Veeva Vault

Electronic Certificate

Version: 4 . 0

Document Number: US-01459

Document Name: Unbranded AML Disease Education Brochure

Country: United States

Product: IDH

Type: Commercial Material (US)

Sub Type: Disease Awareness

Classification:

Certification Statement
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Understanding Acute Myeloid Leukemia (AML)

A guide for diagnosing, testing, and treating patients with AML

Treating Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is a clonal malignancy of the hematopoietic system.[1,2] AML is by far the most common type of acute leukemia in adults.[2,3]

As understanding of molecular abnormalities driving leukemia has increased, development of novel therapies has given promise to providing more treatment options for patients.[4-7] This guide is a resource to help you better understand and treat AML.

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See back cover for additional references.

Acute Myeloid Leukemia

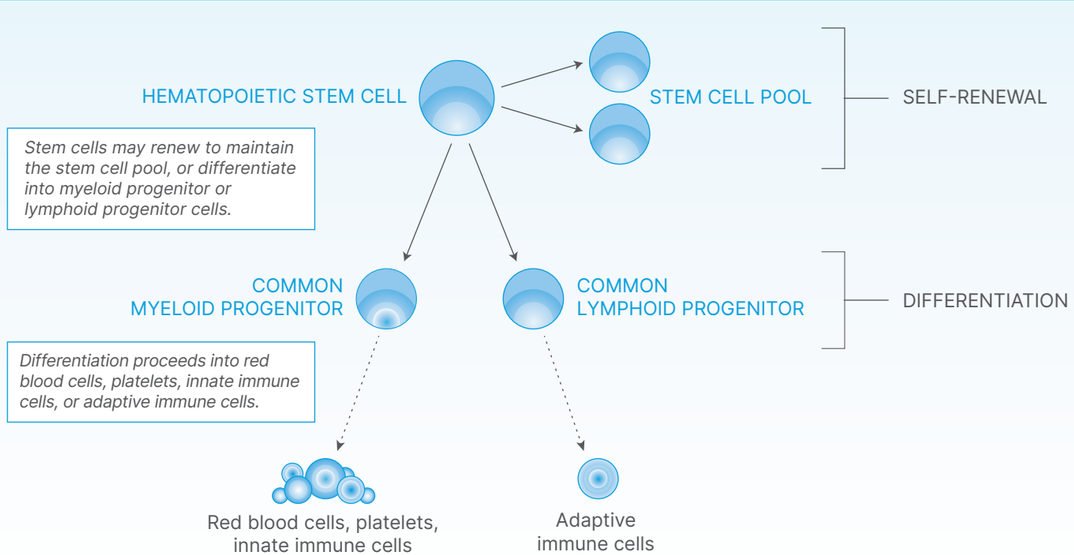
The pathophysiology of AML

Acute myeloid leukemia is a heterogeneous hematopoietic malignancy. It results from inherited and somatic changes to the DNA of hematopoietic precursor cells in the bone marrow.[1,2] AML is a consequence of the proliferation of myeloblasts, which leads to a significant reduction of functional mature blood cells. This can lead to bone marrow failure and death.[8-11]

Normal blood production (hematopoiesis)

Functional hematopoiesis is a process that leads to proliferation and differentiation of blood stem cells and progenitors.[12,13]

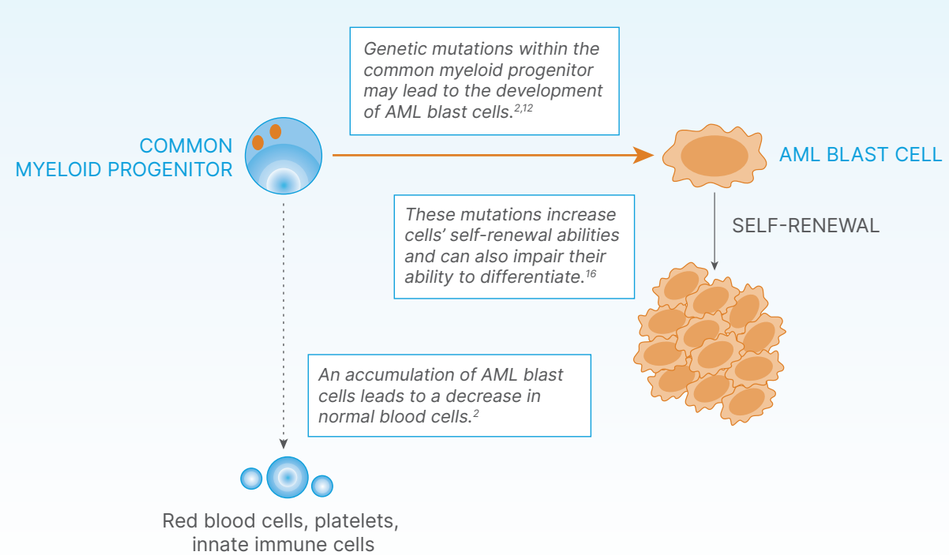
Differentiation of hematopoietic stem cell during hematopoiesis[12]



