Acute Myeloid Leukemia: Assessment and Treatment – Adult – Inpatient/Ambulatory Clinical Practice Guideline

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Introduction

Acute myeloid leukemia (AML) is one of the most common types of leukemia in adults. It is characterized by uncontrolled proliferation of abnormal myeloid precursors that accumulate in the blood and bone marrow. It is generally a disease of older people and is uncommon before the age of 45; the average age when first diagnosed with AML is 69 years. Most cases are *de novo* with no known etiological factors, however therapy-related AML can occur as patients with cancer are treated for their primary malignancy with cytotoxic chemotherapy.[1,2]

This clinical practice guideline was developed with consideration of recommendations from guidelines by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet.

Scope

Intended User(s): Physicians, Advanced Practice Providers, Registered Nurses, Pharmacists, Pathology Laboratory

Objective(s): To inform clinical decisions on the diagnosis and management of patients with AML.

Target Population: Adult patients (18 years or older) newly diagnosed with Acute Myeloid Leukemia who do NOT have the sub-type of acute promyelocytic leukemia (APL).

Clinical Questions Considered:

- What laboratory tests and procedures are recommended in newly diagnosed patients with AML?
- What are known recurrent genetic mutations in newly diagnosed patients that affect survival outcome?
- What tools are recommended for evaluating a patient's fitness for intensive chemotherapy?
- When is midostaurin indicated as a component of induction chemotherapy?
- When is gemtuzumab ozogamicin indicated as a component of induction chemotherapy?

Definitions

Acute myeloid leukemia (AML) – leukemia diagnosed with presence of $\geq$ 20% myeloid blasts in the blood or bone marrow; except for AML with t(15;17), t(8;21), inv(16) or t(16;16) which does not need 20% blasts for diagnosis.[3]

Acute promyelocytic leukemia (APL) – subtype of AML associated with a translocation between chromosomes 15 and 17, t(15;17), resulting in the *PML-RARA* fusion.

Intensive induction chemotherapy – also referred to as "intensive therapy" or "induction therapy"; chemotherapy used to greatly reduce the number of blasts. The standard regimen used consists of an anthracycline and cytarabine.

Recommendations

Diagnostic Procedures

Diagnostic tests

Patients may be diagnosed with acute myeloid leukemia based on of blood tests, however a bone marrow biopsy is generally needed to confirm the diagnosis.

A lumbar puncture is recommended in any patient with clinical symptoms suspicious of central nervous system (CNS) involvement, monocytic disease, high white cell count (>50k), or transplant eligible. In general this should be deferred until after circulating blasts have been cleared.[4,5] *(UW Health Moderate quality of evidence, S recommendation)*

Performance Status (PS)

Although predicted mortality can be affected by a patient's age, it is important to consider all patient-related and disease-related factors to design an appropriate treatment plan. It is recommended to conduct a thorough evaluation of performance status, using a scale such as the Eastern Cooperative Oncology Group (ECOG) scale to quantify the general well-being of a cancer patient and determine their fitness to receive chemotherapy safely. For AML, age and ECOG PS correlate with 30-day induction mortality.[6] *(UW Health Moderate quality of evidence, S recommendation)*

An assessment of comorbidities (i.e., burden and severity of disease) with a standardized tool such as the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI)[7] is also useful and recommended.[8] *(UW Health Moderate quality of evidence, S recommendation)* Online tools are available to easily calculate a patient's HCT-CI score (Calculate HCT-CI or http://www.hctci.org/.)

