NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

Clinical Decision Making in Acute Myeloid Leukemia

NEW RESEARCH GUIDES THERAPEUTIC CHOICES

Key Findings

1

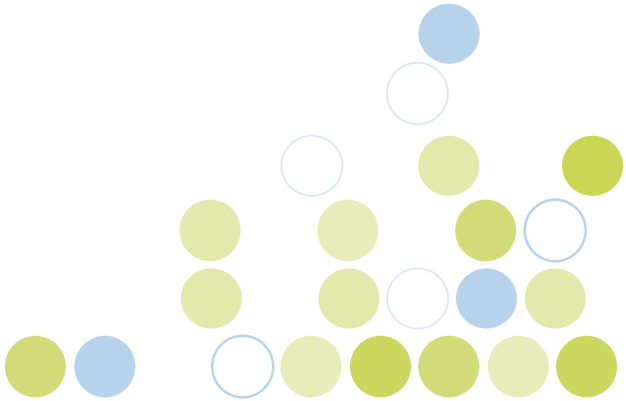
Revised risk stratification based on updated cytogenetics and molecular markers research.

2

Therapy decisions should be based on patient health status and disease risk, not chronological age.

3

Transplant outcomes for AML have steadily improved.



Clinical Decision Making in Acute Myeloid Leukemia (AML)

NEW RESEARCH GUIDES THERAPEUTIC CHOICES

Revised risk stratification

Evolving research is altering how cytogenetics and molecular markers are used to guide therapeutic choices in AML. Table 1 shows risk status based on validated cytogenetics and molecular markers from the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia.

Emerging data indicate that the presence of c-*KIT* mutations in patients with t(8;21), and to a lesser extent inv(16), confers a higher risk of relapse; these patients are considered to have intermediate-risk disease. [1]

For patients with intermediate- and poor-risk cytogenetics, a meta-analysis demonstrated a survival benefit of allogeneic HCT in first complete remission over chemotherapy. [2] Referral for HCT evaluation for these at-risk patients early in their disease stage can significantly improve survival. [3,4]

Risk Status	Cytogenetics	Molecular Abnormalities
FAVORABLE-RISK	Core binding factor: inv(16) or t(16;16) or t(8;21) or t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or presence of FLT3-ITD^{low} or isolated biallelic (double) CEBPA mutation
INTERMEDIATE-RISK	Normal cytogenetics t(9:11) Other non-defined	Core binding factor with KIT mutation Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without poor-risk genetic lesions)
POOR-RISK	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 – non t(9;11) Inv(3), t(3;3) t(6:9) t(9;22)	Normal cytogenetics: with FLT3-ITD mutation TP53 mutation Mutated RUNX1 Mutated ASXL1 Wild-type NPM1 and FLT3-ITD^{high}

Table 1. NCCN risk status based on validated cytogenetics and molecular abnormalities for AML. [1]

Recommended timing for transplant consultation for AML

To supplement the NCCN Guidelines®, the National Marrow Donor Program® (NMDP)/Be The Match® and the American Society for Blood and Marrow Transplantation™ (ASBMT) have jointly developed guidelines for transplant referral timing. [5]

Referral timing guidelines for AML, shown in Table 2, highlight that high-resolution HLA typing should be performed at time of diagnosis for all patients with AML, and identifies those patients who should be referred early after initial diagnosis. This includes all patients with intermediate- and poor-risk cytogenetics and molecular features as well as high-risk disease features.

➤ TRANSPLANT CONSULTATION GUIDELINES: ADULT AML

High-resolution HLA typing is recommended at diagnosis for all patients.

➤ Early after initial diagnosis, all patients with AML including:

- Primary induction failure
- Minimal residual disease after initial therapy
- CR1 - except favorable risk AML [defined as: t(16;16), inv(16), or t(8;21) without c-*KIT* mutation; t(15;17); normal cytogenetics with *NPM1* or isolated biallelic *CEBPA* mutation and without *FLT3*-ITD]
- Antecedent hematological disease (e.g., myelodysplastic syndromes [MDS])
- Treatment-related leukemia
- First relapse
- CR2 and beyond, if not previously evaluated

Table 2. NMDP/Be The Match and ASBMT transplant consultation guidelines for AML in adults. CR1 = first complete remission, CR2 = second complete remission

HCT eligibility: Prognostic factors

Research has shown that chronological age alone is not a contraindication for HCT in patients with AML. [6-8] Comorbidities and performance status are prognostic factors used to determine eligibility for transplant. [9] This is reflected in a steady increase in the number of unrelated donor transplants for patients older than 64 years with AML from 2008 to 2018 (fiscal year data -October 1 - September 30) as shown in Figure 1. [10]

