Guideline Resource Unit
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Acute Myeloid Leukemia

Effective Date: May, 2024

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 including *FLT3* and myeloid driver mutation gene panel by next generation sequencing (NGS).

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 and International Consensus Classification (ICC) classifications, cytogenetic and molecular risk group, as well response to therapy including minimal residual disease when possible.

5. Somatic mutation testing should be done for hereditary myeloid mutation panels in patients with a family history of AML or MDS, or suggestive of inherited predisposing disorders, or mutations found on NGS that are suggestive of inherited predisposition with a high variant allele frequency.

6. Initial assessment should include a determination of the patient's fitness and eligibility for intensive induction chemotherapy. This should take into consideration the severity of major co-morbidities, overall frailty, and patient preference.

7. 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 30-50 x 10^9/L if there is active bleeding.
d. Coagulopathy should be aggressively managed with plasma and fibrinogen concentrates. In patients with suspected or confirmed acute promyelocytic leukemia, INR and PTT should be normalized and platelets corrected to 30 x 10^9 even in patients without active bleeding.
e. Tumor lysis prophylaxis and monitoring should be considered for all patients and individualized based on risk profile.
f. Antifungal prophylaxis should be administered during all phases of chemotherapy. Mould active prophylaxis is indicated during induction chemotherapy.
g. Therapy of febrile neutropenia should include empiric broad spectrum antibiotics according to IDSA guidelines and local sensitivity patterns.
h. The use of growth factor support should be individualized.
i. 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.

8. Fertility-preservation options should be discussed with all patients prior to beginning induction chemotherapy. A serum pregnancy test should be performed prior to initiating therapy in females of child-bearing age.

9. Treatment of previously untreated medically fit patients:
    a. In patients without adverse features at presentation (ex. Hyperleukocytosis, leukostasis, DIC), it is reasonable to delay the initiation of induction chemotherapy to await cytogenetic and molecular results when these results will influence the selection of the induction regimen.
    b. Induction and consolidation regimen selection (see appendix A for regimen details):
        - De novo AML with MDS-related cytogenetic or molecular abnormalities, secondary AML and therapy-related AML: induction and consolidation with liposomal daunorubicin and cytarabine (Vyxeos). FLAG-Ida is also an option.
        - AML with mutated *FLT3*: induction with 7+3+midostaurin, consolidation with high or intermediate dose cytarabine plus midostaurin. 1-2 doses of gemtuzumab ozogamicin (GO) may also be given in induction.
        - Favourable ELN risk groups with CD33 positive AML: Induction with 7+3+GO and consolidation with HIDAC or intermediate dose cytarabine + GO.
        - Intermediate ELN risk groups with CD33 positive AML: Induction with 7+3 +/- GO and consolidation with HIDAC or intermediate dose cytarabine +/- GO. GO should not be given in the consolidation cycle prior to transplant in CR1.
        - All patients not fitting the categories above: Induction with 7+3 and consolidation with HIDAC or intermediate dose cytarabine.

- Empiric induction regimen if cytogenetics and molecular are as of yet unknown and no clinical history of secondary or therapy-related AML (i.e. urgent start): 7+3+GO. GO may then be omitted after day 1 if the patient does not qualify (ex. *FLT3* mutation, adverse risk disease).
- Patients with impaired LVEF: FLAG induction if otherwise medically fit.

10. Risk is determined based of biological features (cytogenetic and molecular findings) as well as determination of measurable residual disease status (see 10). In general:
    i. Favourable risk – Chemotherapy without transplantation, unless other adverse features (e.g. MRD+, inability to administer planned therapy).
    ii. Intermediate risk – Transplantation in CR1 should be considered.
    iii. Adverse risk – Transplantation is recommended in CR1 if eligible.

11. Measurable residual disease (MRD) testing by qRT-PCR should be performed in all patients with core binding factor (CBF) and NPM1-mutated AML, preferably after the second chemotherapy cycle, either from peripheral blood or bone marrow, and at end of consolidation from the bone marrow. Patients with CBF not attaining at least a 3 log reduction in transcripts, or those who are NPM1 MRD positive, should be considered for transplant.

12. For older patients with intermediate or adverse risk cytogenetics in CR1 post-intensive chemotherapy and not proceeding to transplant in CR1, maintenance therapy with oral azacitidine is recommended.

13. In patients deemed medically unfit for intensive induction chemotherapy, or over age 75, the recommended treatment is azacitidine combined with venetoclax as induction followed by maintenance therapy with the same combination. Options for those unable to receive or declining this treatment include palliation +/- hydroxyurea or low dose cytarabine +/-venetoclax. Strong consideration should be given to enrollment into a clinical trial.

14. In patients with refractory disease or relapse, re-induction chemotherapy may be considered depending on fitness, performance status, biologic features and duration of first CR. Intensive re-induction should include a different regimen such as FLAG-Ida, although 3+7 reinduction may be considered if the CR1 duration was very long. If a FLT3 mutation is detected at relapse, gilteritinib is the preferred therapy. Azacitidine + venetoclax may also be considered for re-induction. Enrollment into clinical trials should be strongly considered if eligible, otherwise palliation should be instituted.

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. There are also inherited mutations in myeloid driver genes that can predispose to development of MDS and AML.

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 Question

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

Search Strategy

The original guideline (2008) was generated using systematic literature searches of the Pubmed and Medline databases, 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, 2019, and 2024 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

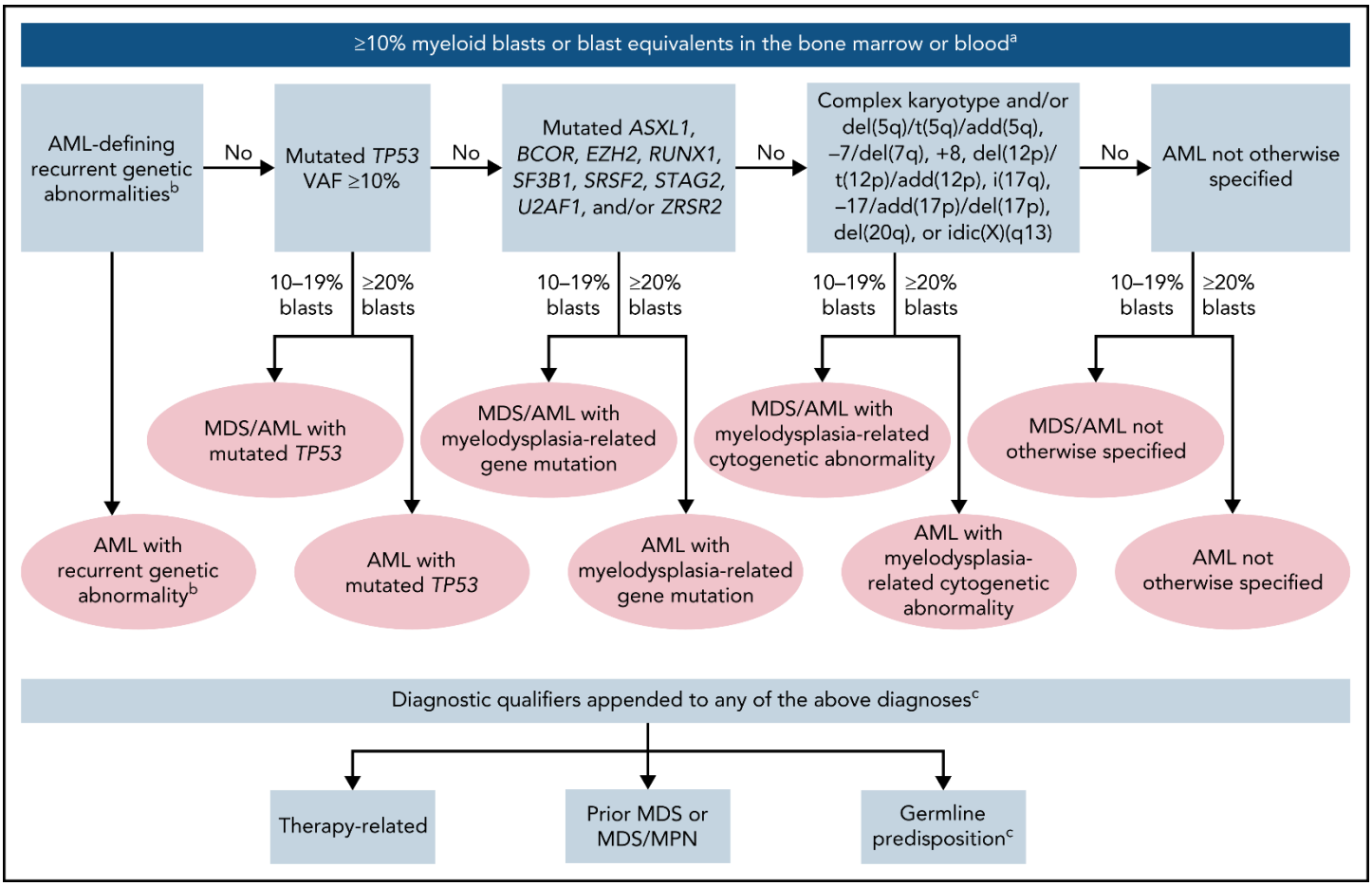
The following guidelines apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

Discussion

I. 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% has traditionally been 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. In 2022, the WHO 5th edition and ICC classification of hematopoietic neoplasms were published which have differing blasts requirements for diagnosis of AML, although both have defined groups of patients with specific genetic subtypes as having AML at a lower blast count or MDS/MPN with blasts less than 20%[2, 3]. Both classification systems highlight the integration of clinical, molecular, morphologic and immunophenotypic parameters for diagnosis of classification of AML and improve prognostication of disease as well as define treatment.

Figure 1. Hierarchical classification by the ICC of AML.[2]



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 and should also be done in relapsed or elderly patients where active therapy would be considered. Results of *FLT3* testing must be available by day 8 of initiation of induction chemotherapy (allelic burden can be provided later).

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).[4, 5] 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.[6] 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.[7] Some patients with germline mutations will have predisposition to development of MDS or AML, or solid tumours and personal and family history of malignancies is important to identify patients to be screened for these mutations.

II. Classification

The AML portion of the WHO classification of myeloid neoplasms was updated in 2022. There is a recognition of the subjective mature of morphologic assessment of dysplasia and increasing importance has been placed on cytogenetics and molecular mutations in the diagnosis and classification of AML. There are two different classifications that have been published with some differences between them; the ICC classification has been incorporated into the most recent ELN guidelines for diagnosis and management of AML. However, it is not yet clear which classification will be adopted in general and both are included here. If there are significant differences in the diagnosis based on which classification is used, having both classifications reported would be useful.

The ICC classifies patients with ≥10% blasts into hierarchical categories defined by 1) AML-defining recurrent genetic abnormalities (see table 1), then presence of mutated *TP53* VAF ≥10%, then mutations in specific myeloid driver genes, then karyotype, and finally into AML not otherwise specified (NOS). See Figure 1 for the ICC hierarchical classification.

Cases of prior MPNs are excluded and classified as accelerated (10-19% blasts) or blast phase (blasts ≥20%). For patients with an MDS/MPN diagnosis is made with blast count 20% however AML-type therapy is recommended once an AML defining recurrent genetic abnormality is detected. Cases with *BCR::ABL1* rearrangement and 10-19% blasts are classified as CML in accelerated phase and are blast phase if ≥20% blasts.

Previous separate AML entities have been changed to diagnostic qualifiers rather than separate categories of AML; i.e. AML with myelodysplasia-related cytogenetic abnormality, therapy-related; AML with myelodysplasia-related gene mutation, prior myelodysplastic syndrome, or AML with myelodysplasia-related gene mutation, germline *RUNX1* mutation (ie gene or syndrome should be specified).

Table 1. AML and related neoplasms and acute leukemias of ambiguous lineage.[2]

<table>
<tr><th colspan="2">AML and related neoplams</th></tr>
<tr><td>AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)*
▪ APL with t(15;17)(q24.1;q21.2)/PML::RARA†
▪ 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
▪ AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A‡
▪ AML with t(6;9)(p22.3;q34.1)/DEK::NUP214
▪ AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1)§
▪ AML with other rare recurring translocations‖
▪ AML with mutated NPM1
▪ AML with in-frame bZIP mutated CEBPA¶
▪ AML with t(9;22)(q34.1;q11.2)/BCR::ABL1*</td><td>Myeloid sarcoma
Acute leukemia of ambiguous lineage
▪ Acute undifferentiated leukemia
▪ MPAL with t(9;22)(q34.1;q11.2)/BCR::ABL1
▪ MPAL with t(v;11q23.3)/KMT2A-rearranged
▪ MPAL, B/myeloid, not otherwise specified
▪ MPAL, T/myeloid, not otherwise specified</td></tr>
<tr><td>Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB)
▪ AML with mutated TP53#
▪ AML with myelodysplasia-related gene mutations
Defined by mutations in ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2
▪ AML with myelodysplasia-related cytogenetic abnormalities**
▪ AML not otherwise specified</td><td>Myeloid proliferations related to Down syndrome
▪ Transient abnormal myelopoiesis associated with Down syndrome
▪ Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm</td></tr>
<tr><td colspan="2">Diagnostic qualifiers††
Therapy-related‡‡
▪ Prior chemotherapy, radiotherapy, immune interventions
Progressed from MDS
▪ MDS should be confirmed by standard diagnostics and >3 mo prior to AML diagnosis
Progressed from MDS/MPN (specify type)
▪ MDS/MPN should be confirmed by standard diagnostics and >3 mo prior to AML diagnosis
Germline predisposition (specify type)</td></tr>
</table>

The WHO has also published a classification system, and this has been adopted in many centres. This defines AML with specific genetic abnormalities separately from those defined by morphologic differentiation and eliminates the term AML NOS. For patients with specific AML-defining genetic abnormalities the 20% blast threshold has been eliminated. The defining genetic abnormalities between the two classifications are similar with several important differences. For example, in patients with *CEBPA* mutations, WHO 2022 includes biallelic (bi*CEBPA*) and single mutations located in the basic leucine zipper (bZIP) region of the gene (smbZIP-*CEBPA*) while ICC 2022 only includes in-frame bZIP *CEBPA* mutations. This distinction was made as recent studies have shown the favorable prognosis associated with *CEBPA* mutation is found mainly in patients with in-frame bZIP *CEBPA* mutations.[2]

Figure 2. Overview of WHO classification of AML.