Table 1. ECOG Performance Status[9]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance 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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Molecular testing

Cytogenetics is the strongest prognostic marker for risk stratification of AML at the time of diagnosis and for selection of post-remission treatment. Molecular genetic testing should include workup for mutations in *NPM1*, *CEBPA*, and *RUNX1* genes because these define specific AML subtypes. Genetic testing should also include *FLT3* (including internal tandem duplication, ITD, and tyrosine kinase domain, TKD, mutations), and *TP53*, and *ASXL1* as these genes have prognostic importance and may impact therapy.[2,4] *(UW Health Moderate quality of evidence, S recommendation)* **Table 2** summarizes recommended tests for patients suspected with AML. *(UW Health Moderate quality of evidence, S recommendation when indicated for all patients. C recommendation when test is listed with qualifiers)* A summary of common recurrent genetic mutations in newly diagnosed AML patients can be found the Appendix.

Table 2. Recommended tests for patients suspected to have AML[4,5,8,10]

Test	Who should get	Purpose
Tests to establish diagnosis		
Complete blood count with differential	All patients	Diagnostic
Bone marrow aspirate and biopsy (pre-chemotherapy)	All patients *Note: In certain patients age >70 years, not transplant eligible with high circulating blast count, may consider deferring bone marrow for molecular analysis.*	Diagnostic
Bone marrow core biopsy for morphology and cytogenetic/molecular testing (pre-chemotherapy)	Recommended in patients with a dry tap	Diagnostic
Tests to determine induction therapy		
Cytogenetics (i.e., karyotyping of G-Banded metaphase chromosomes)	All patients	Diagnostic/Prognostic
Rapid testing for *PML-RARA* by FISH or PCR	Any patients in whom APL is suspected	Diagnostic/Prognostic
Rapid testing for *FLT3* mutations	All patients	Prognostic/Therapeutic
Rapid testing for core binding factor acute myeloid leukemia (i.e. Rapid FISH for t(8;21 and inv(16)/t(16;16)	Patient's age ≤ 65 years with de novo AML	Diagnostic/Prognostic
Tests to help determine consolidation therapy decision		
Molecular testing panel to include but not limited to *NPM1, CEPBA, RUNX1, ASXL1,IDH1, IDH2, TP53*	• Consider in all patients (if not cost prohibitive); • Recommended in all patients with intermediate-risk cytogenetics *In addition to the rapid testing for FLT3 recommended above, any patient with normal cytogenetics should, at minimum, also have testing for NPM1 and CEBPA mutations to identify low risk disease.[11]*	Diagnostic/Prognostic
Testing for *KIT* gene mutations	• Any patient with core binding factor acute leukemia	Prognostic
Additional tests/procedures at diagnosis		
Lumbar puncture (LP)	Any patient with clinical symptoms suspicious of central nervous system (CNS) involvement, monocytic disease, high white cell count (>50k), or transplant eligible; in intensive therapy candidates, LP done after peripheral blasts are cleared in	Diagnostic
MUGA or cardiac echo *Note: MUGA should not delay start of chemotherapy unless suspicion of heart failure*	• Any patient > 60 years old • Any patient with history or clinical evidence of cardiac disease • Any patient w/prior exposure to cardiotoxic drugs or radiation to thorax • Consider in all patients who are candidates for intensive therapy	Assess left ventricular function
HLA typing sample (HLA for DNA extraction)	All patients	Potential blood product usage, eligibility for allogeneic HCT
Urine pregnancy test	Any patient with childbearing potential	Pregnancy status; information on oocyte cryopreservation
Luminex AB Class I, II HLA antibodies	All patients who are candidates for intensive therapy	Platelet alloimmunization, HCT donor selection
Performance Status (i.e., ECOG and HCT-CI)	All patients	Prognostic

Acute Myeloid Leukemia - Risk Stratification of Disease

As stated before, karyotype of the leukemic cell is important because it is a strong prognostic factor for response to induction therapy and survival. Three cytogenetic risk groups based on treatment outcomes exist: favorable/low, intermediate and unfavorable/adverse. **Table 3** summarizes the Euroepan Leukemia Net risk stratification categories.