AML disrupts hematopoiesis

AML disrupts functional hematopoiesis as a consequence of genetic changes in a precursor cell.[12,14]

Disruption of normal hematopoiesis[2,15]



Epidemiology

The Surveillance, Epidemiology, and End Results Program (SEER) estimates that in 2024, there will be 62,770 new cases of leukemia in the United States.[17]

20,800
Estimated new cases of AML

11,220
Estimated mortalities from AML

NCCN

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) note that as the population ages, the incidence of AML, along with myelodysplastic syndromes (MDS), appears to be rising.[18]

AML risk factors

There are well-established risk factors for AML. These include[19,20]:

- Advanced age
- Male sex
- Patient history of another blood disorder
- Prior treatment for cancer
- Smoking exposure[a]

While some individuals diagnosed with AML may have known risk factors, others may not.

[a]There is ongoing research and evidence pointing to the deleterious effects of smoking and its relation to AML.[21,22]

Signs and symptoms at diagnosis

As the symptoms of AML can resemble many other diseases, several tests are necessary to accurately diagnose AML.[23] Patients should be referred to a specialist at the first sign or symptom of a blood disorder or malignancy.

Symptoms can include[11,24,25]:

Pale complexion
due to anemia

Dyspnea
due to anemia

Headache
due to anemia

Bleeding
due to low platelet count

Swollen gums
due to low platelet count

Mild fever
may be related to infection due to low, mature white blood cell levels

Splenomegaly
due to an aggregation of leukemic cells in the spleen

Hepatomegaly
due to an aggregation of leukemic cells in the liver

Weight loss
nonspecific symptom of AML

There are also complications that may be dangerous if left unaddressed. These include[11,24]:

- Intracranial hemorrhage
- Infection

Diagnosing AML

Diagnosing patients with AML is a challenge, and correctly diagnosing AML is of paramount importance to properly plan treatment strategies.[3] Different classification systems for AML have been established.[18,23] These are based on etiology, morphology, immune phenotype, and genetics. The French-American-British (FAB) classification system uses morphology and cytochemical criteria, whereas the World Health Organization (WHO) classification system emphasize genetic abnormalities to further define AML.

The diagnosis of AML is based on the 2022 WHO classification, which recognizes two categories: AML with defining genetic abnormalities and AML defined by differentiation. **Classification of AML defined by differentiation is based on a 20% or more myeloid blast count in the marrow or blood. This blast count threshold has been eliminated for most AML types defined by genetic abnormalities.**[18] An informed understanding of the diagnosis of AML is critical to disease management.[26]

Cytogenetic abnormalities and translocations, along with other abnormalities in molecular profiles, are common in AML.[27-29] This is one reason cytogenetic and molecular analyses have been the standard for stratifying patients with AML into favorable, intermediate, or adverse prognoses.[30]

Prognostic factors include those that are related both to the patient and to the disease.[31] Well-studied aberrations such as t(8;21)(q22;q22.1), inv(16)(p13.1q22), and t(16;16)(p13.1;q22) have helped to define the molecular identities of the disease, lead to new prognostic models, and identify possible targets for new therapeutic drugs.[10,32]

The College of American Pathologists, National Comprehensive Cancer Network® (NCCN®), and European LeukemiaNet (ELN) recommend beginning diagnosis with a complete patient history.[18,23,32]

When taking a patient history, it is important to identify: age, sex, ethnicity, hematologic history, prior malignancies, cytotoxic therapy, immunotherapy, radiotherapy, or any other toxic substance exposure, and additional clinical findings.[23] Knowledge of family history of hematologic disorders or malignancies is also important.

