

Hematopoietic Cell Transplantation for Adults with Acute Myeloid Leukemia: Considerations for Case Management

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INTRODUCTION

Hematopoietic cell transplantation (HCT) is an intensive, potentially curative therapy for blood cancers, such as acute myeloid leukemia (AML). This treatment replaces diseased blood stem cells with healthy cells. For AML, an allogeneic transplant is most common, where the healthy cells come from either a related or unrelated donor or an umbilical cord blood unit (CBU). The treatment process is long, requiring weeks to months of preparation and months to years of recovery and follow-up care.

This article will describe the diagnosis and treatment options for AML, including HCT referral considerations to improve outcomes, such as human leukocyte antigen (HLA) typing at diagnosis, cytogenetics and molecular markers, and age.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

1. Identify high- and intermediate-risk cytogenetic and molecular markers for hematopoietic cell transplantation.
2. Cite how referral timing affects HCT outcomes for patients with AML.
3. Identify when HLA typing should be performed.
4. Use AML and HCT educational resources for patients and clinicians.



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AML OVERVIEW

Considerations at Diagnosis

AML is a rapidly progressing disease that often requires patients to start induction chemotherapy within days to weeks of diagnosis. Diagnosis, according to the 2016 World Health Organization classification system, requires 20% or more blasts in bone marrow or peripheral blood.¹ Further classification of AML type requires careful assessment of pathology, immunohistochemistry, and molecular genetics.²

While symptoms may include fever, weight loss, and petechiae, among the most impactful are fatigue and weakness, which negatively affect their ability to maintain normal activities.³ At diagnosis, patients are acutely ill and fatigued, and yet face a steep learning curve as they are suddenly inundated with information about their disease, treatment options and prognosis.⁴ As a result, patients may have a simplistic understanding of treatment options, and feel as if they have no choice other than to accept the treatment offered. To improve this experience for patients, clinicians must have shared decision making conversations to better understand their patients’ treatment goals and help inform treatment planning.

Treatment Options

The primary consideration for all patients regarding treatment options is eligibility and the option to enroll in a clinical trial. Primary assessment should include genetic mutation testing and evaluation of co-morbidities as those may impact therapy options.⁵ For patients who are fit enough, treatment begins with induction chemotherapy. The typical regimen is cytarabine over seven days followed by idarubicin or daunorubicin over three days, also called “7+3”. Alternate chemotherapy regimens are available for patients who are less able to tolerate this chemotherapy regimen. Ideally induction results in complete remission. And yet, for most patients, relapse is likely, thus consolidation therapy is recommended.² The choice of consolidation therapy depends on disease risk. For favorable-risk disease a chemotherapy regimen may be an appropriate. For intermediate- or high-risk disease allogeneic HCT is recommended.

Clinical trials are vital to improving treatment options for AML. The standard 7+3 regimen hasn’t had meaningful competition in decades. In fact, no new drugs were approved by the U.S. Food and Drug Administration (FDA) for AML between 1990 and March 2017.

April 2017 marked the start of a series of drug approvals by the FDA, almost all targeting specific cytogenetics/molecular markers. The first approval was the oral agent, midostaurin, as an addition to 7+3 for patients with *FLT3* (pronounced “flit”) mutation.⁶ Between April 2017 and November 2018, the FDA approved several new single/combination drug options for AML (Table 1) and more approvals are expected in 2019.

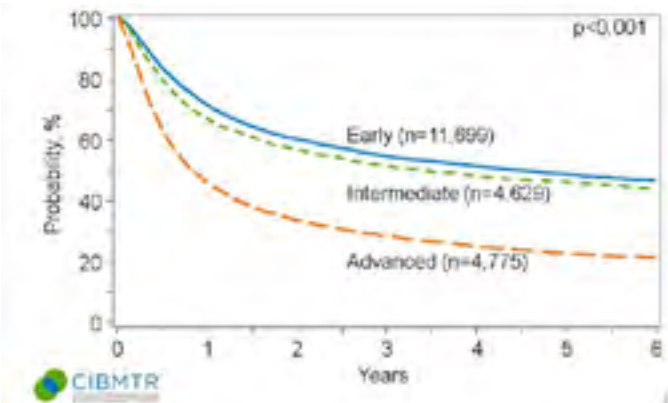
TABLE 1 New FDA-approved drugs for the treatment of AML in 2017-18

| Drug | Targeted use |
|--|----------------------------------|
| Midostaurin ⁶ | <i>FLT3</i> inhibitor |
| Gilteritinib ⁷ | <i>FLT3</i> inhibitor |
| Ivosidenib ⁸ | <i>IDH1</i> inhibitor |
| Enasidenib ⁹ | <i>IDH2</i> inhibitor |
| Daunorubicin and cytarabine liposome ¹⁰ | N/A |
| Glasdegib ¹¹ | <i>BCL₂</i> inhibitor |
| Venetoclax ¹² | <i>BCL₂</i> inhibitor |
| Gemtuzumab ozogamicin ¹³ | CD33-positive AML |