Patients with core binding factor (CBF) leukemia (i.e. t(8;21), inv(16), or t(16;16) without a cKIT mutation) or acute promyelocytic leukemia (APL) with t(15;17) are considered at relatively lower risk of relapse.[12]

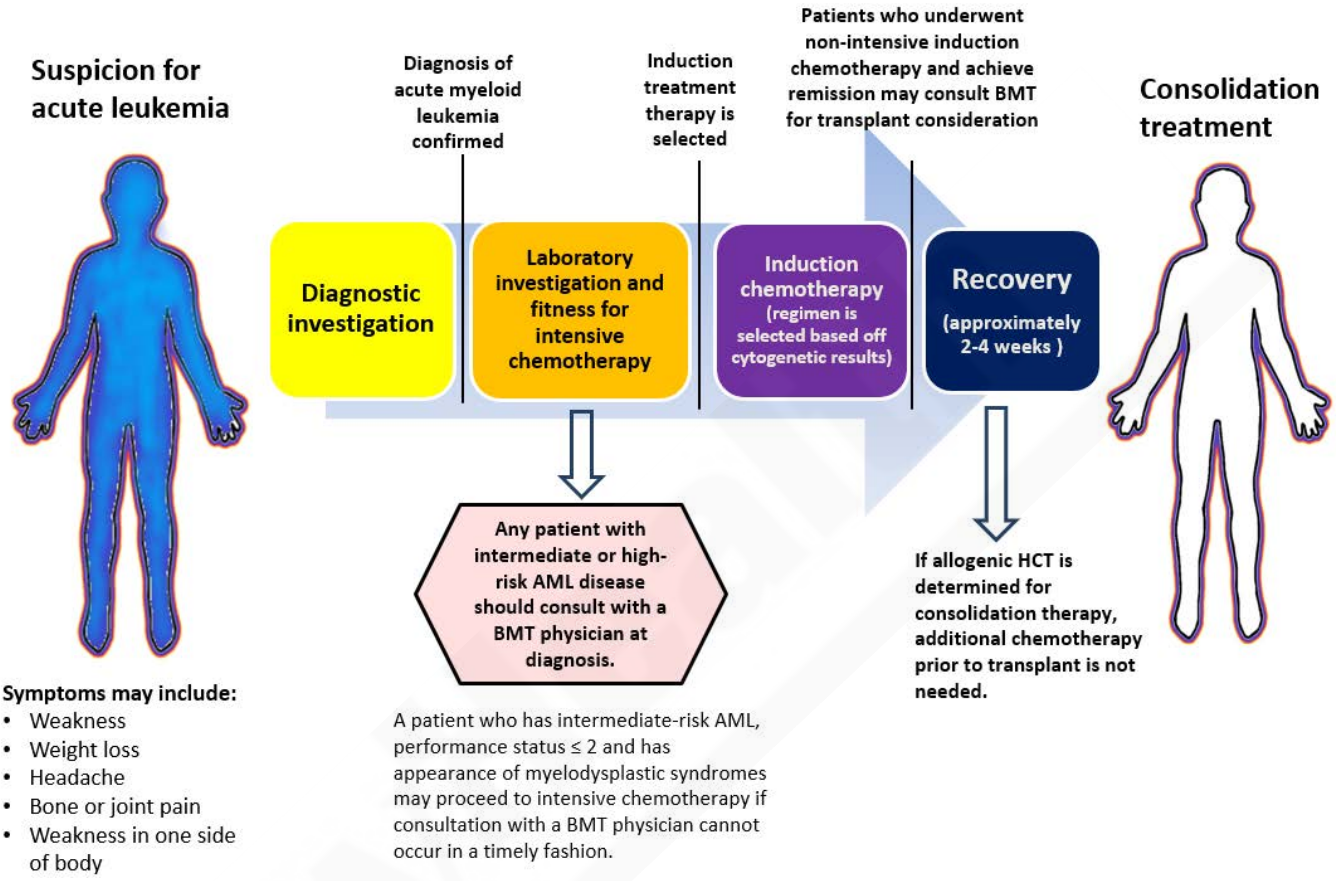
Table 3. European Leukemia Net (ELN) molecular risk stratification[4]