NCCN Guidelines® for AML recommend genetic testing at diagnosis and at each relapse or progression.[18]

Testing methodologies

Testing methodologies require adequate samples of marrow and peripheral blood at diagnosis.[3,33] These are used to build a more complete analysis to get a better picture of the patient's AML genetic status.[18]

Performance score and comorbidity evaluation[3]

Test: WHO performance score
Purpose: Determination of patient health and treatment tolerance
When: Throughout treatment

Blood count testing[3]

Test: Complete blood cell counts and differential
Purpose: Evaluation of bone marrow function and assess hematopoiesis
When: Diagnosis, follow-ups, relapse

Morphology[3]

Test: Bone marrow aspiration and biopsy
Purpose: Blast cell enumeration and lineage assignment, and overview of hematopoiesis
When: Diagnosis, follow-ups, relapse

Multiparameter flow cytometry[3]

Test: Multicolor flow cytometry
Purpose: Understanding of lineage assignment, blast enumeration, and leukemia-associated immunophenotype (LAIP), and assess measurable residual disease
When: Diagnosis, follow-ups, relapse

Cytogenetics[3,34,35]

Test: Karyotyping chromosomal translocations, inversions, and deletions
Purpose: Diagnosis and assessment of risk due to translocations, deletions, and normal or complex karyotypes
When: Diagnosis, follow-ups, relapse
Essential information: Cytogenetic testing is performed by staining cells that have been stopped from changing during cellular division. Through this procedure, a patient's chromosomal health may be understood. Cytogenetic testing for AML can be completed in an average of 7 days

Molecular genetics[3,36-40]

Test: Polymerase chain reaction (PCR) and next generation sequencing (NGS)
Purpose: Diagnostic testing and risk assessment of genome mutations
When: Diagnosis, follow-ups, relapse
Treatment implications: Biomarker testing may confirm a diagnosis or mark a specific genetic mutation
Therapy options: Depending on the result or possible genetic mutation (such as *FLT3*, *IDH1*, *IDH2*), specific gene-related therapy options may become available
Essential information: Molecular genetic tests assess DNA to identify mutations and genomic aberrations. Samples are taken from **bone marrow or peripheral blood**

Cytogenetics and molecular analysis

The first wave of advanced AML treatment came about through cytogenetic analysis.[18] This practice allowed for the detection of structural chromosomal abnormalities, and it remains essential for evaluation of suspected AML diagnosis and assessment.[3,5]

NCCN Guidelines for AML recommend expedited testing for certain actionable mutations such as m*IDH1*. If molecular testing is not available at a patient's treatment center, further evaluation at an outside laboratory or transfer to another institution is recommended.[18]

Driver mutations regulate distinct molecular pathways in the evolution of AML, which can inform disease classification and prognostic stratification.[41] While these are well-known and established markers, the evaluation of molecular genetic lesions as a predictive marker of AML is an active research area.[10,30]

Advances in the field of molecular analysis and sequencing methods have enabled clinicians to uncover the depth and breadth of mutations in AML (such as *DNMT3A*, *IDH1*, and *IDH2*). More than 95% of AML cases contain at least 1 somatic genetic alteration.[6,10,30,42]

Genetic testing results reflect the heterogeneity of AML.[30] Mutations change over the course of a disease, and a molecular profile may be different at diagnosis than it is at relapse.

A short delay for test results does not affect patient outcomes[43,44]

While many testing laboratories have improved turnaround times, in some cases to as few as 3 days, **real-world data also suggests that a short delay for mutational testing to personalize AML management has no negative impact on patient outcomes**.

A large trial utilizing real-world data explored the impact of a short delay for testing on patient outcomes in cases of AML that do not require immediate action (eg, leukostasis). The results revealed that **waiting for molecular test results before treatment selection had no adverse effect on patient survival or remission rates**.

Waiting for genetic and laboratory test results prior to initiating treatment may ensure that patients are given the best treatment option.[45]

Clinical implications

Genetic mutations have important prognostic implications.[46] Cytogenetic and molecular data analysis will help determine risk stratification of AML. Identification of patients who may benefit from specific treatments is critical for improving outcomes.

Functional classes and clinical implications of mutations in AML[42]