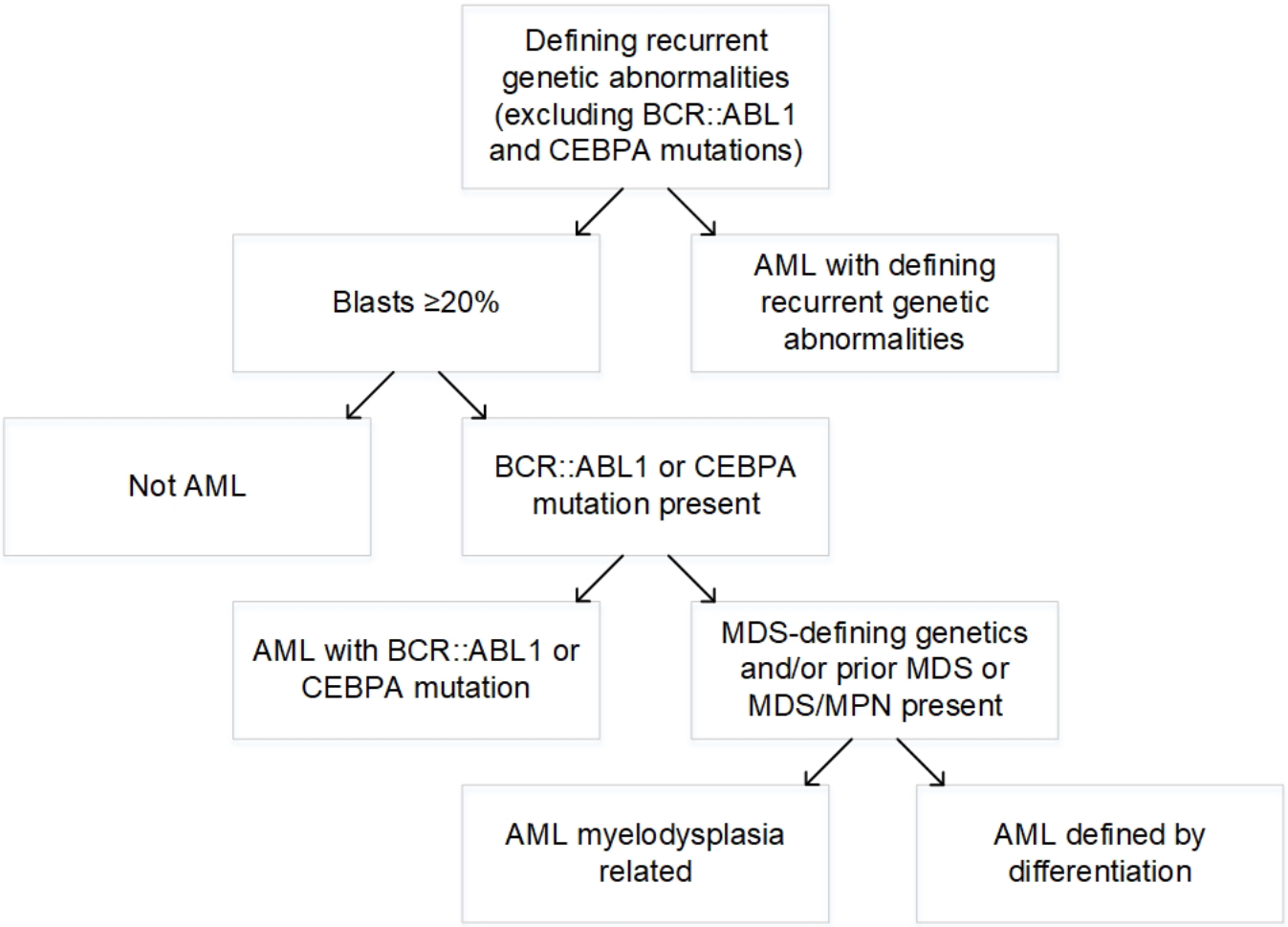


Table 2. Classification of AML by WHO 2022[3].

AML with defining genetic abnormalities
Acute promyelocytic leukemia with PML:RARA fusion
Acute myeloid leukemia with RUNX1::RUNX1T1 fusion
Acute myeloid leukemia with CBFB::MYH11 fusion
Acute myeloid leukemia with DEK::NUP214 fusion
Acute myeloid leukemia with RBM15::MRTFA fusion
Acute myeloid leukemia with BCR::ABL1 fusion
Acute myeloid leukemia with KMT2A rearrangement
Acute myeloid leukemia with MECOM rearrangement
Acute myeloid leukemia with NUP98 rearrangement
Acute myeloid leukemia with NPM1 mutation
Acute myeloid leukemia with CEBPA mutation
Acute myeloid leukemia, myelodysplasia-related
Acute myeloid leukemia with other defined genetic alterations
Acute myeloid leukemia, defined by differentiation
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute basophilic leukemia
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megaloblastic leukemia

Table 3. Cytogenetic and molecular abnormalities defining acute myeloid leukemia, myelodysplasia-related.

Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

Myeloid sarcoma is a tissue-based presentation of AML or transformed MDS, MPN or overlap disorder.

Secondary myeloid neoplasms are defined as secondary to cytotoxic therapy or germline predisposition, and if AML fits criteria for genetic mutations the qualifier should be added “post cytotoxic therapy” or “associated with germline variant.”

AML transformation of MDS or MDS/MPN are classified under AML-MR.

Ancillary Tests

Routine chemistry should be performed to assess hepatic and renal 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.

CMV IgG and IgM should be done as early as possible i.e. if possible before transfusions to obtain baseline CMV infection status.

Screen for pregnancy with bHCG in patients of childbearing potential.

HIV and hepatitis B cAb, hepatitis BsAG and hepatitis B sAb, hepatitis C Ab. Screening should be done for stronglyoides and TB in patients at risk of exposures or latent TB.

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).

Definition of CNS Status

Table 4. Percent blasts

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

Table 5. 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

III. Response Criteria[8]

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.[8-10]

- 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.[11-13]

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.

CR with partial hematologic recovery - patients with morphologic bone marrow blast clearance and partial recovery of both neutrophils (≥0.5 × 10^9/L [500/µL]) and platelets (≥50 × 10^9/L [50 000/µL]); other CR criteria need to be met. If CRh used, Cri should only include patients not meeting definition of CRh.

Molecular complete remission – recognized as a therapeutic objective in acute promyelocytic leukemia but still controversial in other subsets.

Treatment Failure

No response – Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS, or PR.

Refractory disease (RD) – Failure to achieve CR, CRh or Cri by a response landmark ie after 2 courses on intensive induction treatment or 180 days of less-intensive chemotherapy.

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 in at least 2 PB samples at least 1 weeks apart or development of new extramedullary disease.

CR, CRh, or CRi with MRD relapse - For patients initially achieving CR, CRh, or CRi without MRD, the term CR, CRh, or CRi with MRD relapse may be applied if there is evidence of MRD relapse as defined by ELN criteria (conversion of MRD negativity to MRD positivity, or increase of MRD copy numbers ≥1 log10 between any two positive samples).

IV. Prognosis/Risk Stratification

Several factors influence the ability to achieve and maintain a complete remission in acute myeloid leukemia. Significant factors include age, cytogenetic abnormalities, molecular driver mutation testing, and disease response to initial therapy, among others. Presence of minimal residual disease by flow cytometry and quantitative has been associated with worse prognosis, especially with core binding factor mutated AML and *NPM-1* mutated disease.[14] 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.

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.[15] Even when standard chemotherapy is given outcomes are generally inferior to those achieved in younger patients.[16] Treatment related mortality often exceeds any expected transient response in this group.

Table 6. 2022 ELN risk classification by genetics at initial diagnosis[17].

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

†Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.
‡Concurrent KIT and/or FLT3 gene mutation does not alter risk categorization .
§AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
‖Only in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.
¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
#Excluding KMT2A partial tandem duplication (PTD).
**Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
[a]TP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Molecular Abnormalities: In addition to basic cytogenetic analysis, molecular markers are necessary to refine prognostic groups. Karyotyping and Next Generation Sequencing panels for myeloid driver mutations are required as quickly as possible to determine AML subtype, optimal initial treatment, and remission consolidation i.e. ongoing chemotherapy or transplantation and role of maintenance. These results should ideally be available within 7 working days to determine initial therapy. *FLT3* mutation testing is done as a standalone PCR test and *NPM1* is required to determine initial treatment and should be available in a more rapid fashion. In certain cases, more complete molecular profiling, if available, may also influence upfront treatment decisions. In addition, presence or absence of various mutations may determine clinical trial eligibility for targeted therapies.

Germline mutations: It is now recognized that patients with certain inherited mutations carry a higher risk of developing AML and other myeloid neoplasms. Germline predisposition is now recognized as a Diagnostic Qualifier by the ELN for the diagnosis of AML.[17] In addition, the WHO defines subtypes of myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction (germline *CEBPA* P/LP variant, germline *DDX41* P/LP variants and Germline *TP53* P/LP variants), myeloid neoplasms with germline predisposition and pre-existing platelet disorders (germline *RUNX1* P/LP variant, germline *ANKRD26* P/LP variants, and germline *ETV6* P/LP variant), and myeloid neoplasms with germline predisposition and potential organ dysfunction (germline *GATA2* P/LP variants, bone marrow syndromes including Severe Congenital Neutropenia, Shwachman-diamond syndrome and Fanconi anemia, telomere biology disorders, RASopathies, Down syndrome, germline *SAMD9* P/LP variant, germline *SAMD9L* P/LP variants, biallelic germline *BLM* P/LP variant).[3] Some of these can be detected in standard myeloid NGS panels including *RUNX1*, *GATA2* and CEBPA[18] Detection of one of these mutations in a younger patient should prompt somatic mutation testing, using non-hematopoietic tissues such as buccal swabs or cultured fibroblasts. However, dedicated send out germline mutation testing beyond standard NGS myeloid panels is indicated for patients with the following risk factors by the ELN.[17]

Table 7. Indications for germline mutation testing beyond standard NGS panel.

Personal history of ≥2 cancers, 1 of which is a hematopoietic malignancy (order does not matter)
Personal history of a hematopoietic malignancy plus: • Another relative within two generations with another hematopoietic malignancy, or • Another relative within two generations with a solid tumor diagnosed at age 50 or younger, or • Another relative within two generations with other hematopoietic abnormalities
Presence of a deleterious gene variant in tumor profiling that could be a germline allele, especially if that variant is present during remission*
Age of diagnosis of hematopoietic malignancy at an earlier age than average (eg, MDS diagnosed ≤ 40 y)
Germline status of a variant is confirmed by: • Its presence in DNA derived from a tissue source not likely to undergo somatic mutation frequently (eg, cultured skin fibroblasts or hair follicles) AND at a variant allele frequency consistent with the germline (generally considered between 30-60%), or • Its presence in at least two relatives at a variant allele frequency consistent with the germline

*Certain gene alleles (eg, CHEK2 I200T and truncating DDX41 variants) are overwhelmingly likely to be germline and should prompt consideration of germline testing when identified even once.

It is important to note that some patients with hereditary mutations will present at an older age i.e. DDX41 and these tests may not be detected on typical NGS myeloid mutation panels. Testing for patients with a potential hereditary mutation should be done on skin fibroblasts to confirm if the mutation is somatic in nature. Genetic counselling should accompany this testing in clinic, and referrals made for this as well if indicated.

Presence of germline mutations can impact patient care if potential sibling donors are being considered for hematopoietic stem cell transplant. If a somatic mutation is found in a patient then any potential sibling donor should be tested, as this would present a theoretical risk of the donor marrow developing leukemia. For this reason, initiating hereditary panel testing when indicated as soon as

possible after diagnosis of AML is important to avoid transplant delays. In addition, presence of telomere mutations, chromosome fragility or *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.[19] Therefore, detection of a *TP53* mutation in patients with such a history should also prompt consideration of germline mutation testing and may determine choice of conditioning for potential stem cell transplant.

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 [link]. These conditions require chromosomal breakage or telomere length studies (the latter performed as send-out testing). Confirmatory testing by next-generation sequencing for possible Fanconi Anemia is available through AHS, however the common genetic variants associated with Dyskeratosis Congenita and hereditary mutation panels are not available as part of standard NGS myeloid panels and should be done as send out testing in conjunction with the Genetic Resource Centre [link]. It is helpful to get approval of testing in advance and notify them to expect samples as well as ensure it is received.

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 the Genetic Resource Centre if not available on local NGS panel.

V. Minimal (Measurable) Residual Disease

Early response to therapy is one of the most important prognostic factors in acute leukemia. Minimal or measurable residual disease (MRD) is defined as the detection of disease below the threshold of detection by standard morphologic techniques. MRD detection is critical to identify patients at elevated risk of relapse which may influence clinical decision-making. Detection may be performed by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) if a detectable mutation or fusion gene is present, or by multiparameter flow cytometry (MPFC) to detect a leukemia-associated immunophenotype (LAIP). PCR has a higher sensitivity ($\leq 1/10^4$) but is limited to those patients with identifiable mutations. MPFC is less sensitive ($1/10^{3-4}$) but is more broadly applicable as LAIP can be identified in 85-95% of cases. More recently, next generation sequencing (NGS) testing for myeloid associated mutations has also been evaluated for MRD detection. A limitation of all of these techniques is the potential emergence of small subclones with a different phenotype or genotype than the initial dominant clone, although this is usually not an issue with the available mutations detected by PCR techniques.