Risk category	Genetic abnormality
Low	t(8;21)(q22;q22.1) for *RUNX1-RUNx1T1* inv(16)(p14.1q22) or t(16;16)(p13.1;q22) for *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} ***** Biallelic mutated *CEBPA*
Intermediate	Mutated NPM1 with *FLT3*-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions) t(9;11)(p.21.3;q23.3) for *MLL3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1) for *DEK-NUP214* t(v;11q23.3) for *KMT2A* rearranged t(9;22)(p34.1;q11.2) for *BCR-ABL*1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q.26.2) for *GATA2* and *MECOM(EVI1)* -5 or del(5q) -7 -17/abn(17p) Complex karyotype; monosomal karyotypes Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

***** It is important to note that not all patients with ELN favorable-risk AML have a favorable outcome. The presence of the *FLT3*-ITD mutation has been identified as a powerful indicator predicting more frequent and early relapse.[11-13]It is recommended that all patients with FLT3-ITD have a consultation with a blood and bone marrow transplant (BMT) physician.
(UW Health Low quality of evidence, C recommendation)

Treatment for Newly Diagnosed Acute Myeloid Leukemia

Figure. 1. Timeline of AML disease from diagnosis to consolidation treatment



Treatment for AML is divided into two phases: induction and consolidation. Intensive chemotherapy is typically used for induction. The "7+3" regimen which consists of 3 days of IV anthracycline (daunorubicin at least 60-90 mg/m^2 or idarubicin 12 mg/m^2) and 7 days of continuous infusion cytarabine 100-200 mg/m^2/day [4,5] is the standard chemo regimen used. *(NCCN Category 2A)* Dependong on a patient's cytogenetic and past history, other chemo-agents may be appropriate. **Table 4** and **Figure 2** summarize these recommendations.

Table 4. Recommended induction chemotherapy for select patients[4,5] *(NCCN Category 2A)*

PATIENT	QUALIFIER	TREATMENT
AML Induction therapy candidate **(patient ≤ 65 years AND HCT-CI ≤ 3)**	**NONE**	**7 + 3**
	FLT3 positive	**7 + 3 ± midostaurin**
	CBF (CD33-positive)	**7 + 3 + gemtuzumab ozogamicin**
	2° AML, myeloid disorder	**Liposomal daunorubicin and cytarabine**

Consolidation or post-remission therapy may involve more chemotherapy or be a blood stem cell transplant. Chemotherapy is a reasonable first-line consolidation choice for patients with low risk AML (i.e., favorable prognosis.) This includes older patients (age 65-74) with a favorable prognosis. For patients with an intermediate-risk cytogenetic profile, the optimal choice for consolidation therapy is more controversial.

Allogeneic HSCT is associated with the lowest rates of relapse, but the benefit may be offset by its risks (i.e., transplant complications and nonrelapse treatment-related mortality.)
It is important to consider the disease risk (as assessed by cytogenetic and molecular genetic profile) and risk of transplant when deciding most appropriate therapy. In general for younger patients with genetic intermediate-risk AML and low HCT-CI score, a blood stem cell transplant is the most appropriate postremission therapy.[14,15]

If a transplant is being considered for consolidation therapy, determining the availability of a marrow or stem cell donor sooner versus later is critical. Early identification of a donor allows for an immediate transplant if remission induction is a failure and may also help in shared decision-marking when choosing a course of treatment.[16,17]

Table 5. Risk of Relapse following consolidation approach[16]

AML risk group	Chemotherapy or autoHSCT (%)	AlloHSCT (%)
Good	35-40	15-20
Intermediate	50-55	20-25
Poor/very poor	70->90	30-50

