| uw Health	Acute Myeloid Leukemia: Assessment and Treatment - Adult – Inpatient/Ambulatory Guideline Summary

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)

Full Guideline: Acute Myeloid Leukemia: Assessment and Treatment - Adult - Inpatient/Ambulatory

DEFINITIONS

Acute myeloid leukemia (AML)	Leukemia diagnosed with presence of ≥ 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.[1]
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.

Timeline of AML disease from diagnosis to consolidation treatment
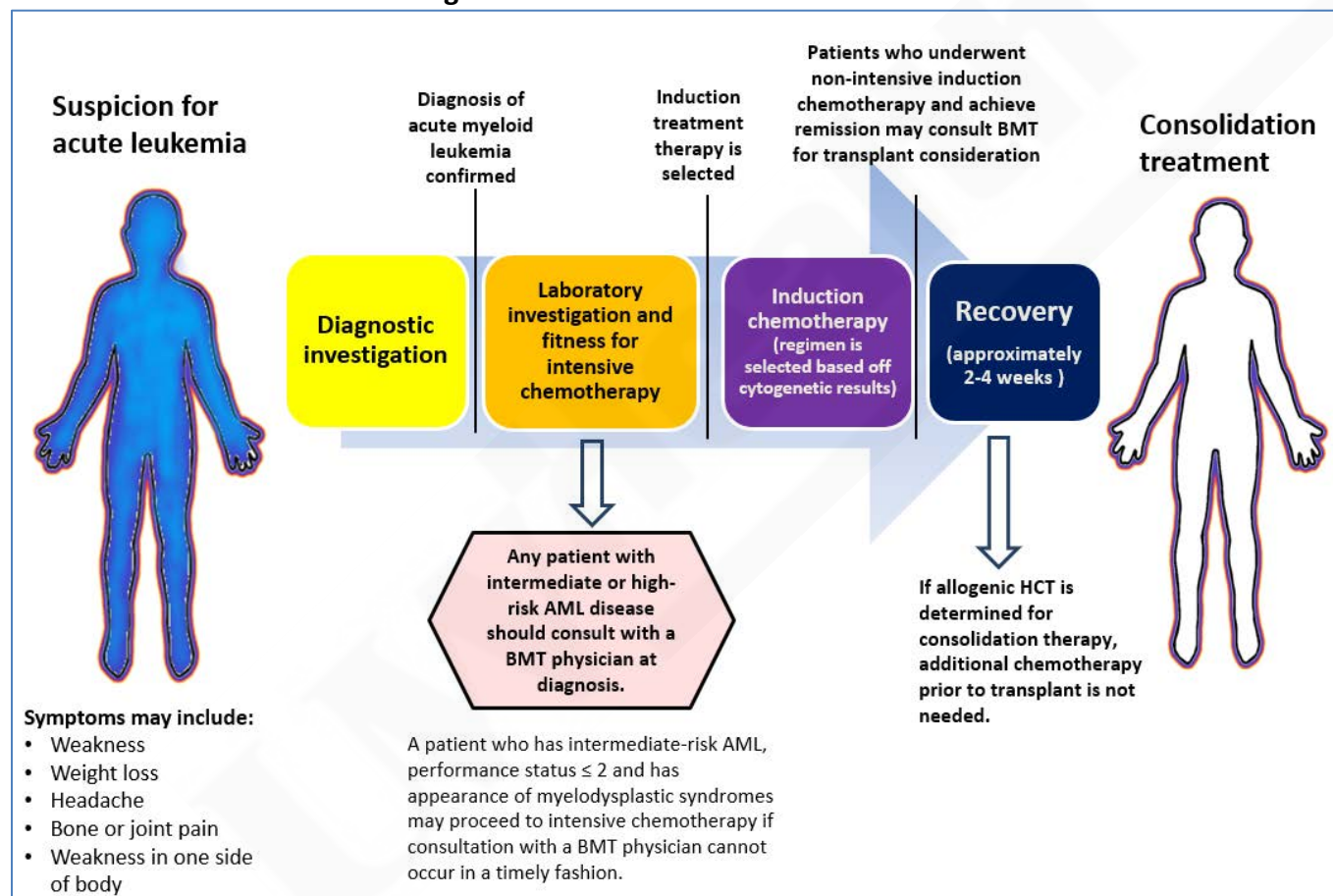
Eastern Cooperative Oncology Group (ECOG) Performance Status scale

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.[2]

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

Recommended tests for patients suspected to have AML[3-5]		
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.[6]*	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

AML- Risk Stratification of disease

Karyotype of the leukemic cell is important because it is a strong prognostic factor for response to induction therapy and survival. Three cytogenetic risk group based on treatment outcomes exist: favorable/low; intermediate and unfavorable/adverse. 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.[7]

European Leukemia Net (ELN) molecular risk stratification[5]

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*

* **Note**: 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.[6-8]It is recommended that all patients with FLT3-ITD have a consultation with a blood and marrow transplant (BMT) physician.