The main subtypes for which PCR-based detection is routinely available include PML-RARA (which is addressed in the APL guidelines), RUNX1-RUNX1T1 associated with t(8;21), CBFB-MYH11 associated with inv(16) and variants, and *NPM1*-mutated AML. MRD detection in these subtypes has been extensively evaluated and has been shown to predict for relapse.[20-22] One of the largest studies in core binding factor (CBF) AML was the French CBF-2006 trial, in which 200 patients were

assessed for MRD by qRT-PCR [90]. Patients who achieved at least a 3 log reduction in transcripts after 2 cycles of intensive chemotherapy (usually one induction and one consolidation) had a 22% cumulative incidence of relapse at 3 years compared to 54% in those not achieving this threshold ($p<0.001$). In multivariate analysis, a $\geq$ 3 log reduction in MRD was the only independent predictor of relapse; *KIT* mutations did not independently predict for relapse [90].

NPM1 mutations can also be monitored by qRT-PCR, and a number of studies have shown that MRD positivity by RT-PCR is highly predictive of relapse.[23, 24] A study by the UK NRCI found that persistence of detectable *NPM1* transcripts in peripheral blood (PB) after the second cycle of chemotherapy was associated with a higher risk of relapse (82%) vs. 30% for MRD negative patients (HR 4.80, P<0.001), and a lower OS (24% vs. 75%; HR 4.38, P<0.001). This effect was seen even in patients with a co-existing *FLT3*-ITD mutation.[23] A follow-up study from the same group found that, of 100 patients with persistent low copy number *NPM1* MRD at the end-of-treatment (EOT), defined as a transcript level <1%, who were not transplanted in CR1, 58% progressed by one year and 42% did not progress; some had a disappearance of transcripts with follow-up. Patients not achieving at least a 4.4 log reduction by EOT, or with concomitant FLT3-ITD, were at higher risk of relapse. Therefore, very low *NPM1* transcript levels do not always indicate imminent relapse, but are at higher relapse risk and require close monitoring. A more recent NCRI analysis found that patients who were MRD positive for NPM1 by qRT-PCR after cycle 2 benefitted from HSCT in CR1, while those who were MRD negative had no overall survival difference compared with those not transplanted[127].

MPFC has also been extensively evaluated and found to predict for relapse.[20, 25, 26] 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).[22] The study demonstrated that, in patients with MRD (LAIP-positive cells) of >0.1% after induction cycle 1 and after two cycles of chemotherapy, there was a significant increase 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.[25]

Another prospective study, reporting findings from the United Kingdom National Cancer Research Institute AML16 Trial, evaluated the prognostic utility of MRD in older patients undergoing induction chemotherapy. MRD negativity amongst patients who achieved CR was reported in 51% (n=286) of patients after first treatment cycle, and 64% (n= 279) of patients after the second cycle, 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. A higher risk of early relapse was also reported amongst MRD-positive patients (median time to relapse 8.5 vs. 17.1 months in MRD-negative patients).[26]

The prognostic utility of MRD in pre-hematopoietic stem cell transplant (HSCT) patients has also been evaluated. One study evaluated 99 patients receiving myeloablative HSCT 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% in MRD+ patients versus 17.6% in MRD-negative patients. After adjustment for cytogenetic risk, secondary disease, incomplete blood count recovery, and abnormal karyotype pre-HSCT, MRD-positive HSCT was associated with increased overall mortality (HR 4.05; p <0.001) and relapse (HR 8.49, p <0.001) when compared to MRD-negative patients undergoing HSCT.[27] A subsequent retrospective study confirmed the poor prognosis and high relapse rate of patients with MRD detectable disease by MPFC just prior to transplant[28]; the relapse risk (70%) in this study was comparable to that of patients with morphologically active disease at transplant. High levels of *NPM1* MRD by RT-PCR pre-HSCT has also been found to predict for a higher relapse rate.[29] A more recent report found that the increased relapse risk of pre-transplant MRD occurs across all 3 ELN2022 risk categories[link]. This relapse risk is most pronounced for patients undergoing reduced intensity conditioning (RIC) transplants[30], and may in some instances impact decision-making in terms of the type of pre-transplant conditioning used.

ELN guidelines for MRD testing were published in 2018[31] and were updated in 2021.[32] These recommended that CR_{MRD} be included as a response designation. These guidelines also recommend that qRT-PCR be available for assessment of response for RUNX1-RUNX1T1, CBFB-MYH11, and *NPM1*, after 2 cycles of chemotherapy in peripheral blood (PB), and at end-of-treatment in bone marrow (BM). For other AML patients, MRD assessment in BM by MPFC is recommended.

It was also recommended that serial monitoring by qRT-PCR be considered for those patients with RUNX1-RUNX1T1, CBFB-MYH11 or *NPM1* mutations who are not proceeding to transplant. Conversion of MRD negativity to positivity, or a > 1 log increase in transcript levels, if confirmed on repeat testing, indicates a risk of impending relapse.[33, 34] Although MRD monitoring can predict impending relapse and lead to pre-emptive treatment, including HSCT, prior to overt hematologic relapse, the impact of serial MRD testing on survival has not been clearly delineated, and the frequency of monitoring is unclear. A recent prospective randomized trial from the UK NCRI found that, for patients with both *NPM1* and *FLT3*-ITD mutations, serial monitoring for *NPM1* by RT-PCR every 3 months resulted in an overall survival benefit as compared with no monitoring[link]. For other patients, there was no OS benefit for serial molecular monitoring.

Mutational profiling by NGS can also be used for MRD detection after chemotherapy, and can be predictive of relapse,[35] however, this was not recommended by ELN for MRD assessment outside of clinical trials. NGS-based MRD testing for *FLT3*-ITD was also recently reported to be highly predictive of relapse,[30] and when performed pre-transplant has also been found to be predictive for both relapse and for benefit with gilteritinib maintenance therapy[128][link]. This test is not currently being used in Alberta but may become necessary if gilteritinib is approved as maintenance therapy based on the recent MORPHO study[link]. MRD detection after non-intensive induction with HMA+venetoclax, using MPFC, has also found to be predictive of RFS and OS.[36] The utility of MRD in the treatment

decision-making with non-intensive therapy is unclear, but may be useful in guiding decision-making for potential transplant candidates.

Recommendations

1. For patients with CBF or *NPM1*-mutated AML receiving intensive induction chemotherapy, MRD should be measured using qRT-PCR following the second treatment cycle using peripheral blood or bone marrow (if available) and should be repeated at the end-of-treatment bone marrow.

2. Patients with CBF not achieving at least a 3 log reduction by RT-PCR after 2 cycles of intensive chemotherapy are at higher risk of relapse and should be considered for allogeneic HSCT in CR1.

3. Patients with residual *NPM1* positivity by RT-PCR, either after 2 cycles of intensive chemotherapy or at end-of-treatment, are at higher risk of relapse and should be considered for allogeneic HSCT in CR1.

4. For other AML patients, MRD should be assessed using MPFC on the end-of-induction and end-of-treatment bone marrows. Patients with MRD positivity should be considered for HSCT in CR1, if not already being done.

5. For patients undergoing allogeneic HSCT, MRD should be assessed prior to transplant.

6. The evidence does not support the routine use of NGS for MRD detection or monitoring at this time. However, this may change as more sensitive detection techniques become available.

7. The evidence does not support using routine MRD monitoring after completion of chemotherapy. However, in certain higher risk situations, monitoring may be appropriate (e.g. *NPM1* mutation with concomitant *FLT3*-ITD mutation, CBF with *KIT* mutation, or those with residual low-level MRD positivity and not being transplanted in CR1). In these cases, monitoring of PB or BM every 3 months for at least one year would be reasonable. Reappearance of transcripts, or a $\geq$1 log increase, if confirmed on repeat testing, would warrant a change in therapy, including consideration of HSCT.

8. There is insufficient evidence to support the routine use of MRD testing with non-intensive therapy at this time. However, it may be indicated in patients being considered for HSCT, as it may influence the choice of conditioning regimen or the decision regarding whether to proceed with transplantation.

VI. Treatment[37-39]

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. Performance status, comorbid medical conditions and age are factors which influence the ability of an individual to tolerate induction therapy.

In patients undergoing intensive chemotherapy a central venous catheter 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 x 10^9/L if there is no evidence of bleeding or to keep a platelet level of approximately 50 x 10^9/L if there is active bleeding.

Tumour 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 tumor lysis.

Antifungal prophylaxis should be considered during all phases of chemotherapy depending on local incidence of invasive fungal infections.[37, 39] 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.[40]

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.

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

Cryopreservation of sperm should be discussed with male patients and a serum pregnancy test should be performed in female patients. Despite time-related barriers to fertility preservation in women with AML, fertility preservation options should be discussed.

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

Fit Patients

Table 8. Prognosis by 2022 European LeukemiaNet Risk group in patients receiving intensive induction in the multicentre Beat AML Cohort.[41]

Risk	N	CR/CRi (%)	OS (%)
Favourable	117	86	~65
Intermediate	92	59	~35
Adverse	136	49	~20

N=number of patients, CR/CRi=complete remission/complete remission with incomplete count recovery, OS=overall survival

Induction: Induction chemotherapy for AML has evolved beyond standard cytarabine plus anthracycline (7+3) for all patients. The specific induction protocol recommended now varies by AML subgroup and is summarized below. See appendix A for regimens:

1. **De novo AML with myelodysplasia-related changes (AML-MRC), secondary AML and therapy-related AML: Induction and consolidation with CPX-351 (Vyxeos^{R}).**[42-44] Vyxeos is a liposomal encapsulation of cytarabine and daunorubucin in a 5:1 molar ratio. A phase 3 trial randomized 309 patients (median age 67) in these AML subgroups to induction with Vyxeos versus a daunorubicin/cytarabine 7+3 regimen. Vyxeos was associated with a superior rate of CR/Cri (47.7% vs 33.3%), median overall survival (9.33 versus 5.95 months) and 5 year overall survival (18% versus 8%). A greater proportion of patients in the Vyxeos arm proceeded to allo-HCT (34% vs. 25%). Additionally, a landmark survival analysis from time of allo-HCT suggested that those who received Vyxeos experienced superior post-transplant survival (HR 0.46). The initial Vyxeos induction course consists of 100 units/m^2 on days 1, 3 and 5. A second induction course at 100 mg/m^2 on days 1 and 3 can be used for patients who do not achieve a CR/CRi after first induction. Consolidation consists of 65 units/m^2 on days 1 and 3. The UK NCRI AML19 trial randomized 189 somewhat younger patients (median age 56) with high risk AML (predominantly AML-MRC and secondary AML) to FLAG-Ida versus Vyxeos: while there was no difference in overall or event-free survival between the groups, relapse-free survival was significantly longer in the Vyxeos group (22.1 vs. 8.35 months). Additionally, in an exploratory subgroup of patients with MDS-related gene mutations, overall survival was significantly longer in the Vyxeos group (38.4 vs. 16.3 months)[129].

2. **AML with mutated *FLT3* (Internal tandem duplication (ITD) or tyrosine kinase domain (TKD) variants): Induction with 7+3+midostaurin and consolidation with HIDAC or intermediate dose cytarabine + midostaurin**. Midostaurin is added 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.[45]

3. **Other favourable or intermediate ELN risk groups with CD33 positive AML: Induction with 7+3+gemtuzumab ozogamicin (GO) and consolidation with HIDAC or intermediate dose cytarabine + GO.** GO is a humanized anti-CD33 antibody conjugated to a cytotoxic agent, calicheamicin. The ALFA-0701 trial randomized patients to 7+3+GO or 7+3 alone in patients age 50-70 years.[46] While CR rates in the 2 arms were similar (~70%), the 3 year event-free survival was superior in the GO group (39.8 vs. 13.6%). A subsequent meta-analysis of 5 randomized controlled trials totaling 3325 patients, including ALFA-0701, found that GO was associated with a reduced risk of relapse and superior 5-year relapse-free and overall survival. The survival benefit was seen in those with favourable and intermediate risk cytogenetics, but not those with adverse risk cytogenetics.[47, 48] A recent UK NCRI trial found that intermediate-risk AML patients age 60 and older who received 2 doses of GO with induction had an OS benefit post-allogeneic transplant[133]. This has not yet been studied prospectively in younger patients. A subsequent subgroup analysis of the ALFA study found that favourable or intermediate risk patients with certain signaling mutations, including *FLT3, NRAS, KRAS, PTPN11, JAK2, or CBL*, had an overall survival benefit with GO, while those with other mutations did not benefit[130]. Therefore, mutation profiling, if available, may allow refinement of the use of GO in these patients. The UK NCRI group found in their MIDOTARG trial that using 1-2 dose of GO combined with 3+7 and followed by midostaurin was safe, and produced higher levels of MRD negativity compared with patients not receiving GO[131]. These studies, although not definitive, suggest that GO may also benefit FLT3 mutated patients. The German AMLSG 09-09 study found that patients with NPM1 mutations have a higher likelihood of achieving MRD negativity and a lower relapse rate when GO is added to induction therapy[132]; a survival benefit in NPM1 mutated patients was also seen in the ALFA study[130]. This supports the routine use of GO in NPM1 mutated patients. In consolidation, GO is given in combination with HIDAC or intermediate dose cytarabine for up to 2 cycles. In patients planned for allogeneic hematopoietic cell transplant in CR1, GO should be omitted in the consolidation cycle prior to transplant, in order to minimize the risk of post-transplant veno-occlusive disease.