When to Refer to a BMT Physician

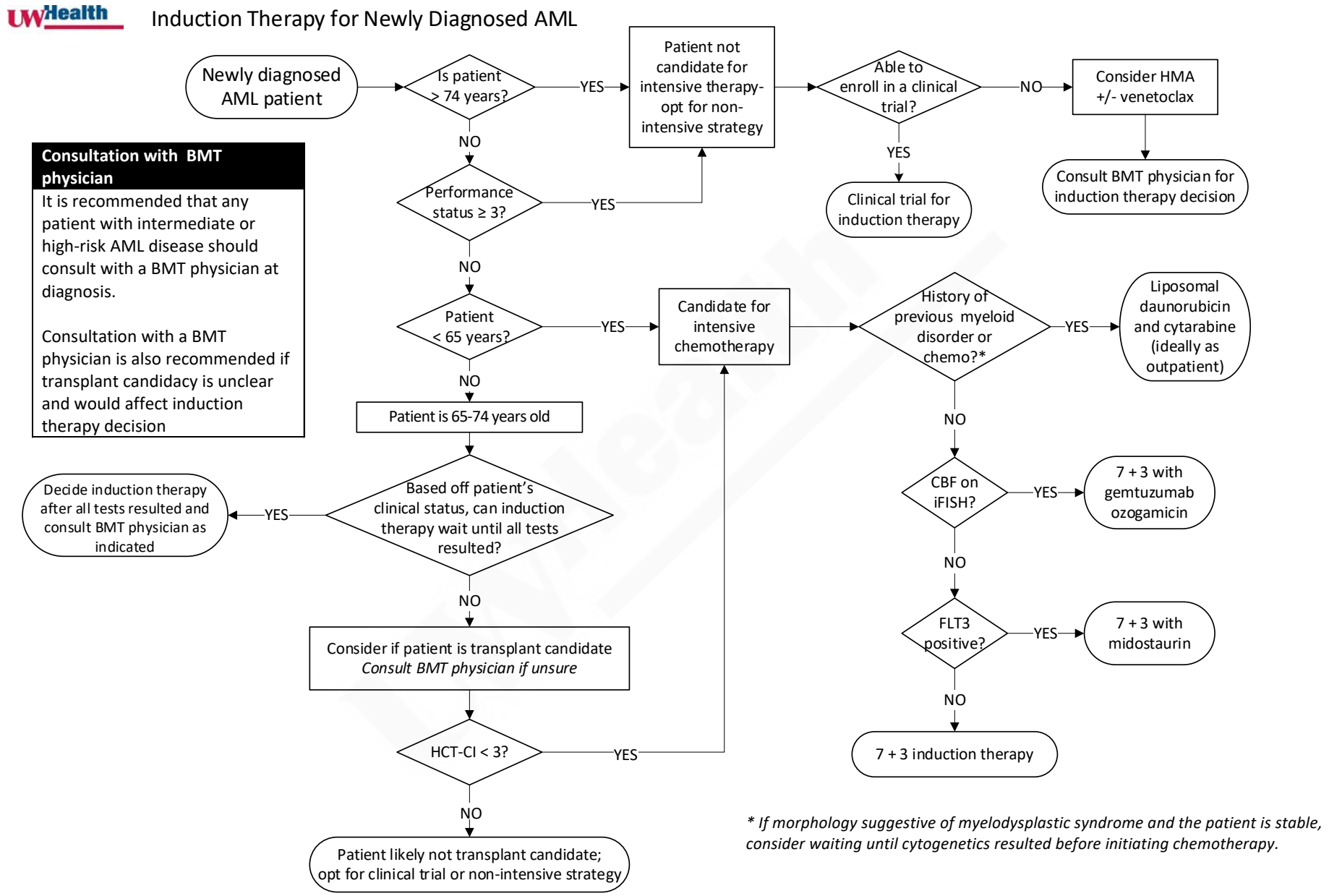
Consultation with a BMT physician is recommended at diagnosis (e.g., during hospital stay for induction chemotherapy) for AML patients who: *(UW Health Low quality of evidence, S recommendation)*

- have a *FLT3*-ITD mutation
- have intermediate risk or high risk AML disease profile
- have unclear transplant candidacy and that would affect induction decision

- For immediate consultation with a BMT Physician, call the Access Center (Toll free 800-472-0111 or if in Madison 608-263-3260)

- For non-UW Health Physicians who wish to make a referral, call BMT Program Manager at 608-262-0455.
  Please provide patient information (name, DOB, demographic information, diagnosis and payor information) when making referral request.