Adults over the age of 65 are typically under-represented in clinical trials and increasing their participation is important to changing the standards of care for this age group. In general, over half of patients with cancer will not have a local trial available for them.¹⁴ The Jason Carter Clinical Trials Program offered through the National Marrow Donor Program® (NMDP)/Be The Match® is working to make it easier for patients with blood cancers like AML and blood disorders to find and join trials. There are nearly 300 actively recruiting clinical trials in the U.S. related to AML treatment. This program offers a simple online search tool, easy-to-read trial descriptions, one-on-one support, and travel grants for eligible patients. Learn more at JCCTP.org.

HCT REFERRAL FOR CONSULTATION

AML is the most common clinical indication for patients undergoing allogeneic HCT. Appropriate HCT referral timing greatly impacts outcomes for patients. It’s well documented that eligible patients have better outcomes when they undergo HCT during first complete remission (CR1) (Figure 1).^{15,16}

FIGURE 1 Survival after Unrelated Donor HCT for AML, 2006–2016

And yet, nearly half of patients with AML who undergo unrelated donor HCT receive their transplant during their second complete remission or later.¹⁶ Possible reasons for this include:

- Late referrals to a transplant center
- Aggressive disease which progresses or relapses before HCT
- Perceived lack of a suitable donor
- Patients decline treatment with HCT

It's understandably difficult for clinicians to stay current on disease-specific referral timing information. While AML is the most common indication for HCT, according to a NMDP/Be The Match survey, community clinical care providers saw on average 15 people with AML in any given year.¹⁷ Gaps have been identified in oncologists' knowledge of AML, including risk stratification by cytogenetics/molecular markers, and perception of chronologic age as a barrier to HCT referral.¹⁷

Cytogenetics and Molecular Abnormalities

Using results from meta-analyses of patients with AML from multiple clinical trials, researchers have classified AML cytogenetic and molecular markers into three main categories: favorable-, intermediate- and poor-risk.² Free evidence-based resources to assess risk factors and referral timing include:

- [AML Guidelines](#), created by the National Comprehensive Cancer Network® (NCCN®). Create a free account to access and see page AML-A for the risk status table.
- [HCT Referral Guidelines](#), jointly provided by the

NMDP/Be The Match and the American Society for Blood and Marrow Transplantation (ASBMT).

Available in print or as a mobile app.

Once the AML risk status is identified, treatment planning conversations can continue, and talking about AML prognosis with patients is not easy. In one study on the patient experience talking about disease risk and prognosis, most participants felt this information “only predicts the end of their lives, which they felt took away hope.”¹⁸ Free tools are available to help clinicians have these conversations and offer support to patients:

- [AML Treatment Conversation Guide](#), co-created by the NMDP/Be The Match and The Leukemia & Lymphoma Society, helps clinicians and patients discuss prognosis and treatment options.
- The Be The Match [Patient Support Center](#) offers free support programs and resources for patients and caregivers. For example, through the *Peer Connect* program, they can talk with someone who had AML and underwent HCT. Request a connection at BeTheMatch.org/PeerConnect

Age

A historical barrier of chronologic age alone limiting a patient's treatment options has been lifted. Research continues to show that physiologic age factors can be used to help determine potential HCT outcomes.^{19,20} In 2018, nearly 1,300 allogeneic transplants facilitated by the NMDP/Be The Match were for patients 65 years of age or older.²¹ The number of HCT recipients 70 years of age or older is also rising, and they represented 6% of allogeneic transplants for blood cancers in 2017.¹⁶

The decision to undergo induction chemotherapy followed by allogeneic HCT depends on patient factors, including performance status, cytogenetics/molecular markers, and comorbidities. Unfortunately, poor-risk cytogenetics/molecular markers and comorbidities are more likely in older patients, 60 years and older.²² The HCT comorbidity index, or HCT-CI, is a tool used by transplant physicians that can help predict outcomes based on organ function.