4. **All patients not fitting the categories above: Induction with 7+3 and consolidation with HIDAC or intermediate dose cytarabine.** With regards to cytarabine dosing in induction, studies examining higher doses of cytarabine have not shown an increased CR rate but have demonstrated an increased treatment related mortality.[49-51] 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 (see table 8 above). Consider repeating cytogenetic analysis if initially abnormal as part of the remission documentation.[39] Other regimens such as FLAG[134] (fludarabine

+ high-dose cytarabine + G-CSF) or NOVE (mitoxantrone + etoposide) may need to be considered in the case of significant left ventricular dysfunction.

Delaying induction chemotherapy to await cytogenetic/molecular data to allow for selection of the appropriate induction protocol: As described above, selection of an evidence-based intensive induction regimen requires, at minimum, cytogenetic (karyotype) and molecular (*FLT3*) data (unless there is a history that allows for a diagnosis of secondary or therapy-related AML). In Alberta, these results can be expected several business days after collection of the diagnostic bone marrow, leading to concerns around delays in initiating induction chemotherapy. A large German registry study examined whether delays in initiating intensive induction chemotherapy affects outcome in a population of >2000 AML patients [link]: Treatment delays of 0-5, 6-10, 11-15 and >15 days were equally not associated with remission rate and overall survival. This result should not be interpreted as meaning that it is broadly acceptable for patients to be delayed 15 or more days before starting induction chemotherapy. Indeed, the registry data revealed that patients presenting with adverse proliferative features (higher marrow blast count, higher white cell count, higher LDH) tended to be treated with minimal delay. Rather, it is reasonable to conclude that in patients presenting without adverse features (for example, elevated WBCs, high marrow blasts, elevated LDH, disseminated intravascular coagulation), a delay until cytogenetic and molecular data are available to guide induction protocol selection is acceptable. In those with adverse features, empiric induction with 7+3+GO is recommended, Day 4 and/or day 7 GO may be omitted once molecular and cytogenetic studies are resulted (for example, if there is an adverse risk karyotype or a *FLT3* mutation).

Refractory disease/re-induction: If CR is not achieved after one cycle of induction chemotherapy, re-induction is appropriate if performance status and organ function are adequate and if there are no uncontrolled infections. Re-induction may consist of a repeat of 7&3 chemotherapy or a different regimen such as NOVE, NOVE-HiDAC,[52] FLAG-Ida, high dose cytarabine (HiDAC), or VPCy (see appendix A for regimens). In those with AML-MRC, secondary AML or therapy-related AML, Vyxeos re-induction is also reasonable. Although there is significant interest in lower intensity re-induction regimens, such as venetoclax combinations, there is insufficient data at this time to recommend these in lieu of intensive re-induction, but may be considered if patients are unfit or decline intensive reinduction.[53] At this time, there is insufficient evidence to recommend one intensive re-induction protocol over another,[54, 55] thus decisions should be individualized based on patient and disease characteristics as well as institutional experience. 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 leading to CR is in the order of 30-50%. If no remission is achieved after 2 cycles of induction chemotherapy, curative outcome is unlikely and palliation may become the goal of care; although this decision should be individualized based on disease characteristics, patient age and comorbidities.

Gilteritinib for refractory FLT3 AML: An important exception to the above discussion of re-induction is those with *FLT3* mutated (ITD or TKD) AML. Gilteritinib, an oral FLT3 inhibitor, was compared to high intensity or low intensity salvage chemotherapy in those with refractory *FLT3* mutated AML (after

1-2 cycles of induction) in a phase 3 RCT.[56] Gilteritinib was associated with superior overall survival, a higher rate of CR/Cri, and less grade ≥3 adverse events versus either high intensity re-induction or low intensity therapy.

Consolidation: If CR has been achieved, then further therapy is necessary for potential cure. The nature of consolidation therapy must be individualized for each patient based on an 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.[49, 50] 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.

- **Favourable risk patients:** In patients with AML with t(8;21), inv 16 or *NPM1* mutation, 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.[57-59] MRD assessment is paramount to making decisions around the use of allo-HSCT in CR1 (see the MRD section for further details). In those not proceeding to allo-HSCT in CR1, our recommendation is 3-4 cycles of HiDAC plus GO. A recent retrospective study from Edmonton and Vancouver found similar outcomes with 2 cycles of consolidation compared with 3,[60] but this requires confirmation in a prospective study.
- **Intermediate risk patients**: HiDAC has been shown to be preferable over lower dose cytarabine in this cytogenetic group as well[58, 61] 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.[62-65] The transplant related mortality gap between matched related and unrelated donors has been shown to be significantly reduced in recent years.[66, 67] A suitable hematopoietic stem cell donor should be sought in all cases to aid in decision-making about HSCT. If a matched sibling donor is found, a related myeloablative stem cell transplant should proceed as soon as possible, ideally after one cycle of HiDAC. If there are no suitable family donors, the patient should proceed through 3-4 cycles of HiDAC +/- GO or midostaurin consolidation while a matched-unrelated donor is obtained. If no matched donor is available, the decision to proceed with a haploidentical or mismatched unrelated donor allo-HSCT should be individualized based on AML characteristics, patient comorbidities and patient preference.
- **Adverse risk patients:** All efforts should be undertaken to find a matched, haploidentical, or mismatched unrelated donor or cord blood unit for eligible patients. During the period of HSCT-donor search, the patient should receive ongoing cycles of HiDAC or Vyxeos consolidation (if secondary, therapy-related AML or AML-MRC) up to a total of 4 cycles.

Recommendations

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

2. Tumour lysis prophylaxis and monitoring should be considered for all patients and individualized based on risk profile.

3. Mold-active antifungal prophylaxis should be initiated with induction chemotherapy.

4. Fertility-preservation options should be discussed with women and men prior to beginning induction chemotherapy.

5. In patients without adverse features at presentation (ex. hyperleukocytosis, leukostasis, DIC), it is reasonable to delay the initiation of induction chemotherapy to await cytogenetic and molecular results when these results will influence the selection of the induction regimen.

6. Induction and consolidation regimen selection (see appendix A for regimen details):
   - De novo AML-MRC, secondary AML and therapy-related AML: induction and consolidation with Vyxeos. FLAG-Ida is also an option.
   - AML with mutated FLT3: induction with 7+3+midostaurin, consolidation with high or intermediate dose cytarabine plus midostaurin. 1-2 doses of GO can also be safely administered with this regimen.
   - Favourable ELN risk groups with CD33 positive AML: Induction with 7+3+GO and consolidation with HIDAC or intermediate dose cytarabine + GO.
   - Intermediate ELN risk groups with CD33 positive AML: Induction with 7+3 +/- GO and consolidation with HIDAC or intermediate dose cytarabine +/- GO. GO should not be given in the consolidation cycle prior transplant in CR1.
   - All patients not fitting the categories above: Induction with 7+3 and consolidation with HIDAC or intermediate dose cytarabine.
   - Empiric induction regimen if cytogenetics and molecular are as of yet unknown and no clinical history of secondary or therapy-related AML (i.e. urgent start): 7+3+/- GO. GO may then be omitted after day 1 based on cytogenetic and molecular results (e.g. FLT3 mutation, adverse risk disease).

7. Refractory disease/re-induction (see appendix A for regimen details):
   - If CR is not achieved after one cycle of induction chemotherapy, re-induction is appropriate if performance status and organ function are adequate and if there are no uncontrolled infections.

- There is insufficient evidence to recommend one intensive re-induction protocol over another, thus decisions should be individualized based on patient and disease characteristics as well as institutional experience.
- An exception is FLT3 mutated AML where single agent gilteritinib is superior to re-induction chemotherapy.

8. The decision to proceed with allogeneic HCT in CR1 should be individualized based on patient factors (preference, comorbidities, performance status), disease factors (disease risk, MRD if favourable risk disease) and donor availability.

VII. Maintenance

Based on the data from QUAZAR-AML-001 trial[68] the patients fulfilling all the following criteria benefited from oral azacitidine (ONUREG) maintenance treatment with prolonged overall and relapse free survival:

- Age ≥55\
- De novo or secondary AML
- In remission following intensive induction therapy +/- consolidation
- Intermediate or poor risk cytogenetics (Not based on molecular risk classification, i.e. patients with *NPM1*- mutated AML will also qualify and likely benefit the most)[link]
- Ineligible or not planned for HSCT
- Adequate bone marrow recovery with ANC≥0.5 and platelet ≥20

Exclusions:

- HSCT candidate
- CR/CRi following non-intensive treatment
- Advanced hepatic tumors (oral azacitidine is contraindicated in patients with advanced malignant hepatic tumors)[69] [link]
- AML associated with presence of t(8;21), inv(16)/t(16;16) or t(15;17) or t(9;22) karyotypes

This will therefore be offered to patients meeting the study enrollment criteria above. The optimal duration of maintenance therapy is unclear; for now it will be continued indefinitely until further data are available. However, these is no clear evidence that this treatment is curative, and in the QUAZAR study the OS curves merged after 4 years. It is not a substitute for transplant or consolidation therapy; however, it may be used if patients become unfit and are not considered suitable candidate for consolidation therapy.

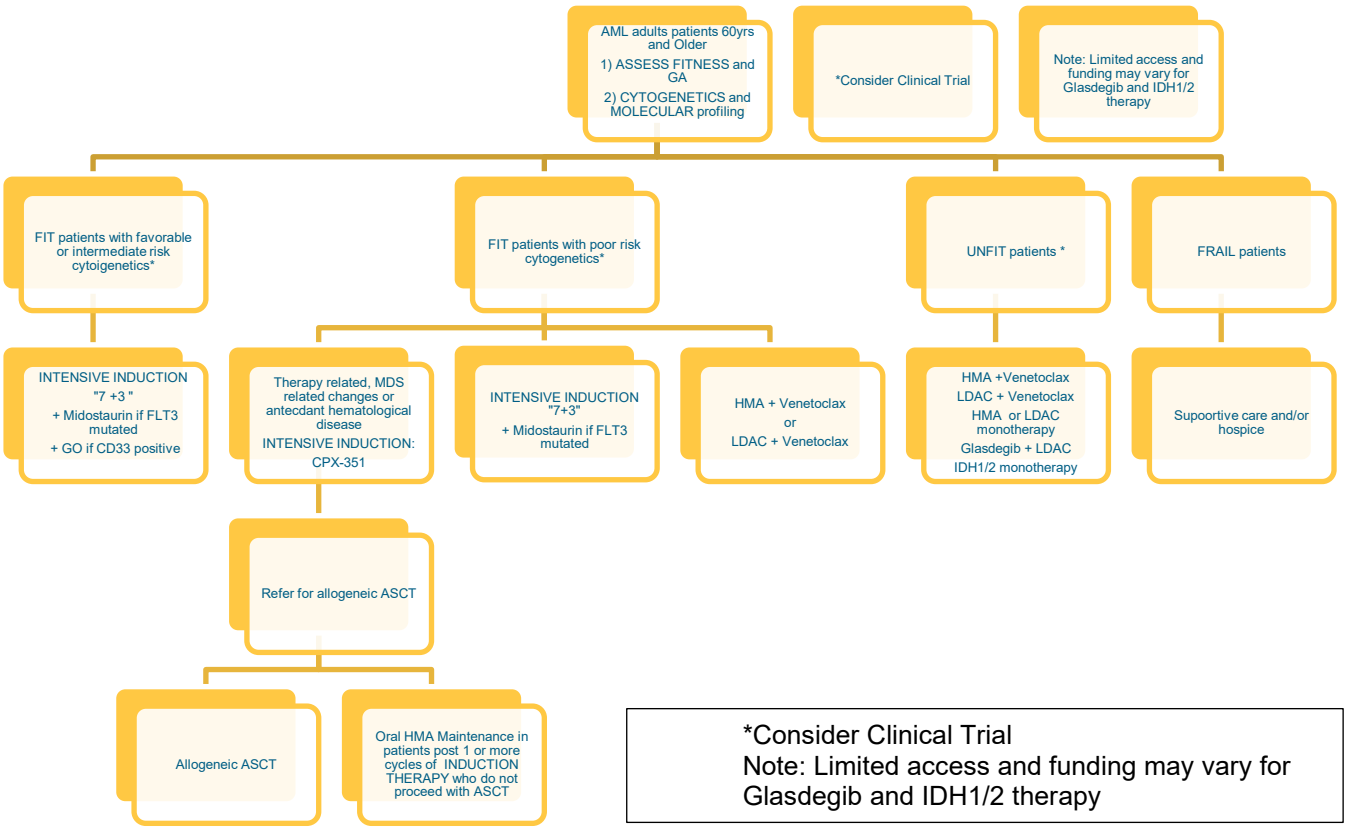
Unfit patients: The AML treatment landscape has evolved over the past few years and led to more treatment options for the care of older adults, who have inferior clinical outcomes. The National

Comprehensive Cancer Care Network (NCCN) defines older patients as age ≥ 60 years,[70] while the European Leukemia Network (ELN) defines older age as ≥ 60–65 years.[71]

In 2019, an estimated 21,450 new cases and 10,920 deaths were reported in the United States. (Cancer Statistics Review, 1975-2016 - SEER Statistics, n.d.). Older adults account for most cases, with a median age at diagnosis of 68 years. Incidence rates of AML increase with age from 1.3 per 100,000 in adults < 50 years, to 5.1 per 100,000 in patients 50–64 years, to 20.1 per 100,000 in those ≥ 65 years. Five-year overall survival (OS) is poor and estimated to be 28.3% for all patients with AML and as low as <10% in patients ≥ 60 years.[72] Elderly AML is distinct based on both disease- and patient-specific differences complicated by poorer functional, cognitive status, co-morbidities, unfavorable cytogenetics and/or mutations as well as multidrug resistance being more common in older adults.[73] The incidence of secondary AML (sAML) increases with age and represents higher risk AML.[74] These are all independent risk factors for poorer response to chemotherapy and lower complete remission (CR) rates compared to younger patients. Older AML patients often have poorer physiologic reserves and experience greater treatment-related toxicity.[71]

We suggest that therapeutic decisions NOT be based solely on chronological age. Evaluation of AML patients is based on performance status, using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale, which is based on clinicians' general impression. Poor performance status (ECOG ≥ 3) can predict functional status and prognosis well; however, is not consistent.[75-77] Unfortunately, clinical gestalt has limitations in elderly AML. These patients can more often develop rapid disability due to the acuity of the disease, which further complicates assessments of their health. It is strongly recommended that we implement standardized fitness assessments using geriatric assessments for more objective fitness assessments. A geriatric assessment (GA) is a comprehensive method to identify vulnerabilities in older adults that may impact their treatment.[77, 78] A GA includes functional status, physical performance and falls, comorbid medical conditions, psychological health, social activity/support, medications, nutritional status, and cognition.[79] Understanding functional status includes: daily living (ADLs) and instrumental activities of daily living (IADLS) and by using performance-based measures such as grip strength or the Short Physical Performance Battery.[80] Studies have demonstrated that GA can predict prognosis in elderly AML.[77] The NCCN, the American Society of Clinical Oncology, and the International Society of Geriatric Oncology recommend GA in patients ≥ 65.[79, 81, 82]

Figure 3: Summary treatment recommendations for elderly AML patients.