Figure 2. Treatment selection for newly diagnosed AML[5,18,19]



** If morphology suggestive of myelodysplastic syndrome and the patient is stable, consider waiting until cytogenetics resulted before initiating chemotherapy.*

Table 6. Indications for Allogeneic Hematopoietic-Cell Transplantation[20] *(UW Health Low quality of evidence, C recommendation)*

Age 16 to 60-65 years	Age > 60-65 years
• First complete remission (in general excluding favorable-risk AML) • Other high-risk clinical features (e.g. therapy-related AML; secondary AML following a preceding myelodysplastic syndrome or myeloproliferative neoplasm) • Persisting minimal residual disease detectable by means of a quantitative real-time PCR assay or multicolor flow cytometry • Primary induction failure: alternative or investigational regimens to achieve complete remission followed by allografting • Second or higher complete remission; first relapse; satisfactory outcome with delay of HCT requires prompt attainment of second complete remission without major infectious or other condition that compromises later HCT	• Patients younger than 75 years of age who are physically able to undergo transplantation, with careful consideration of coexisting conditions and patient goals; clinical and biologic indications similar to those for younger patients

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- NCCN Guidelines
- Hiddemann W, ed. *Handbook of Acute Leukemia.* Switzerland: Adis; 2016.

Time Period: July 2018 to January 2019

The following is a list of various search terms that were used individually or in combination with each other for literature searches on PubMed: Acute myeloid leukemia, fitness, HCT-CI, bone marrow transplant, performance status, induction therapy, disparities, risk, guideline.

Methods to Select the Evidence:

Literary sources were selected with the following criteria in thought: English language, subject age (i.e., >18 years), publication in a MEDLINE core clinical journal and strength of expert opinion (e.g., international or national guideline).

Methods Used to Formulate the Recommendations:

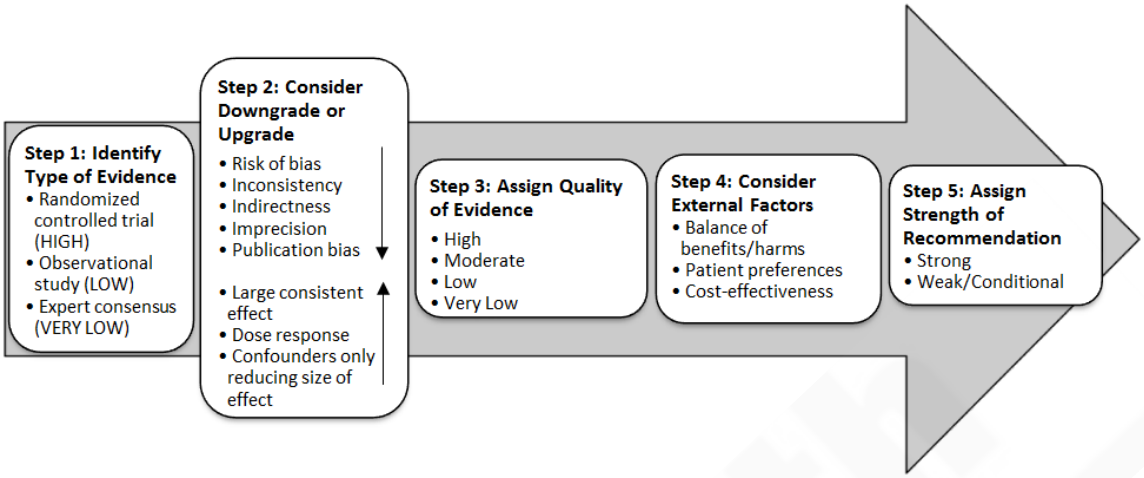
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong (S)	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)

