3 g/m^2 every 12 hours on days 1, 3 and 5

Intermediate Dose Cytarabine

- Cytarabine 1 g/m^2 every 12 hours on days 1, 3 and 5

Azacitidine

Azacitidine 75mg/m^2 s/c days 1-7 or days 1-5, 8,9

Low Dose Cytarabine

Cytarabine 20 mg s/c days 1-10 q 4-5 weeks
Cytarabine 40 mg s/c days 1-10 q 4-5 weeks

APPENDIX B: ECOG PERFORMANCE STATUS[136]

Table B1. ECOG (Eastern Cooperative Oncology Group) performance status

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to be or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.