Treatment Options

Azacytidine (AZA) was studied in older patients (median age 75 years) with AML with > 30% blasts in a randomized phase III study. Azacytidine was associated with a trend towards better OS compared to conventional care regimens (CCR, standard induction chemotherapy, LDAC, or supportive care only) (10.4 months vs. 6.5 months, P=0.10).[83] AZA was compared to CCR in another phase III trial, in patients with low bone marrow blast counts of 20–30% (median age 70 years).[84] In this study, azacytidine was associated with improved OS (24.5 months vs. 16 months, P=0.05), as well as shorter fewer hospitalizations and number of days spent in the hospital.[84]

Venetoclax + HMA: A phase Ib escalation and expansion trial for older patients (median age 74 years) ineligible for intensive chemotherapy evaluated venetoclax (400 or 800 mg) with a HMA (decitabine 20 mg/m^2/day for 5 days or azacytidine 75 mg/m^2/day for 7 days) in 28-day cycles.[85] Poor risk cytogenetics was present in 49% of subjects. Venetoclax 400 mg combined with HMA was associated with 73% CR + CRi. CR + CRi occurred in 67% of all dosed patients. CR +CRi was achieved in 60% of those with poor risk cytogenetics and 65% for patients ≥ 75 years.[85] Median duration of CR+CRi was 11.3 months. Median survival was 17.5 months although, not reached in Venetoclax 400 mg cohort.[85] The phase III trial of venetoclax (target dose 400 mg) with azacytidine

(75mg/m^2 SC day 1-7) in 28-day cycles compared to azacytidine-placebo in elderly AML treatment naïve patients, demonstrated OS benefit favoring combination therapy. In a cohort of 431 patients, with median age of 76 years, the median OS was 14.7 months versus 9.6 months (HR 0.66, p <0.001) with composite CR rates of 66.4% vs 28.3%, (p <0.001) in favor of combination. Key adverse events included nausea (any grade 44%), febrile neutropenia and grade 3 neutropenia (42%) as well as grade 3 thrombocytopenia (45%). Serious adverse events were reported in 83% (combo therapy) versus 73% (Aza-placebo therapy).[86] Overall, the incidence of tumor lysis syndrome (TLS) with HMA/venetoclax in AML is low when the WBC count is not elevated [link]. It is suggested that hydration and allopurinol prophylaxis are still routinely recommended for the first cycle of therapy but can be safely discontinued if there is no evidence of TLS. Inpatient hospitalization is not required for initiation of therapy but should be considered if frequent outpatient monitoring is challenging, or if the patient may be at increased risk for complications based on leukocytosis (WBC >25), impaired renal function, or other comorbid conditions. It is suggested that WBC be lowered to <25 with hydroxyurea or cytarabine before initiating venetoclax therapy to minimize tumor lysis risk.[87]

Initiation of venetoclax includes a 3-day ramp-up and in absence of required dose adjustments, venetoclax is provided as: 100 mg once on Day 1, 200 mg once on day 2, and 400 mg once daily on day 3 and beyond.

When using strong or moderate CYP3A4 inhibitor such as posaconazole or fluconazole, the dosing of venetoclax is reduced by 80% and 50%, respectively. See Table 10 for summary of drug interactions and venetoclax dose reductions.[86, 87] As patients are usually severely neutropenic for at least 3 weeks during induction, prophylactic antimicrobials are recommended, e.g. antibacterial such as levofloxacin (not cipro due to drug interaction with venetoclax), antifungal (e.g. posaconazole, adjusting the venetoclax dose accordingly) and valacyclovir.

The combination therapy of HMA + venetoclax works quickly, with a median time to response of approximately 1 month. Since most patients will begin treatment with cytopenias and nearly all patients will have cytopenias by the end of the first cycle, it is suggested to repeat a staging bone marrow be performed ~day 21; if blast excess persists, commence the next cycle by day 29 without treatment dose interruption. A bone marrow assessment is suggested within first 2 cycles of treatment in all cases. This is performed to determine whether cytopenias are therapy-related or due to persistent AML. Identifying response early is crucial as continuation of venetoclax without temporary holds or delays in the subsequent cycles may result in prolonged aplasia and a higher risk of serious infections.[86, 87]

If patients are in CR—defined as <5% blasts, it is recommended to pause venetoclax and delay initiation of the second cycle for up to 14 days or until recovery of neutropenia, at minimum neutrophils ≥0.5 × 10^9/L. The effect of venetoclax is most pronounced on neutrophils, so often neutropenia is therapy-related. If persistent disease exists (>5% blasts), treatment should continue without delay and without a change in the venetoclax dose or schedule, with plan for a repeat biopsy before the third cycle to reassess response. If there has not been a meaningful blast reduction or

hematologic response after 3-4 cycles of therapy, consider stopping treatment if alternate options exist. The presence of *NPM1* and/or *IDH* mutation is associated with higher rates of clinical response while the presence of signaling mutations, particularly *FLT3*-ITD, and/or biallelic *TP53* mutations pose high relapse risk.[88]

Once remission achieved, the main challenge in successfully keeping patients on continued treatment while avoiding grade 3/4 hematologic toxicities, most notably neutropenia. Consider decreasing venetoclax dosing days especially if hematologic recovery takes >14 days after interrupting venetoclax for neutropenia and/or thrombocytopenia. Consider stepwise reductions in venetoclax dosing: 21 days → 14 days → 10 days. Additional reductions to consider include reducing HMA dose intensity by 25-50% if prolonged cytopenias persist with marrow hypocellularity If prolonged or severe cytopenias are recurrent after achieving remission, the recommendation is to decrease the number of days of venetoclax per cycle rather than reduction of the dose of venetoclax. Although data are limited, it does not appear that a shorter duration of venetoclax post remission compromises durability of response.[87, 89] [abstract link]

Additional strategies for limiting the depth and duration of cytopenias post remission include additional use of supportive G-CSF for grade 3/4 neutropenia to support ongoing cycles. If cytopenias worsen at any point during treatment or do not respond to dose pauses/adjustments, a repeat marrow evaluation is recommended to rule out disease progression.

Recommendation

Venetoclax and Azacitidine is recommended for patients with AML who are unfit for induction therapy. The use of mold-active azole is suggested as antifungal prophylaxis and venetoclax dose adjustments are needed when using with CYP3A4 inhibitors. Assessment of HMA + Ven response is suggested by cycle 2 and venetoclax dose changes are suggested once remission is achieved.

Venetoclax + LDAC: VIALE-C was a Phase III randomized trial of Venetoclax (600 mg daily) with LDAC versus LDAC alone in AML who were ineligible for IC (median age 76 years). This study included 20% of patients who had received prior HMA. The planned primary analysis showed a 25% reduction in risk of death with venetoclax plus LDAC vs LDAC alone (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.52-1.07; P = .11), with non-significant median OS of 7.2 vs 4.1 months, respectively. Additional 6-month follow-up demonstrated a significant difference with median OS of 8.4 months for the venetoclax arm (HR, 0.70; 95% CI, 0.50-0.98; P = .04). Composite CR rates were 48% and 13% for venetoclax plus LDAC and LDAC alone, respectively. Grade ≥3 adverse events (venetoclax vs LDAC alone) were febrile neutropenia (32% vs 29%), neutropenia (47% vs 16%), and thrombocytopenia (45% vs 37%). Venetoclax plus LDAC demonstrates clinically meaningful improvement in remission rate and OS vs LDAC alone, with a manageable safety profile. Results confirm venetoclax plus LDAC as an alternative frontline treatment for unfit AML patients. This option

is targeted for patients who are unable or unwilling to received Azacytidine subcutaneously at treatment centers.[90, 91]

Recommendation
Venetoclax and LDAC may be given for patients with AML who are unfit for induction therapy and unable to receive HMA + venetoclax therapy. However, venetoclax is not funded for this indication. If venetoclax is not available, LDAC alone is an acceptable alternative.

Venetoclax-based regimens have become very common in AML elderly treatment but challenges with this non-curative chemotherapy regimen still exist. Common challenges include tumor lysis syndrome, severe bone marrow suppression, and drug-drug-interactions. Data from real-world experience are emerging[92] and practical guidance are available.[86]

Other Oral AML therapies: Glasdegib, a hedgehog pathway inhibitor, was studied in a phase II randomized trial for older patients with AML or high-risk MDS (median age 76 years) unfit for intensive chemotherapy. (Cortes et al., 2019)Glasdegib 100 mg oral daily was administered continuously with LDAC 20 mg SC BID x 10 days per 28 day cycles. Median OS was 8.8 (6.9-9.9) months with glasdegib/LDAC and 4.9 (3.5-6.0) months vs LDAC monotherapy (hazard ratio, 0.51; 80% CI, 0.39-0.67, P = 0.0004) CR was achieved in 17.0% versus 2.3% patients in the glasdegib/LDAC and LDAC arms, respectively, (P < 0.05). It was considered well tolerated and safe therapy with nonhematologic grade 3/4 toxicities of pneumonia (16.7%) and fatigue (14.3%).[93] Glasdegib received FDA approval for treatment of AML in older or unfit patients but is not CADTH approved for use in Canada.

For patients with IDH1/2 mutant AML, Ivosidenib and enasidenib target *IDH1* and *IDH2* mutations respectively and were initially approved in the relapsed/refractory (R/R) setting. [link]

Mutations in isocitrate dehydrogenase 2 (*IDH2*) occur in ~12% of AML patients. Mutated *IDH2* proteins neomorphically synthesize 2-hydroxyglutarate resulting in DNA and histone hypermethylation, this leads to block in cellular differentiation. Use of inhibitors lead to cellular differentiation and maturation. IDH2 inhibitor, Enasidenib 100 mg once daily showed ORR of 40.3%, with a median response duration of 5.8 months in R/R AML. Median OS was 9.3 months, and in ~20% of patients who attained CR, OS was 19.7 months.[94] Enasidenib was studied in phase I/II trial newly diagnosed mutant-IDH2 AML (N=39), median age was 77 years (range 58-87). ORR was 30.8% with CR of 18%. At a median follow-up of 8.4 months, the median duration of any response was not reached (NR). Median overall survival was 11.3 months and was NR for responders. A median number of enasidenib cycles was 6.0 (range 1-35) with most common treatment-related adverse event being indirect hyperbilirubinemia (31%).[95] A phase II study of newly diagnosed, mutant-IDH2 AML patients (median age 75 years), assigned enasidenib 100 mg oral daily plus azacytidine (n=68) compared to azacytidine only (n=33). 74% in the combination group vs 36%; in azacytidine monotherapy group achieved an OR (odds ratio 4·9 [95% CI 2·0-11·9]; p=0·0003).