National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Recognition of Potential Health Care Disparities: Socioeconomic status (SES) may explain some proportion of disparities in acute leukemia mortality in minorities. However there does not appear to be a strong association between SES and AML for adults.[21]

Appendix A. Common recurrent gene mutations in newly diagnosed AML in adults[2,20]

Mutated Gene	Frequency	Clinical Significance
FLT3-ITD	20-25%	• More common in NK AML • Associated with unfavorable outcome, particularly in patients with high allelic burden versus lower allelic burden • Patients with *FLT3*-ITD positive AML may benefit from allogeneic HCT in first complete remission; this beneficial effect may be restricted to patients with high mutant to wild type ITD ratio • Prognosis affected by concomitant NPM1 mutation status and prognostic significance not fully established with widespread use of *FLT3* inhibitors
NPM1	25-35%	• More common in NK AML (<60%) than in AML with cytogenetic abnormalities. • Increased incidence in younger patients • Coexisting chromosomal abnormalities do not affect prognosis • Frequently associated with other mutations (e.g., *FLT3*-ITD, and mutations in *DNMT3A*, *IDH1*, *IDH2*, and *TET2*) • More favorable prognosis in absence of high allelic burden *FLT3*-ITD mutation • Genetic marker for assessment of minimal residual disease
CEBPA	6-10%	• More common in NK AML (<20%) than in AML with cytogenetic abnormalities. • Increased incidence in younger patients • Coexisting chromosomal abnormalities do not affect prognosis • Associated with favorable outcome • Associated with familial AML
KIT	About 10%	• More common in CBF AML (present in 25-35%) than in non-CBF AML • Poor prognosis more notable in AML with t(8;21) than inv(16)
DNMT3A	18-22%	• More common in NK AML (<35%) than in AML with cytogenetic abnormalities. • Increased incidence in older adults • Clonal hemopoiesis of indeterminate potential (CHIP) mutation • Inferior prognosis particularly when present with other mutations (e.g., *IDH2*) • Prognosis affected by type of *DNMT3A* mutations (i.e., R882 vs non-R882) and patient age
IDH and IDH2	5-15% (*IDH1*) 10-20% (*IDH2*)	• More common in NK AML (<30%) than in AML with cytogenetic abnormalities. • Incidence of *IDH2* mutation increased with older age • *IDH1* and *IDH2* are associated with concomitant NPM1 mutations • *IDH2* can represent distinct AML disease subtype • Enasidenib (IDH2 inhibitor) approved for relapsed or refractory IDH2-mutated AML
NRAS	About 15%	• Associated with NPM1 and biallelic CEPBA mutations and with inv(16) or t(16;16) and inv(3) or t(3:3) • Mutant RAS may be predictive of sensitivity to cytarabine • Favorable outcomes with $NRAS^{G12/G13}$ mutation in presence of *NPM1* and *DNMT3A* mutations
TET2	5-20%	• More common in NK AML (<25%) than in AML with cytogenetic abnormalities. • Increased incidence in older adults • CHIP mutation • Mutually exclusive with *IDH1* and *IDH2* mutations
ASXL1	5-15%	• Increased incidence in older adults • Associated with secondary AML evolving from a myelodysplastic syndrome • *ASXL1* mutations predictive of inferior outcome • Frequent concurrent mutations (e.g., in *RUNX1*, *SRSF2*, and *IDH2*)
RUNX1	5-20%	• Increased incidence in older adults • Associated with secondary AML evolving from a myelodysplastic syndrome • *RUNX1* mutations predictive of resistance to induction therapy and of inferior outcome • Associated with autosomal dominant familial platelet disorder conferring a redisposition to AML

NK= normal karyotype CBF=core binding factor

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