In order to make this curative therapy available to more patients, efforts to reduce the toxicity of HCT have resulted in reduced-intensity preparative regimens and improved supportive care. Researchers and clinicians are studying strategies to improve the health and resiliency of older

patients, making them more able to tolerate HCT. Geriatric/frailty assessments and tailored pre-habilitation are promising but they are not widely used, despite being simple and fast.^{23,24} A **new** Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial 1704 will prospectively look at how to improve health assessments and prediction of toxicity and mortality in older patients undergoing HCT.²⁵

DONOR SEARCH

Once the referral for HCT consultation has been made, it may take time to find a donor. While related donors may need minimal time for testing and preparation, the search process for unrelated donors can take longer to complete. Unfortunately, 7 out of 10 people who need an allogeneic HCT won't have a matching donor in their family. For patients at a higher risk of relapse, time is of the essence.

Results of the Southwest Oncology Group 1203 clinical trial, led by John M. Pagel, found that outcomes for patients with poor-risk AML could be improved simply by starting the donor search earlier.²⁶ Recognizing that the donor search takes time, and that for poor risk AML time spent in CR1 may be short, the researchers hypothesized that more transplants during CR1 could improve outcomes. To study this they had expedited human leukocyte antigen (HLA) typing done for a group of patients with poor-risk cytogenetics. Patients in the study had a higher rate of relapse-free survival compared to historical data (32% vs. 22%, $p=0.05$). These results suggest that patients can have better outcomes simply by finding an unrelated donor and undergoing allogeneic HCT quickly.

Based on NCCN Guidelines, NMDP/Be The Match recommends that HLA typing be performed at time of diag-

nosis for all patients with AML. Therefore, NMDP/Be The Match is leading a pilot program to equip a select number of inpatient hematology/oncology units with HLA swab kits to promote early HLA testing in an effort to improve outcomes for patients with AML. With this program, patients will be buccal swabbed for HLA typing at time of diagnosis. The physicians will then receive the patients' HLA typing and a preliminary donor search report noting how likely it is that the patient will have an available HLA-matched donor on the Be The Match Registry.[®] By providing this information early, physicians and patients will have information to inform treatment options which will lead to well-informed post-induction treatment plans and ultimately better outcomes.

All clinicians should keep HLA testing at time of diagnosis in mind for patients with AML. HCT may not be necessary, but the risks of delayed testing, which may result in relapse before HCT, are serious.

CONCLUSION

AML is an aggressive, life-threatening blood cancer. With cytogenetic and molecular testing, more tailored treatment options have recently become available. Additionally, while barriers to effective treatment exist, they can be overcome. Use of physiologic age factors is expanding the number of patients over the age of 60 years who are able to undergo successful HCT, and strategies to improve access to HCT during CR1 can increase overall survival. Working together, clinicians and case managers can enhance care-coordination to benefit patients with AML. ■

[Click here](#) for references.



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EMAIL: patientinfo@nmdp.org

ORDER: [BeTheMatch.org/request](https://www.bethematch.org/request)

CALL: 1 (888) 999-6743

TRANSLATED RESOURCES: [BeTheMatch.org/translations](https://www.bethematch.org/translations)

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Questions

- Classification of acute myeloid leukemia (AML) includes careful assessment of:
 - Pathology
 - Immunohistochemistry
 - Molecular genetics
 - All of the above
- The most impactful symptom as reported by patients is:
 - Fever
 - Weight loss
 - Feeling acutely ill and fatigue
 - Petechiae
- Primary assessment should include genetic mutation testing and evaluation of comorbidities as the results may impact therapy options.
 - True
 - False
- Because relapse is likely, for patients with intermediate- or poor-risk disease, HCT is recommended.
 - True
 - False
- Although clinical trials are vital to improving treatment options for AML, what percentage of patients with cancer will not have a local clinical trial available for them?
 - Over 30%
 - Over 40%
 - Over 50%
 - Over 60%
- When do eligible patients have better outcomes when they undergo HCT?
 - During the first complete remission
 - During the second complete remission
 - During the third complete remission
 - It doesn't matter
- What are possible reasons for the delay in HCT?
 - Late referral to transplant center
 - Aggressive disease
 - Perceived lack of a suitable donor
 - All of the above
- Once the AML risk status is identified, treatment planning conversations can continue, and talking about AML prognosis with the patient is not easy.
 - True
 - False
- A historical barrier of limiting treatment options based on chronologic age alone has been lifted.
 - True
 - False
- Because finding an HCT donor may take some time, NMDP/Be The Match recommends that HLA typing be performed at time of diagnosis for all patients with AML.
 - True
 - False

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Answers

May 2019

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