Functional class	Known mutations	Clinical implications
Signaling and kinase pathway	*FLT3*, *KRAS*, *NRAS*, *KIT*, *PTPN11*, and *NF1*	These are present in approximately two-thirds of AML cases. Type 1 mutations lead to aberrant activation and proliferation.[42] Targeted therapies and ongoing studies address the *FLT3* and *KIT* mutations.
Epigenetic modifiers (DNA methylation and chromatin modification)	*DNMT3A*, *IDH1*, *IDH2*, *TET2*, *ASXL1*, *EZH2*, and *MLL/KMT2A*	Somatic mutations are found in >50% of patients with AML.[30,42] Some of these mutations and epigenetic modifiers are associated with a worse prognosis. Targeted therapies exist to address some of these epigenetic mutations.
Nucleophosmin	*NPM1*	One of the 3 most common mutations in AML, *NPM1* mutations, specifically those without the *FLT3-ITD* mutation, are associated with overall favorable outcomes.[42,47] There are ongoing trials investigating *NPM1*-mutated AML.
Transcription factors	*CEBPA*, *RUNX1*, and *GATA2*	Transcription factor mutations occur in 20% to 25% of adults with AML.[42,48] Some are associated with a poor prognosis. Novel therapeutic agents for master-regulator transcription factors have yet to be developed.
Tumor suppressors	*TP53*	Uncommon in de novo AML, these mutations occur in about 15% of therapy-related AML (tAML) cases or AML with MDS-related changes and in less than 10% of AML patients overall.[42,49] They are associated with poor survival. Evaluation for a targeted treatment to *TP53* is ongoing.
RNA splicing factors	*SRSF2*, *U2AF1*, *SF3B1*, and *ZRSR2*	RNA splicing factor mutations are found in about 10% of patients with AML. These are associated with older age, less proliferative disease, poor response rates, and decreased survival.[42] No current therapies that target RNA splicing factor mutations are approved for AML.
Cohesin complex	*RAD21*, *STAG1*, *STAG2*, *SMC1A*, and *SMC3*	These mutations have a strong association with the *NPM1* mutation, but a clear prognostic impact in AML patients has yet to be identified.[50] Evaluation for a targeted treatment involving cohesin complex is ongoing.[51]

Obtaining full diagnostic results has been shown to have a clinical benefit for patients.[18]

Classifications of Acute Myeloid Leukemia

Heterogeneous patient population

It is important to remember that for patients 60 years and older, de novo AML, secondary AML, and AML that has progressed following treatment (otherwise known as refractory AML) are each associated with unique considerations that require different approaches to treatment.[18]

NCCN Guidelines state that the initial evaluation of AML will help determine treatment options. In the initial evaluation, it is important to[18]:

- Characterize disease-specific factors that may provide prognostic information, such as: prior toxic exposure, antecedent myelodysplastic conditions, and abnormalities in karyotypic and molecular profiles
- Obtain patient-specific factors, including assessment of comorbid conditions, that may affect an individual's treatment options

De novo AML

Patients initially diagnosed with AML and without a clinical history of MDS, myeloproliferative neoplasia (MPN), or exposure to cancer-causing therapies are known as having de novo AML.[8]

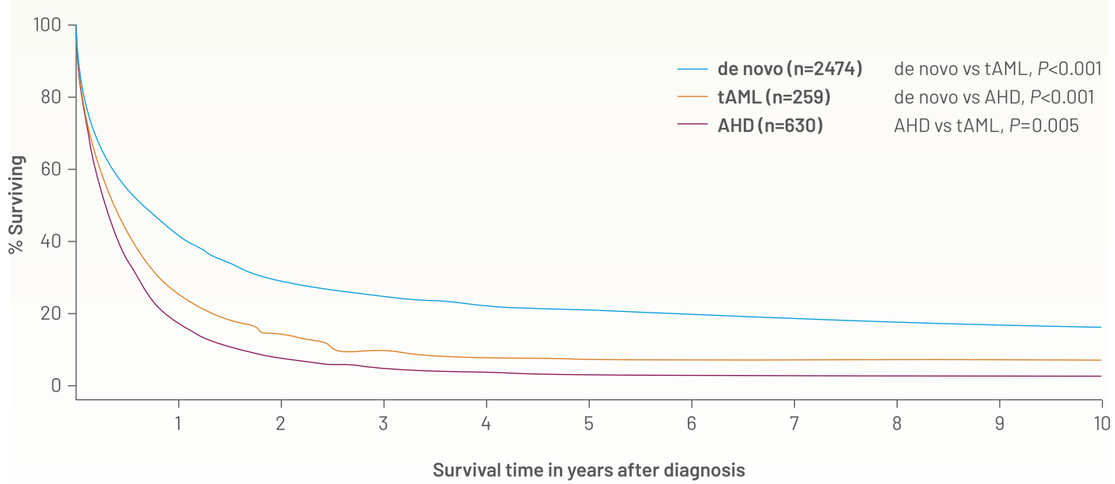
Although research has examined the epidemiology of AML, its etiology is not well understood. Evidence does show that AML occurs at a higher rate in males.[17,52]