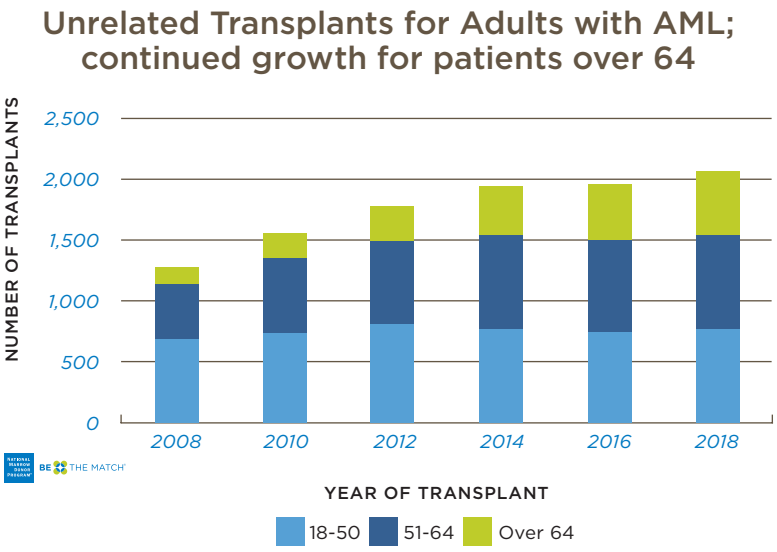


Figure 1. NMDP/Be The Match-facilitated transplants for adults with AML, by age and fiscal year of transplant

Clinical advances improve transplant survival

Overall survival at 1- and 2-years after unrelated donor HCT has improved steadily over time as shown in Table 3. **Improvement in survival has occurred even as greater numbers of older patients are undergoing transplant.**

Better risk-stratification using AML cytogenetics and molecular markers contributed to improvements in survival. Other reasons for improved survival rates include the monitoring of minimal residual disease (MRD), which allows for preemptive therapy with persistent or recurrent disease [11], and improved management of post-transplant complications. [12-14]

Disease status at time of transplant can also significantly affect outcomes. **Research has shown that transplant in early stage disease can lead to significantly improved survival.** [3,4] Figure 2 shows this for adult patients with AML undergoing unrelated donor HCT. [15]

Several studies have shown that unrelated donor and sibling donor HCT outcomes in AML are comparable, including a study of 197 patients ≥50 years with AML in complete remission. [16-17]

Improved Survival Over Time - AML

Year of HCT	Number of Cases	One-Year Survival	Two-Year Survival
2013-2016	5,626	64%	53%
2009-2012	4,400	58%	48%
2004-2008	3,198	53%	42%
1987-2003	2,245	34%	27%

Table 3. Unrelated HCT improved 1- and 2-year survival over time in adults with AML

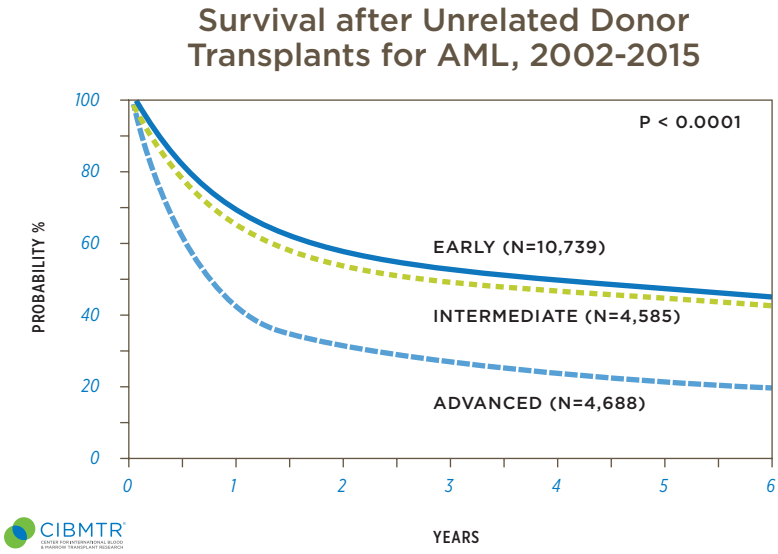


Figure 2. AML survival, unrelated donor HCT, by disease status. Early = first complete remission (CR1), Intermediate = second complete remission (CR2) or subsequent CR, Advanced = primary induction failure or active disease

Clinical Decision Making in AML

NEW RESEARCH GUIDES THERAPEUTIC CHOICES

Clinical Action Points

1

Apply cytogenetics and molecular markers for AML risk-stratification to determine prognosis and therapeutic options.

2

Counsel older patients on HCT as a therapeutic choice based on disease risk and health status, not on chronological age.

3

Order high-resolution HLA typing at diagnosis.

4

Recommend a transplant consultation early after initial diagnosis for patients with intermediate- or poor-risk cytogenetics and molecular markers or other high-risk disease features.

SUPPLEMENT TO YOUR TREATMENT GUIDELINES

Our Recommended Timing for Transplant Consultation guidelines provide you with information wherever you are.

Updated annually, the guidelines provide up-to-date referral timing based on the latest research.

Available free in print, mobile app and online: **BeTheMatchClinical.org/guidelines**

References:

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2018. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed October 1, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

We are the global leader in providing a cure to patients with life-threatening blood and marrow cancers like leukemia and lymphoma, as well as other diseases. We manage the world's largest registry of potential marrow donors and cord blood units, connect patients to their donor match for a life-saving marrow or umbilical cord blood transplant and educate health care professionals and patients. We conduct research through our research program, CIBMTR® (Center for International Blood and Marrow Transplant Research®), in collaboration with Medical College of Wisconsin.
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