Risk of Relapse following consolidation approach[9]

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

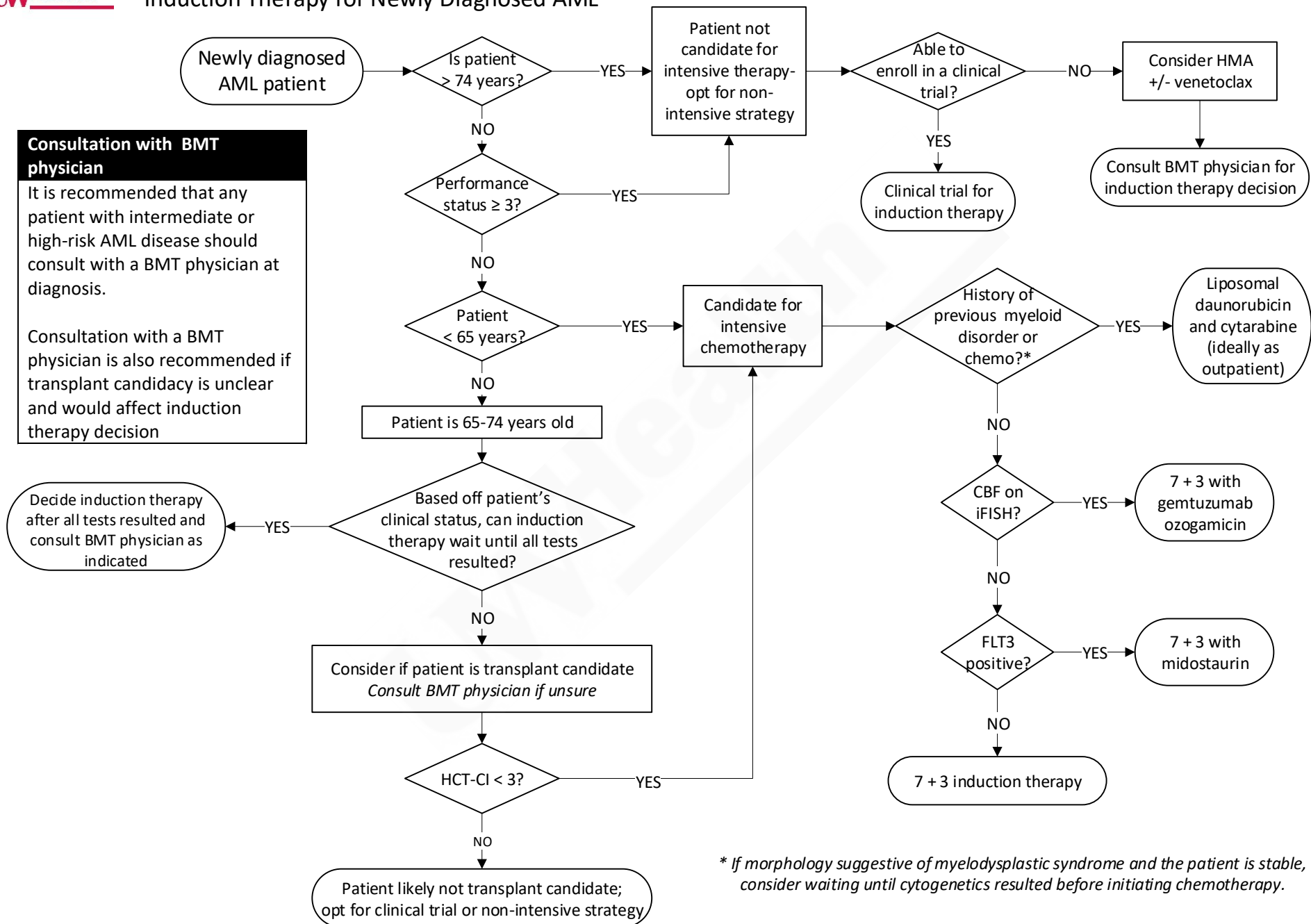## When to Refer to a Blood and Marrow Transplant (BMT) Physician

Consultation with a BMT physician is recommended at diagnosis (e.g., during hospital stay for induction chemotherapy) for AML patients who:
- have a FLT3-ITD mutation
- have intermediate risk or high-risk AML disease profile
  have unclear transplant candidacy and that would affect induction decision

To contact a UW Health BMT Physician	• 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.

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Induction Therapy for Newly Diagnosed AML

Newly diagnosed AML patient

Is patient > 74 years? —YES→ Patient not candidate for intensive therapy- opt for non-intensive strategy →

NO

Able to enroll in a clinical trial? —NO→ Consider HMA +/- venetoclax

YES

Clinical trial for induction therapy

Consult BMT physician for induction therapy decision

Consultation with BMT physician

It is recommended that any patient with intermediate or high-risk AML disease should consult with a BMT physician at diagnosis.

Consultation with a BMT physician is also recommended if transplant candidacy is unclear and would affect induction therapy decision

Performance status ≥ 3? —YES→

NO

Patient < 65 years? —YES→ Candidate for intensive chemotherapy →

NO

Patient is 65-74 years old

History of previous myeloid disorder or chemo?* —YES→ Liposomal daunorubicin and cytarabine (ideally as outpatient)

NO

Decide induction therapy after all tests resulted and consult BMT physician as indicated ←YES— Based off patient's clinical status, can induction therapy wait until all tests resulted?

NO

CBF on iFISH? —YES→ 7 + 3 with gemtuzumab ozogamicin

NO

Consider if patient is transplant candidate
Consult BMT physician if unsure

FLT3 positive? —YES→ 7 + 3 with midostaurin

NO

HCT-CI < 3? —YES→

NO

7 + 3 induction therapy

Patient likely not transplant candidate; opt for clinical trial or non-intensive strategy

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

Appendix A. Common recurrent gene mutations in newly diagnosed AML in adults[10,11]

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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