Common treatment-related grade 3 or 4 adverse events with combination were thrombocytopenia. Serious treatment-related adverse events were reported in 43% patients in the combination group and 44% patients in the azacytidine-only group: including febrile neutropenia, differentiation syndrome and pneumonia. Overall, enasidenib plus azacytidine was well tolerated and significantly improved ORR versus azacytidine monotherapy, suggesting that this regimen for elderly treatment naïve AML.[96]

Isocitrate dehydrogenase 1 (*IDH1*) mutations occur in 6 to 10% of AML patients. In the phase 1 dose-escalation and dose-expansion study of ivosidenib 500 mg PO daily in *IDH1*-mutated R/R AML. CR or CR with partial hematologic recovery was achieved in 30% and ORR was 41.6% with median duration of responses ranging 6.5 – 9.3 months treatment was well-tolerated. Specifically, IDH differentiation syndrome occurs with therapy and presents with significant neutrophil-predominant leukocytosis and nonspecific symptoms such as fever, hypotension, and effusions. This occurred in 16% of patients.[97, 98]

An open-label, single-arm, multicenter clinical trial of single-agent ivosidenib (500 mg PO daily) used for newly diagnosed AML with an *IDH1* mutation included patients ≥75 years. Twenty-eight patients were treated (median age 77 years; range: 64–87 years); with majority (79%) having therapy-associated or myelodysplasia-related AML. CR+CRh was achieved in 12/28 patients (42.9%) and based on the results, the FDA approved use in newly diagnosed *IDH1* mutated AML.[98]

Ivosidenib plus azacytidine combination was also studied in an open-label, multicenter, phase Ib trial for newly diagnosed elderly AML with mutated *IDH1* ineligible for intensive therapy. Ivosidenib 500 mg once daily continuously with subcutaneous azacytidine 75 mg/m^2 on days 1-7 in 28-day (median age, 76 years; range, 61-88 years). Median treatment duration was 15.1 months (range, 0.3-32.2 months with ORR of 78.3% and CR was 60.9%. With median follow-up of 16 months, median duration of response in responders had not been reached. The 12-month OS was 82.0%. Treatment-related grade ≥ 3 adverse events occurring in > 10% of patients were neutropenia (22%), anemia (13%), thrombocytopenia (13%), and QTC prolongation (13%). All grade IDH differentiation syndrome (17%). This combination was overall well tolerated, and responses were deep and durable, with most complete responders achieving *IDH1* mutation clearance.[99]

Phase 3 studies involving *IDH1*-mutated AML patients ineligible for intensive induction chemotherapy treated with ivosidenib (500 mg once daily) and subcutaneous or intravenous azacytidine (75 mg m2 x 7 days in 28-day cycles) versus matched placebo and azacytidine also showed significant benefit. The primary end point was event-free survival, defined as the time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first. **In the** intention-to-treat population of 146 patients: 72 in the ivosidenib-and-azacytidine group and 74 in the placebo-and-azacytidine group, with a median follow-up of 12.4 months, EFS was significantly longer in the ivosidenib-and-azacytidine group than in the placebo-and-azacytidine group (hazard ratio for treatment failure, relapse from remission, or death, 0.33; 95% confidence interval [CI], 0.16 to 0.69; P = 0.002). Median OS was 24.0 months with

ivosidenib and azacitidine versus 7.9 months with placebo and azacitidine (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; P = 0.001). Grade 3 or higher AEs included febrile neutropenia (28% with ivosidenib and azacytidine and 34% with placebo and azacytidine) and neutropenia (27% and 16%, respectively). Bleeding events of any grade was 41% and 29%, respectively with any grade of infection being 28% with ivosidenib and azacytidine and 49% with placebo and azacytidine. Differentiation syndrome of any grade occurred in 14% of the patients receiving ivosidenib and azacytidine and 8% of those receiving placebo and azacytidine.[100]

Overall, a meta-analysis of 1109 *IDH*-mutated AML patients from 10 articles (11 cohorts) found a CR rate, ORR rate, and 2-year OS rate, of relapsed or refractory (R/R) IDH-mutated AML (394 patients) were 21%, 40%, 15% with median OS and median EFS of 8.21 months and 4.73 months, respectively. In contrast, for newly diagnosed I*DH* mutated AMLs (N=715) the CR rate, and ORR rate, were 47%, and 65%, respectively. The 2-year survival (OS) rate and 2-year event-free survival (EFS) rates were 45% and 29%, respectively. Gastrointestinal adverse events were the most frequently occurring all-grade adverse events and hematologic adverse events were the most frequently occurring ≥ grade 3 adverse events.[101]

A systematic review of RCTs concluded an objective response (OR) was reported in 63-74% of the patients with IDH inhibitors (ivosidenib for IDH-1 and enasidenib for IDH-2) + azacytidine as compared to 19-36 % of the patients with azacytidine monotherapy in newly diagnosed medically unfit AML patients. OR was reported in 39.1-46 % of the AML patients who relapsed/refractory. Survival rates were significantly improved with the use of ivosidenib. ≥Grade 3 IDH differentiation syndrome and QT prolongation were reported in 3.9-10 % and 2-10 % of the patients, respectively. IDH inhibitors have been found to be safe and effective in treating both treatment naïve and R/R AML. However, no survival benefit was reported with enasidenib. More randomized multicenter double-blinded clinical studies are needed to confirm these results and compare them with other targeting agents.[102]

Recommendation

Enasidenib and ivosidenib are not currently funded in Canada. However, given the results of the above phase 3 trial, the combination of ivosidenib plus azacitidine would be an acceptable alternative to ven-aza as frontline treatment for unfit patients with IDH1 mutated AML, if available.

Table 9: Summary of lower-intensity treatment options in older AML patients.[91]

Lower-intensity regimens	Median age (years)	N	CR (%)	Median OS (months)	Toxicity of Treatment	Study Reference
Low dose cytarabine ± ATRA (20 mg twice daily, for 10 days, every 4 weeks until progression)	74	102	18	Not available, improved with LDAC	• No difference	Burnett et al., 2007
vs. Hydroxyurea ± ATRA		99	1 (P<0.05)			
Decitabine (20 mg/m2, for 5 days, every 4 weeks until progression)	73	242	17.8	7.7	• Death rate did not differ between groups	Kantarjian et al., 2012
vs. LDAC or supportive care		243	7.8 (P<0.05)	5 (P=0.020)		
Azacytidine (75 mg/m2/day for 7 days, every 4 weeks for at least 6 cycles)	70		18	24.5	• No increased toxicity vs CCR • Fewer hospital admissions compared to CCR (3.4 vs. 4.3 per patient-year) • Higher rate of fever requiring intravenous antibiotics in the CCR group (1.1 vs. 0.6 instances per patient-year)	Fenaux et al., 2010
vs. CCR (IC, LDAC, BSC)			16 (P>0.05)	16 (P<0.05)		
Venetoclax + HMA (Venetoclax ramp-up* with decitabine 20 mg/m2/day for 5 days OR azacytidine 75 mg/m2/day for 7 days)	74	145	67	17.5	• Common AEs (>30%): GI symptoms, febrile neutropenia, and fatigue • AE leading to venetoclax dose interruption (47%) • No significant TLS	DiNardo et al., 2019
Venetoclax + LDAC (Venetoclax ramp-up* with LDAC 20 mg/m2/day)	74	82	54	10.1	• Febrile neutropenia (42%) • Thrombocytopenia (38%) • WBC count decreased (34%)	Wei et al., 2019
Glasdegib with LDAC (Glasdegib 100 mg/day on days 1 to 28)	76	88	17	8.8	• Higher pneumonia, grade 3–4 in the combination group (16.7% vs. 14.6%) • Fatigue, grade 3–4 (14.3%)	Cortes et al., 2019
vs. LDAC		44	2 (P<0.05)	4.9 (P<0.05)		
Gemtuzumab ozogomycin (6 mg/m2 on day 1, 3 mg/m2 on day 8)	77	118	27	4.9	• No difference in AEs compared to BSC	Amadori et al., 2016
vs. BSC		119	30 (P>0.05)	3.6 (P<0.05)		
Ivosidenib (Dose range, 200–1200 mg daily for 28 days)	77	34	30	Not available yet	• Diarrhea (53%), nausea (38%) • Peripheral edema (26%) • Differentiation syndrome: leukocytosis and nonspecific symptoms (18%)	Roboz et al., 2019
Enasidenib (Total doses of 50–650 mg daily for 28days)	77	39	18	11.3 (data for responders not yet available)	• Grade 3–4 cytopenias (21%) • Indirect hyperbilirubinemia (31%) • GI complaints (23%) • Fatigue (18%)	Pollyea et al., 2019

The Unfit Patient with Relapsed AML

Relapse of AML after CR is frequently seen in elderly AML and prognosis is then extremely poor with a median OS of at highest 6 months.[103] Treatment with curative intent may be attempted for the "younger elderly" who are fit for IC with possibility to undergo HSCT after second CR. Salvage IC should only be considered for exceptionally fit patients with late relapses (> 1 year) without poor-risk features and targetable mutations. For patients with *IDH1/2* or *FLT3* mutations, targeted treatment with ivosidenib or enasidenib (if available, not currently funded in Alberta), or gilteritinib have been shown to be effective and described above. When targetable mutations are absent, less intensive treatment with HMA + venetoclax is the preferred option for less- fit patients who are naïve to these agents. However, for those relapsing on HMA + venetoclax there is no standard treatment in the absence of a targetable mutation, and enrollment in clinical trials is encouraged. However, for most patients, especially those with poor-risk features and/or early relapse, treatment is mainly palliative.[104]

VIII. Supportive Care

Growth Factors

Neutropenia is a common cause of significant morbidity in patients with AML. Myeloid growth factors such as granulocyte-colony stimulating factor (G-CSF) have been extensively studied in various hematologic malignancies with benefits in accelerating neutrophil count recovery, decreasing duration of fever, and reducing length of hospital stay. When studied in older patients with AML, G-CSF has not shown survival benefits.[103, 105, 106] There are also theoretical concerns about stimulation of leukemic cell growth so the routine use of G-CSF in patients with active leukemia is not recommended. G-CSF can be used for consolidation therapy when remission has been achieved but cost effectiveness is sometimes questioned. GCSF have be used for treatment related neutropenia caused by HMA + venetoclax and is an option in patients who have achieved a remission with persistent grade 3 or more neutropenia (see above HMA +Ven section).

Antimicrobial Prophylaxis: The use of HMAs and venetoclax is high risk for infections with febrile neutropenia as high as 50% during treatment, therefore, antibacterial, and antiviral prophylaxis is recommended. Mold-active azole (posaconazole, voriconazole, or isavuconazole) should also be considered based on duration of previous neutropenia and regional susceptibilities to fungal infections, with appropriate venetoclax dose adjustments if azoles (or other strong CYP3A4 inhibitors) are used. Dose adjustments for concomitant azole administration and other drug-drug interactions are shown in Table 10.

Mold-active azoles can be used with midostaurin, but monitoring of QTc intervals is recommended (e.g. 3x/week). For gilteritinib monotherapy, no benefit of antifungal prophylaxis however, prophylaxis should be considered in patients pretreated with chemotherapy or patients with long lasting neutropenia. For ivosidenib and enasidenib, no clear recommendations have been made but if using

CYP3A4 inhibitor, reduce ivosidenib dose to 250 mg/day. No evidence recommendations were made for patients on Glasdegib but evaluation on individual basis based on patient history and clinical status is suggested. Detailed statements are published for various AML therapies.[107]

Table 10: Venetoclax dosing requirements (adapted from[87]).

Metabolic Interaction	Examples[a]	Dose Reduction (%)	New Daily Dose (mg)[b]
Strong CYP3A4 inhibitors	Clarithromycin, itraconazole, ketoconazole, voriconazole, HIV protease inhibitors	75	100
	Posaconazole	≥75	70-100
Moderate CYP3A4 inhibitor	Aprepitant, cimetidine, ciprofloxacin, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil	50	200
P-glycoprotein inhibitor	Amiodarone, carvedilol, cyclosporine, dronedarone, quinidine, ranolazine, verapamil	50	200
Strong CYP3A4 inducers	Carbamazepine, efavirenz, phenytoin, rifampin	—	Avoid use
Child-Pugh C cirrhosis		50	200
Renal impairment		None	400

[a]Examples listed are not exhaustive of all inhibitors, inducers.
[b]Dose administsered once daily.

Palliative Care

Given the poor outcomes associated with AML in the older adult population, incorporation of palliative care services is strongly encouraged. Integration of palliative care with oncology care has shown benefit in multi-site randomized control trial of patients > 60 years with AML undergoing intensive chemotherapy. 74 AML patients were randomized to usual care (UC) versus 86 with integrated palliative care (IPC) while undergoing intensive chemotherapy across 4 tertiary care academic hospitals in the United States. Of 160 participants, the median (range) age was 64 (19.7-80.1) years. Compared with those on UC, IPC participants had better QOL with lower depression, anxiety, and PTSD symptoms. Benefits of reduced psychological distress were seen at week 2 and were sustained to week 24. Among patients who died, those receiving IPC were more likely to be involved in end of life (EOL) care planning and less likely to receive chemotherapy near the EOL.[108]

Further analysis of this study showed that IPC intervention facilitated better patient coping strategies, and this accounted for better patient reported outcomes as above.[109]

IX. 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.[110] 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).[111] 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 11. Treatment approaches and outcomes for mixed-phenotype acute leukemia (Retrospective data, both children and adults).[111]

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

X. CNS Prophylaxis/ Disease Treatment[112]

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,[113-115] 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.[113] Diagnosis of CNS leukemia is typically confirmed by the identification of leukemic blasts on cytocentrifuge preparations of cerebrospinal fluid after lumbar puncture. For patients with cranial nerve palsies or other localizing signs, an MRI with gadolinium should be done, as the presence of fixed leptomeningeal disease may need radiotherapy in addition to intrathecal chemotherapy.

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,[116] however, even after successful therapy, treatment in this setting is associated with high relapse rates.[117] 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.[117, 118]

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 some time during induction therapy, with intrathecal chemotherapy administered at the same time. If the cerebrospinal fluid is positive for leukemic cells the patient should be treated as above.

XI. 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 1-2 months 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.

XII. New Therapies Not Yet Approved

Second-generation *FLT3* inhibitors (quizartinib, gilteritinib, crenolanib) are being actively investigated in combination with chemotherapy, both in the frontline and relapsed setting, but are not approved for these indications.

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.[121] This agent has now been approved by the FDA and Health Canada for this indication but is not publicly funded in Canada. Ivosidenib is a selective IDH1 inhibitor which has shown activity in IDH1 mutated disease in early clinical trials.[121] It has been shown to increase survival when used upfront in combination with azacitidine[100]; it has not yet been approved or funded in Canada for this indication but may be available as part of a clinical trial.

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),[122] *DOT1L* (associated with MLL overexpression/rearrangements),[123] Polo-like kinase-1, *CXCR4*[124, 125] and menin inhibitors.[126] 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.