Secondary AML

Secondary AML (sAML) is defined as AML with antecedent hematological disease (AHD).[53-57] sAML accounts for approximately 25% of all AML cases and is associated with poor outcomes.[53,57] sAML develops following an initial diagnosis of:

- MDS
- MPN
- Aplastic anemia
- New diagnosis that presents alongside dysplasia
- AML that arises post-cytotoxic therapy (AML-pCT)

A poorer prognosis associated with sAML and tAML when compared with de novo AML[54]



Overall survival (OS) was shown to be significantly worse for AML with AHD and tAML compared with de novo AML regardless of treatment.[54]

Relapsed/Refractory (R/R) AML

After a period of remission, it is possible that cancer cells return to the bone marrow.[58] Refractory AML occurs when patients have not achieved complete remission after 2 cycles of chemotherapy.

The prognosis of patients with R/R AML is poor with a median OS of 3 to 7 months.[59] For patients with relapsed AML, retreatment with previously used induction regimens may produce remission again.[58]

Treatment Options

Achieving remission is the first step in controlling the disease[18]

Treatment of acute leukemia is divided into induction chemotherapy (for eligible patients) and post-remission therapy.[18] While remission is always the goal of therapeutic treatment, it is important for patients to tolerate subsequent treatments to achieve disease control.

Chemotherapy and consolidation therapy

Chemotherapy involves the use of a planned sequence of treatments. In the majority of AML subtypes, patients will be treated with 7 days of continuous-infusion cytarabine and 3 days of an anthracycline.[10] For high-risk R/R patients, salvage regimens composed of low-dose cytarabine alongside anthracycline and alkylating medications are used.[60]

Consolidation therapy is given to patients who achieve complete remission after chemotherapy.[10] Consolidation therapy outcomes in patients 60 years of age and older remain unsatisfactory. Patients with an unfavorable genetic risk, clinically significant comorbidities, or both, are unlikely to benefit from this therapy.

NCCN Guidelines for AML state the best way to judge the efficacy of intensive induction chemotherapy is to obtain bone marrow aspirate and biopsy 14 to 21 days after initiating therapy.[18]

Allogeneic hematopoietic-cell transplantation

Allogeneic hematopoietic-cell transplantation (HCT) is the most common type of stem cell transplantation used to treat AML and offers the strongest antineoplastic therapy option.[10] HCT can be used following complete remission with consolidation therapy.[18] Before recommending HCT, it is important to weigh the risks of this treatment and consider the type of leukemia, previous treatments, patient age, and general health.[61,62]

Targeted therapies

About 96% of AML patients present with at least one driver mutation.[41] Advancements in biologic research have led to the development of targeted therapies.[63] Since 2017, the FDA has approved treatments that target specific mutations in the proteins encoded by the genes *IDH1*, *IDH2*, and *FLT3*. Additionally, therapies have been developed to target CD33 and BCL2.

NCCN Guidelines for AML recommend expediting molecular and genetic test results for immediately actionable mutations or chromosomal abnormalities at diagnosis to help stratify available treatment options.[18]

Targeted therapies and their actions can be broadly categorized into 3 main groups[64-66]:

- Therapies targeting oncogenic driver mutations of AML (eg, FLT3 and IDH1/2 inhibition). These mutation-specific agents target driver mutations
- Therapies targeting maintenance pathways (eg, anti-apoptotic effect of BCL2 overexpression)
- Targeted delivery of cytotoxic agents to the leukemic cells (eg, antibody-drug conjugate targeting CD33)

While turnaround times for mutational analysis results are faster than ever, studies have also demonstrated that a short delay for mutational testing to personalize AML management has no negative impact on patient outcomes.[43,44]

Hypomethylating therapies

Hypomethylating agents (HMA) such as azacitidine and decitabine are options that can be used to treat patients ineligible for intensive chemotherapy.[67] Retrospective studies have suggested that HMA treatment in older patients might achieve similar or better survival rates than patients who receive intensive therapy.[68]

Clinical trials

For some patients, participating in clinical trials may provide the best path forward.[69] If you have a patient who might be a good candidate, consult clinicaltrials.gov for appropriate studies currently recruiting AML patients.

Treatment Outcomes

Ongoing assessment helps evaluate disease progression

AML is a multidimensional disease.[18,70] Clinicians have options when it comes to monitoring their patients' health. Accurate and comprehensive assessment will aid in evaluating disease progression and treatment accuracy.