References

1. Deschler B, Lubbert M. Acute myeloid leukemia: epidemiology and etiology. *Cancer*. 2006;107(9):2099-2107.
2. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. Sep 15 2022;140(11):1200-1228.
3. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. Jul 2022;36(7):1703-1719.
4. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951.
5. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood*. 2012;119(1):34-43.
6. Pui CH, Ribeiro RC, Hancock ML, Rivera GK, Evans WE, Raimondi SC, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *The New England journal of medicine*. 1991;325(24):1682-1687.
7. Larson RA. Cytogenetics, not just previous therapy, determines the course of therapy-related myeloid neoplasms. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(19):2300-2302.
8. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2003;21(24):4642-4649.
9. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-474.
10. de Greef GE, van Putten WL, Boogaerts M, Huijgens PC, Verdonck LF, Vellenga E, et al. Criteria for defining a complete remission in acute myeloid leukaemia revisited. An analysis of patients treated in HOVON-SAKK co-operative group studies. *British journal of haematology*. 2005;128(2):184-191.
11. Ossenkoppele G, Schuurhuis GJ. MRD in AML: time for redefinition of CR? *Blood*. 2013;121(12):2166-2168.
12. Marcucci G, Mrozek K, Ruppert AS, Archer KJ, Pettenati MJ, Heerema NA, et al. Abnormal cytogenetics at date of morphologic complete remission predicts short overall and disease-free survival, and higher relapse rate in adult acute myeloid leukemia: results from cancer and leukemia group B study 8461. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(12):2410-2418.
13. Chen Y, Cortes J, Estrov Z, Faderl S, Qiao W, Abruzzo L, et al. Persistence of cytogenetic abnormalities at complete remission after induction in patients with acute myeloid leukemia: prognostic significance and the potential role of allogeneic stem-cell transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(18):2507-2513.
14. Yin JA, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. *Blood*. 2012;120(14):2826-2835.

15. Anderson JE, Kopecky KJ, Willman CL, Head D, O'Donnell MR, Luthardt FW, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. *Blood*. 2002;100(12):3869-3876.
16. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006;106(5):1090-1098.
17. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. Sep 22 2022;140(12):1345-1377.
18. Al-Issa K, Nazha A. Molecular landscape in acute myeloid leukemia: where do we stand in 2016. *Cancer biology & medicine*. 2016;13(4):474-482.
19. University of Chicago Hematopoietic Malignancies Cancer Risk T. How I diagnose and manage individuals at risk for inherited myeloid malignancies. *Blood*. 2016;128(14):1800-1813.
20. San Miguel JF, Vidriales MB, Lopez-Berges C, Diaz-Mediavilla J, Gutierrez N, Canizo C, et al. Early immunophenotypical evaluation of minimal residual disease in acute myeloid leukemia identifies different patient risk groups and may contribute to postinduction treatment stratification. *Blood*. 2001;98(6):1746-1751.
21. Perea G, Lasa A, Aventin A, Domingo A, Villamor N, Queipo de Llano MP, et al. Prognostic value of minimal residual disease (MRD) in acute myeloid leukemia (AML) with favorable cytogenetics [t(8;21) and inv(16). *Leukemia*. 2006;20(1):87-94.
22. Sievers EL, Lange BJ, Alonzo TA, Gerbing RB, Bernstein ID, Smith FO, et al. Immunophenotypic evidence of leukemia after induction therapy predicts relapse: results from a prospective Children's Cancer Group study of 252 patients with acute myeloid leukemia. *Blood*. 2003;101(9):3398-3406.
23. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. *The New England journal of medicine*. 2016;374(5):422-433.
24. Kronke J, Schlenk RF, Jensen KO, Tschurtz F, Corbacioglu A, Gaidzik VI, et al. Monitoring of minimal residual disease in NPM1-mutated acute myeloid leukemia: a study from the German-Austrian acute myeloid leukemia study group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(19):2709-2716.
25. Terwijn M, van Putten WL, Kelder A, van der Velden VH, Brooimans RA, Pabst T, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(31):3889-3897.
26. Freeman SD, Virgo P, Couzens S, Grimwade D, Russell N, Hills RK, et al. Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(32):4123-4131.
27. Walter RB, Gooley TA, Wood BL, Milano F, Fang M, Sorror ML, et al. Impact of pretransplantation minimal residual disease, as detected by multiparametric flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(9):1190-1197.
28. Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, et al. Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia: Time to Move Toward a Minimal Residual Disease-Based Definition of Complete Remission? *J Clin Oncol*. Feb 1 2016;34(4):329-36.
29. Dillon R, Hills R, Freeman S, Potter N, Jovanovic J, Ivey A, et al. Molecular MRD status and outcome after transplantation in NPM1-mutated AML. *Blood*. Feb 27 2020;135(9):680-688.
30. Grob T, Sanders MA, Vonk CM, Kavelaars FG, Rijken M, Hanekamp DW, et al. Prognostic Value of FLT3-Internal Tandem Duplication Residual Disease in Acute Myeloid Leukemia. *J Clin Oncol*. Feb 1 2023;41(4):756-765.
31. Schuurhuis GJ, Heuser M, Freeman S, Bene MC, Buccisano F, Cloos J, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131(12):1275-1291.
32. Heuser M, Freeman SD, Ossenkoppele GJ, Buccisano F, Hourigan CS, Ngai LL, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. Dec 30 2021;138(26):2753-2767.
33. Rücker FG, Agrawal M, Corbacioglu A, Weber D, Kapp-Schwoerer S, Gaidzik VI, et al. Measurable residual disease monitoring in acute myeloid leukemia with t(8;21)(q22;q22.1): results from the AML Study Group. *Blood*. Nov 7 2019;134(19):1608-1618.

34. Yin JA, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. *Blood*. Oct 4 2012;120(14):2826-35.
35. Jongen-Lavrencic M, Grob T, Kavelaars FG, Al Hinai ASA, Zeilemaker A, Erpelinck-Verschueren C, et al. Prospective Molecular MRD Detection By NGS: A Powerful Independent Predictor for Relapse and Survival in Adults with Newly Diagnosed AML. *Blood*. 2017;130:LBA-5.
36. Maiti A, DiNardo CD, Wang SA, Jorgensen J, Kadia TM, Daver NG, et al. Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia. *Blood Adv*. Apr 13 2021;5(7):1876-1883.
37. British Committee for Standards in H, Milligan DW, Grimwade D, Cullis JO, Bond L, Swirsky D, et al. Guidelines on the management of acute myeloid leukaemia in adults. *British journal of haematology*. 2006;135(4):450-474.
38. Oliansky DM, Appelbaum F, Cassileth PA, Keating A, Kerr J, Nieto Y, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults: an evidence-based review. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2008;14(2):137-180.
39. Nccn. Acute Myeloid Leukemia Version. 3.2019 2019.
40. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. *J Clin Oncol*. May 10 2018;36(14):1443-1453.
41. Lachowiez CA, Long N, Saultz J, Gandhi A, Newell LF, Hayes-Lattin B, et al. Comparison and validation of the 2022 European LeukemiaNet guidelines in acute myeloid leukemia. *Blood Adv*. May 9 2023;7(9):1899-1909.
42. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. *J Clin Oncol*. Sep 10 2018;36(26):2684-2692.
43. Othman J, Wilhelm-Benartzi C, Dillon R, Knapper S, Freeman SD, Batten LM, et al. A randomized comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: the UK NCRI AML19 trial. *Blood Adv*. Aug 22 2023;7(16):4539-4549.
44. Lancet JE, Uy GL, Newell LF, Lin TL, Ritchie EK, Stuart RK, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. Jul 2021;8(7):e481-e491.
45. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *The New England journal of medicine*. 2017;377(5):454-464.
46. Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. Apr 21 2012;379(9825):1508-16.
47. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. Aug 2014;15(9):986-96.
48. Appelbaum FR, Bernstein ID. Gemtuzumab ozogamicin for acute myeloid leukemia. *Blood*. Nov 30 2017;130(22):2373-2376.
49. Weick JK, Kopecky KJ, Appelbaum FR, Head DR, Kingsbury LL, Balcerzak SP, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood*. 1996;88(8):2841-2851.
50. Bishop JF, Matthews JP, Young GA, Bradstock K, Lowenthal RM. Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and updated results of the Australian Leukemia Study Group. *Leukemia & lymphoma*. 1998;28(3-4):315-327.
51. Petersdorf SH, Rankin C, Head DR, Terebelo HR, Willman CL, Balcerzak SP, et al. Phase II evaluation of an intensified induction therapy with standard daunomycin and cytarabine followed by high dose cytarabine for adults with previously untreated acute myeloid leukemia: a Southwest Oncology Group study (SWOG-9500). *American Journal of Hematology*. 2007;82(12):1056-1062.
52. Trifilio SM, Rademaker AW, Newman D, Coyle K, Carlson-Leuer K, Mehta J, et al. Mitoxantrone and etoposide with or without intermediate dose cytarabine for the treatment of primary induction failure or relapsed acute myeloid leukemia. *Leuk Res*. Apr 2012;36(4):394-6.
53. Taylor S, Murthy GSG, Runaas L, Michaelis LC, Carlson K, Atallah EL, et al. Re-induction with venetoclax combinations or IDH inhibitors result in similar remission rates and lower treatment related morbidity among AML patients initially receiving intensive induction chemotherapy. *Leuk Res*. Sep 2023;132:107348.

54. Megías-Vericat JE, Martínez-Cuadrón D, Sanz M, Montesinos P. Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review. *Ann Hematol*. Jul 2018;97(7):1115-1153.
55. Fu W, Hu Y, Lu G, Xu L, Gao L, Chen J, et al. Re-induction therapy in patients with acute myeloid leukemia not in complete remission after the first course of treatment. *Ann Hematol*. Feb 2023;102(2):329-335.
56. Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. *N Engl J Med*. Oct 31 2019;381(18):1728-1740.
57. Schlenk RF, Dohner K, Krauter J, Frohling S, Corbacioglu A, Bullinger L, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *The New England journal of medicine*. 2008;358(18):1909-1918.
58. Bloomfield CD, Lawrence D, Byrd JC, Carroll A, Pettenati MJ, Tantravahi R, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. *Cancer research*. 1998;58(18):4173-4179.
59. Byrd JC, Ruppert AS, Mrozek K, Carroll AJ, Edwards CG, Arthur DC, et al. Repetitive cycles of high-dose cytarabine benefit patients with acute myeloid leukemia and inv(16)(p13q22) or t(16;16)(p13;q22): results from CALGB 8461. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(6):1087-1094.
60. Sawler D, Sanford D, Brandwein JM, Sandhu I, Hogge D, Saini L. Two Cycles of Consolidation Chemotherapy Are Associated with Similar Clinical Outcomes to Three Cycles in AML Patients with Favorable Risk Cytogenetics. *Blood*. 2017;130:464.
61. Farag SS, Ruppert AS, Mrozek K, Mayer RJ, Stone RM, Carroll AJ, et al. Outcome of induction and postremission therapy in younger adults with acute myeloid leukemia with normal karyotype: a cancer and leukemia group B study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23(3):482-493.
62. Cassileth PA, Lynch E, Hines JD, Oken MM, Mazza JJ, Bennett JM, et al. Varying intensity of postremission therapy in acute myeloid leukemia. *Blood*. 1992;79(8):1924-1930.
63. Zittoun RA, Mandelli F, Willemze R, de Witte T, Labar B, Resegotti L, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *The New England journal of medicine*. 1995;332(4):217-223.
64. Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *The New England journal of medicine*. 1998;339(23):1649-1656.
65. Visani G, Olivieri A, Malagola M, Brunori M, Piccaluga PP, Capelli D, et al. Consolidation therapy for adult acute myeloid leukemia: a systematic analysis according to evidence based medicine. *Leukemia & lymphoma*. 2006;47(6):1091-1102.
66. Sierra J, Martino R, Sanchez B, Pinana JL, Valcarcel D, Brunet S. Hematopoietic transplantation from adult unrelated donors as treatment for acute myeloid leukemia. *Bone marrow transplantation*. 2008;41(5):425-437.
67. Moore J, Nivison-Smith I, Goh K, Ma D, Bradstock K, Szer J, et al. Equivalent survival for sibling and unrelated donor allogeneic stem cell transplantation for acute myelogenous leukemia. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2007;13(5):601-607.
68. Roboz GJ, Ravandi F, Wei AH, Dombret H, Thol F, Voso MT, et al. Oral azacitidine prolongs survival of patients with AML in remission independently of measurable residual disease status. *Blood*. Apr 7 2022;139(14):2145-2155.
69. Ravandi F, Roboz GJ, Wei AH, Döhner H, Pocock C, Selleslag D, et al. Management of adverse events in patients with acute myeloid leukemia in remission receiving oral azacitidine: experience from the phase 3 randomized QUAZAR AML-001 trial. *J Hematol Oncol*. Aug 28 2021;14(1):133.
70. Tallman MS, Wang ES, Altman JK, Appelbaum FR, Bhatt VR, Bixby D, et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. Jun 1 2019;17(6):721-749.
71. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
72. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica*. Dec 2012;97(12):1916-24.
73. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age and acute myeloid leukemia. *Blood*. May 1 2006;107(9):3481-5.
74. Oliai C, Schiller G. How to address second and therapy-related acute myelogenous leukaemia. *Br J Haematol*. Jan 2020;188(1):116-128.