Monitoring hematologic values during treatment

After the initial diagnosis of AML, intensive induction chemotherapy can begin in appropriate patients.[71] Seven to 10 days after completion of induction chemotherapy, bone marrow evaluation should take place. Remission status should be assessed between Days 28 and 35 since this is when peripheral blood counts begin to recover from induction chemotherapy.

Transfusion status and hematologic parameters

Certain types of therapies (chemotherapy, some targeted therapies) can be myelosuppressive.[72] This may lead to serious adverse events such as anemia, thrombocytopenia, and neutropenia.

Patients with AML who present with anemia or thrombocytopenia may require transfusion.[73] Reasonable thresholds for red blood cell (RBC) transfusion are hemoglobin counts between 7 and 8 g/dL.

Dependence on transfusions is associated with diminished quality of life and poor outcomes.[74] Evidence shows that for high-risk MDS, transfusion independence during first-line therapy is associated with increased progression-free survival and OS.[75]

Assessment of clinical outcomes

Commonly expressed remission classifications

Complete remission (CR): hematologic complete remission is defined as meeting all of the following criteria[76]:

- <5% blasts in the bone marrow
- No circulating blasts
- No extramedullary disease
- Absolute neutrophil count (ANC) >1000/µL
- Platelets >100,000/µL
- Transfusion independence[a]

CR with partial hematologic recovery (CRh): defined as <5% marrow blasts, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/µL and ANC >500/µL).[76]

CR with incomplete hematologic recovery (CRi): defined as <5% marrow blasts, either ANC <1000/µL or platelets <100,000/µL, and transfusion independence but with cytopenia (usually thrombocytopenia).[76]

NCCN Guidelines state that complete remission in AML rates rarely exceed 70% in younger patients and 50% in older patients.[18]

Partial response (PR): defined as demonstrating all CR criteria except either or both of the following[77]:

- At least a 50% decrease in the marrow blast percentage compared with pretreatment levels (rather than the <5% threshold for CR)
- A less-advanced MDS classification than prior to treatment

Morphologic leukemia-free state (MLFS): defined as <5% blasts and no blasts with Auer rods or extramedullary disease.[18]

[a]There are different criteria for transfusion independence, but a rigorous understanding is defined as an individual receiving no RBC transfusions for at least 56 days.[42,65]

AML: A growing body of evidence

Acute myeloid leukemia is a cancer that affects the blood and bone marrow.

AML is a heterogeneous and complex disease.[5,10] Over the past 15 years, a better understanding of AML's molecular genetic abnormalities has yielded important prognostic information. Applying these discoveries into therapy is only beginning.

Test your patients at diagnosis and relapse.[18,78] Genetic mutations change the course of the disease, and the molecular profile may change.

It is important to remember that for patients 60 years and older, AML type plays an important role in patient treatment.[18,38] De novo AML, secondary AML, and relapsed or refractory AML are each associated with unique considerations that require different approaches to treatment.

Just as knowledge of the biology driving AML has increased, so too has the development of novel treatment options grown.[63] From chemotherapy and consolidation therapy to targeted therapies, there are modern treatment options for AML that can give clinicians and patients alike reason to move forward with greater confidence.

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Selections from the NCCN Guidelines

The NCCN is a not-for-profit association of over 30 cancer centers dedicated to patient care, research, and education. For 25 years, NCCN has developed tools that are evidence-based and consensus-driven to ensure all patients receive preventive, diagnostic, treatment, and supportive services that are most likely to lead to optimal outcomes.

The NCCN Guidelines offer support for physicians, nurses, pharmacists, payers, support staff, and patients on many topics related to AML. These guidelines are important aids in the decision-making process in AML care.

NCCN Guidelines for AML

- Note that as the population ages, the incidence of AML and other myelodysplastic syndromes rises
- Recommend genetic testing at diagnosis and at each relapse or progression
- Recommend expediting molecular and genetic test results for immediately actionable mutations or chromosomal abnormalities at diagnosis to help stratify available treatment options
- Recommend that if molecular testing is not available at a patient's treatment center, further evaluation at an outside laboratory or transfer to another institution is recommended
- State that the initial evaluation of AML will help determine treatment options. Within this evaluation it is important to:
  - Obtain patient-specific factors including assessment of comorbid conditions that may affect an individual's treatment options
  - Determine prior malignancies and prior treatments
- State the best way to judge the efficacy of intensive induction chemotherapy is to obtain bone marrow aspirate and biopsy 14 to 21 days after the start of therapy
- Remind clinicians that CR rates rarely exceed 70% in younger patients and 50% in older patients

For the complete NCCN Guidelines, please visit the NCCN website.