75. Klepin HD, Estey E, Kadia T. More Versus Less Therapy for Older Adults With Acute Myeloid Leukemia: New Perspectives on an Old Debate. *Am Soc Clin Oncol Educ Book*. Jan 2019;39:421-432.
76. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood*. May 23 2013;121(21):4287-94.
77. Sherman AE, Motyckova G, Fega KR, Deangelo DJ, Abel GA, Steensma D, et al. Geriatric assessment in older patients with acute myeloid leukemia: a retrospective study of associated treatment and outcomes. *Leuk Res*. Sep 2013;37(9):998-1003.
78. Loh KP, Klepin HD. Geriatric assessment in acute myeloid leukemia: current and future landscape. *Blood Adv*. Sep 25 2018;2(18):2418.
79. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol*. Aug 1 2018;36(22):2326-2347.
80. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol*. May 10 2007;25(14):1824-31.
81. Mohile SG, Velarde C, Hurria A, Magnuson A, Lowenstein L, Pandya C, et al. Geriatric Assessment-Guided Care Processes for Older Adults: A Delphi Consensus of Geriatric Oncology Experts. *J Natl Compr Canc Netw*. Sep 2015;13(9):1120-30.
82. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. Aug 20 2014;32(24):2595-603.
83. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. Jul 16 2015;126(3):291-9.
84. Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol*. Feb 1 2010;28(4):562-9.
85. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17.
86. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med*. Aug 13 2020;383(7):617-629.
87. Lai C, Bhansali RS, Kuo EJ, Mannis G, Lin RJ. Older Adults With Newly Diagnosed AML: Hot Topics for the Practicing Clinician. *Am Soc Clin Oncol Educ Book*. May 2023;43:e390018.
88. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. Jan 9 2020;135(2):85-96.
89. Mei M, Aldoss I, Marcucci G, Pullarkat V. Hypomethylating agents in combination with venetoclax for acute myeloid leukemia: Update on clinical trial data and practical considerations for use. *Am J Hematol*. Mar 2019;94(3):358-362.
90. Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. Jun 11 2020;135(24):2137-2145.
91. Abdallah M, Xie Z, Ready A, Manogna D, Mendler JH, Loh KP. Management of Acute Myeloid Leukemia (AML) in Older Patients. *Curr Oncol Rep*. Jul 28 2020;22(10):103.
92. Winters AC, Gutman JA, Purev E, Nakic M, Tobin J, Chase S, et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. *Blood Adv*. Oct 22 2019;3(20):2911-2919.
93. Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. Feb 2019;33(2):379-389.
94. DiNardo CD, Pollyea DA, Jonas BA, Konopleva M, Pullarkat V, Wei A, et al. Updated Safety and Efficacy of Venetoclax with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia. *Blood*. 2017;130:2628.
95. Pollyea DA, Tallman MS, de Botton S, Kantarjian HM, Collins R, Stein AS, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*. Nov 2019;33(11):2575-2584.
96. DiNardo CD, Schuh AC, Stein EM, Montesinos P, Wei AH, de Botton S, et al. Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial. *Lancet Oncol*. Nov 2021;22(11):1597-1608.

97. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. *N Engl J Med*. Jun 21 2018;378(25):2386-2398.
98. Roboz GJ, DiNardo CD, Stein EM, de Botton S, Mims AS, Prince GT, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. Feb 13 2020;135(7):463-471.
99. DiNardo CD, Stein AS, Stein EM, Fathi AT, Frankfurt O, Schuh AC, et al. Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia. *J Clin Oncol*. Jan 1 2021;39(1):57-65.
100. Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. *N Engl J Med*. Apr 21 2022;386(16):1519-1531.
101. Chen X, Xing H, Xie X, Kou L, Li J, Li Y. Efficacy and safety of FDA-approved IDH inhibitors in the treatment of IDH mutated acute myeloid leukemia: a systematic review and meta-analysis. *Clin Epigenetics*. Jul 11 2023;15(1):113.
102. Aiman W, Ali MA, Basit MA, Omar Z, Suleman M, Hassan M, et al. Efficacy and tolerability of isocitrate dehydrogenase inhibitors in patients with acute myeloid leukemia: A systematic review of clinical trials. *Leuk Res*. Jun 2023;129:107077.
103. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. Jan 21 2010;115(3):453-74.
104. de Leeuw DC, Ossenkoppele GJ, Janssen J. Older Patients with Acute Myeloid Leukemia Deserve Individualized Treatment. *Curr Oncol Rep*. Nov 2022;24(11):1387-1400.
105. Amadori S, Suciu S, Jehn U, Stasi R, Thomas X, Marie JP, et al. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study. *Blood*. Jul 1 2005;106(1):27-34.
106. Wheatley K, Brookes CL, Howman AJ, Goldstone AH, Milligan DW, Prentice AG, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol*. Jun 2009;145(5):598-605.
107. Stemler J, de Jonge N, Skoetz N, Sinkó J, Brüggemann RJ, Busca A, et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association. *Lancet Haematol*. May 2022;9(5):e361-e373.
108. El-Jawahri A, LeBlanc TW, Kavanaugh A, Webb JA, Jackson VA, Campbell TC, et al. Effectiveness of Integrated Palliative and Oncology Care for Patients With Acute Myeloid Leukemia: A Randomized Clinical Trial. *JAMA Oncol*. Feb 1 2021;7(2):238-245.
109. Nelson AM, Amonoo HL, Kavanaugh AR, Webb JA, Jackson VA, Rice J, et al. Palliative care and coping in patients with acute myeloid leukemia: Mediation analysis of data from a randomized clinical trial. *Cancer*. Dec 15 2021;127(24):4702-4710.
110. Weinberg OK, Arber DA. Mixed-phenotype acute leukemia: historical overview and a new definition. *Leukemia*. 2010;24(11):1844-1851.
111. Matutes E, Pickl WF, Van't Veer M, Morilla R, Swansbury J, Strobl H, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. *Blood*. 2011;117(11):3163-3171.
112. Grossmann V, Haferlach C, Nadarajah N, Fasan A, Weissmann S, Roller A, et al. CEBPA double-mutated acute myeloid leukaemia harbours concomitant molecular mutations in 76.8% of cases with TET2 and GATA2 alterations impacting prognosis. *British journal of haematology*. 2013;161(5):649-658.
113. Holmes R, Keating MJ, Cork A, Broach Y, Trujillo J, Dalton WT, Jr., et al. A unique pattern of central nervous system leukemia in acute myelomonocytic leukemia associated with inv(16)(p13q22). *Blood*. 1985;65(5):1071-1078.
114. Shihadeh F, Reed V, Faderl S, Medeiros LJ, Mazloom A, Hadziahmetovic M, et al. Cytogenetic profile of patients with acute myeloid leukemia and central nervous system disease. *Cancer*. 2012;118(1):112-117.
115. How J, Minden MD, Brian L, Chen EX, Brandwein J, Schuh AC, et al. A phase I trial of two sequence-specific schedules of decitabine and vorinostat in patients with acute myeloid leukemia. *Leukemia & lymphoma*. 2015;56(10):2793-2802.
116. Lee EJ, Van Echo DA, Egorin MJ, Nayar MS, Shulman P, Schiffer CA. Diaziquone given as a continuous infusion is an active agent for relapsed adult acute nonlymphocytic leukemia. *Blood*. 1986;67(1):182-187.
117. Sanders KE, Ha CS, Cortes-Franco JE, Koller CA, Kantarjian HM, Cox JD. The role of craniospinal irradiation in adults with a central nervous system recurrence of leukemia. *Cancer*. 2004;100(10):2176-2180.

118. Mayadev JS, Douglas JG, Storer BE, Appelbaum FR, Storb R. Impact of cranial irradiation added to intrathecal conditioning in hematopoietic cell transplantation in adult acute myeloid leukemia with central nervous system involvement. *International journal of radiation oncology, biology, physics*. 2011;80(1):193-198.
119. Cortes JE, Kantarjian H, Foran JM, Ghirdaladze D, Zodelava M, Borthakur G, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(29):3681-3687.
120. Perl AE, Altman JK, Cortes JE, Smith CC, Litzow M, Baer MR, et al. Final Results of the Chrysalis Trial: A First-in-Human Phase 1/2 Dose-Escalation, Dose-Expansion Study of Gilteritinib (ASP2215) in Patients with Relapsed/Refractory Acute Myeloid Leukemia (R/R AML). *Blood*. 2016;128(22):1069.
121. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.
122. Konopleva M, Pollyea DA, Potluri J, Chyla BJ, Busman T, McKeegan E, et al. A Phase 2 Study of ABT-199 (GDC-0199) in Patients with Acute Myelogenous Leukemia (AML). *Blood*. 2014;124(21):118.
123. Stein EM, Altman JK, Collins R, DeAngelo DJ, Fathi AT, Flinn I, et al. AG-221, an Oral, Selective, First-in-Class, Potent Inhibitor of the IDH2 Mutant Metabolic Enzyme, Induces Durable Remissions in a Phase I Study in Patients with IDH2 Mutation Positive Advanced Hematologic Malignancies. *Blood*. 2014;124(21):115.
124. Muller-Tidow C, Bug G, Lubbert M, Kramer A, Krauter J, Valent P, et al. A randomized, open-label, phase I/II trial to investigate the maximum tolerated dose of the Polo-like kinase inhibitor BI 2536 in elderly patients with refractory/relapsed acute myeloid leukaemia. *British journal of haematology*. 2013;163(2):214-222.
125. Dohner H, Lubbert M, Fiedler W, Fouillard L, Haaland A, Brandwein JM, et al. Randomized, phase 2 trial of low-dose cytarabine with or without volasertib in AML patients not suitable for induction therapy. *Blood*. 2014;124(9):1426-1433.
126. Fiskus W, Boettcher S, Daver N, Mill CP, Sasaki K, Birdwell CE, et al. Effective Menin inhibitor-based combinations against AML with MLL rearrangement or NPM1 mutation (NPM1c). *Blood Cancer J*. Jan 11 2022;12(1):5.
127. Othmann J, Potter N, Ivey A, et al. The benefit of allogeneic transplant in 1st complete remission in NPM1 mutated AML with or withour FLT3-ITD is restricted to those testing positive for MRD after induction - an analysis of the UK NCRI AML17 and AML19 studies. Blood 2023;142(Suppl 1);142:425.
128. Levis M, Hamadani M, Logan B, Jones RJ, Singh AK, Litzow M, et al. Gilteritinib as Post-Transplant Maintenance for Acute Myeloid Leukemia With Internal Tandem Duplication Mutation of *FLT3.* J Clin Oncol 2024(Mar 12); https://doi.org/10.1200/JCO.23.02474.
129. Othmann J, Dhillon R, Wilhelm-Bernartzi C, et al. Genomic correlates of outcome in a randomized comparison of CPX-351 and FLAG-Ida in high-risk acute myeloid leukemia and myelodysplastic syndrome: results from the UK NCRI AML19 trial. Blood 2023;140(Suppl 1):1036.
130. Fournier E, Duployez N, Ducourneau B, Raffoux E ,Turlure O, Caillot D, et al. Mutational profile and benefit of gemtuzumab ozogamicin in acute myeloid leukemia. Blood 2020;135(8):542-546.
131. Russell N, Cumming O, Othmann J, Dillon R, Potter N, Wilhelm-Bernartzi C, et al. Gemtuzumab-based induction chemotherapy combined with midostaurin for flt3 mutated aml. Updated toxicity and interim survival analysis from the ncri aml19v2 “midotarg” pilot trial. EHA 2023; 386313; P484.
132. Kapp-Schwoerer S, Weber D, Corbacioglu A, Gaidzik VI, Paschka P, Kronke J, et al. Impact of gemtuzumab ozogamicin on MRD and relapse risk in patients with NPM1-mutated AML: results from the AMLSG 09-09 trial. Blood. 2020;136(26):3041-3050.
133. Freeman, SD, Thomas A, Thomas I, Hils K, Vyas P, Gikles A, et al. Fractionated vs single-dose gemtuzumab ozogamicin with determinants of benefit in older patients with AML: the UK NCRI AML18 trial. Blood 2023;142(20):1697-1707.
134. Saini L, Brandwein J, Turner R, Larratt L, Hamilton M, Peters A, et al. The FLAG Chemotherapy Regimen Is an Alternative to Anthracycline Based Therapy for the Treatment of Acute Myeloid Leukemia for Patients with Pre-Existing Cardiac Disease. Eur J Haematol. 2016 Nov. 97(5):471-478.

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

7&3&GO

- 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
- Gemtuzumab Ozogomycin 3 mg/m^2 days 1, 4, 7

7&3 & Midostaurin

- 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
- Midostaurin 50 mg twice daily days 8-21

CPX-351 induction

Daunorubicin 44 mg/m^2 and Cytarabine 100 mg/m^2 liposome on Days 1,3,5
(reinduction only 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

HiDAC & GO

- Cytarabine 3 g/m^2 every 12 hours on days 1, 3 and 5
- Gemtuzumab Ozogomycin 3 mg/m^2 day 1 (for 2 cycles)

HiDAC & Midostaurin

- Cytarabine 3 g/m^2 every 12 hours on days 1, 3 and 5
- Midostaurin 50 mg twice daily days 8-21

CPX-351 consolidation

- Daunorubicin 29 mg/m^2 and Cytarabine 65 mg/m^2 liposome on Days 1,3,5

Intermediate Dose Cytarabine

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

Azaciticine/Venetoclax
First cycle

- Azacitidine 75mg/m^2 s/c days 1-7
- Venetoclax ramp up to maximum 400 mg daily dose for 28 days (depending on co-administered medications)
- Subsequent cycles dictated by response, co-administered medications and cytopenias

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

Oral Azacytidine

- 300mg po daily for 14 days, repeat every 28 days until disease progression or unacceptable toxicity [(5)].

Appendix B: ECOG Performance Status[117]

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.

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including hematologists, radiation oncologists, medical oncologists, surgeons, nurses, pathologists, and pharmacists. 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.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

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; CEBPACCAAT/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; CRc, Complete cytogenic remission; Cri, 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

Disclaimer

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.

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Conflict of Interest Statements

Dr. Joseph Brandwein reports receiving speaker honoraria from Abbvie and Amgen, and has participated in an advisory board for Abbvie, Amgen, BMS, Daiichi-Sankyo, Jazz, Pfizer, Astellas, Avir, and Taiho.

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