NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

Clinical Decision Making in AML

NEW RESEARCH GUIDES THERAPEUTIC CHOICES

Key Findings

1

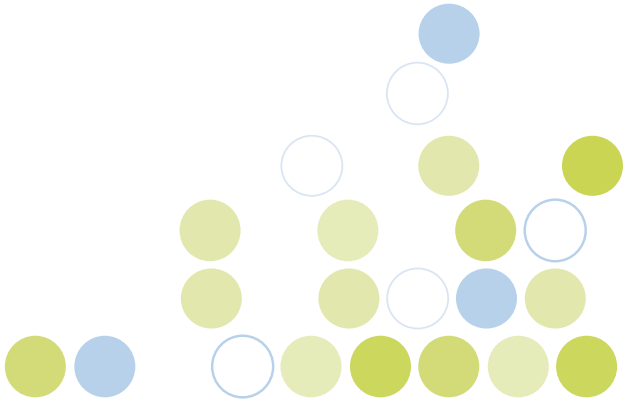
Revised risk stratification based on updated molecular markers and cytogenetics research.

2

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

3

Improved outcomes of transplant for AML.



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Revised risk stratification

Evolving research is altering how cytogenetic 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 National Comprehensive Cancer Network (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) t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
INTERMEDIATE-RISK	Normal cytogenetics +8 alone t(9:11) Other non-defined	
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

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 cytogenetic/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 AML patients should undergo evaluation for HCT, including:

- 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 biallelic CEBPA mutation and without FLT3-ITD]
- Antecedent hematological disease (e.g., myelodysplastic syndrome [MDS])
- Treatment-related leukemia
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- 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

New research: HCT eligibility and age

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 2007 to 2015 as shown in Figure 1. [10]

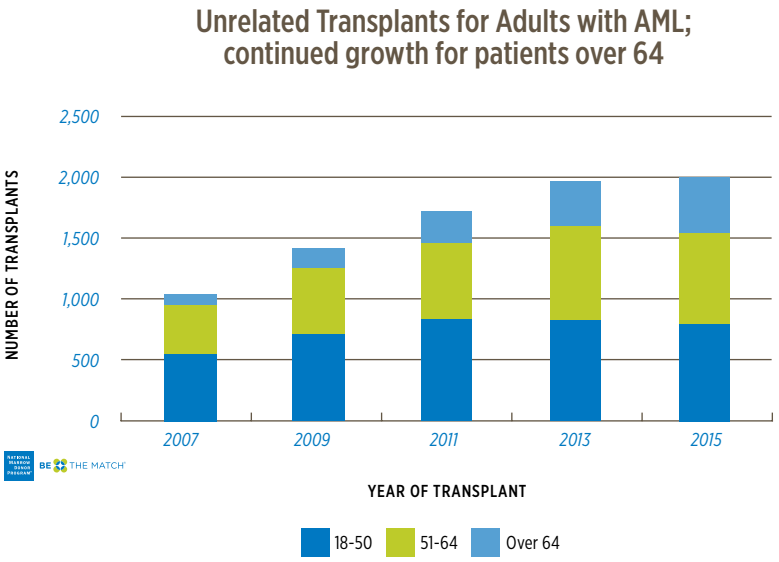

Figure 1. NMDP/Be The Match-facilitated transplants for adults with AML, by age and year of transplant

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 molecular markers and cytogenetics has 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 Act	Number of Cases	One-Year Survival	Two-Year Survival
2011-2013	3,809	60%	49%
2007-2010	3,574	57%	45%
2002-2006	2,285	48%	38%
1987-2001	1,606	31%	24%

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

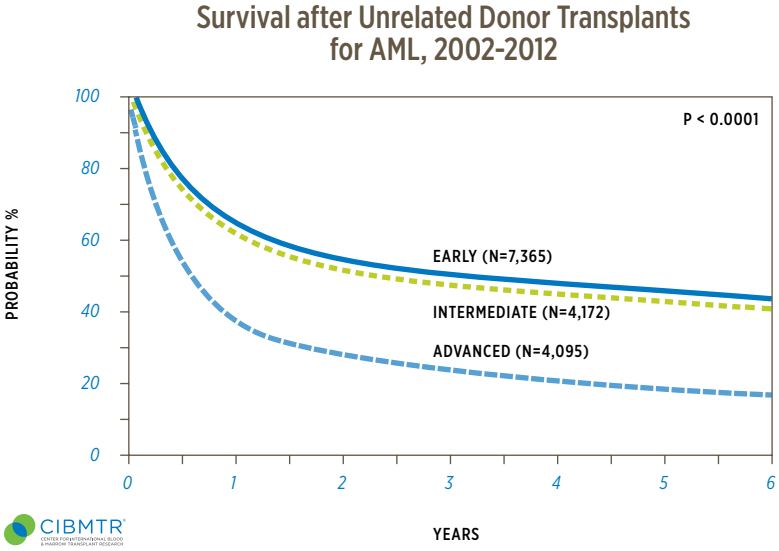

Figure 2. AML survival, unrelated donor HCT, by disease status.

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Clinical Action Points

1

Apply cytogenetic 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

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

SUPPLEMENT TO YOUR TREATMENT GUIDELINES

Our Recommended Timing for Transplant Consultation guidelines provide you with the HCT referral-timing information you need most.

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.1.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed March 3, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
2. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: Systematic review and meta-analysis of prospective clinical trials. JAMA. 2009; 301(22): 2349-2361.
3. Pidala J, Lee SJ, Ahn KW, et al. Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. Blood. 2014; 124(16): 2596-2606.
4. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007; 110(13): 4576-4583.
5. 2016 NMDP/Be The Match and ASBMT referral timing guidelines – AML.
6. Devine SM, Owzar K, Blum W, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: Results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trials Network 0502. J Clin Oncol. 2015; 33(35): 4167-4175.
7. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. 2010; 28(11): 1878-1887.
8. Rashidi A, Ebadi M, Colditz GA, DiPersio JF. Outcomes of allogeneic stem cell transplantation in elderly patients with acute myeloid leukemia: A systematic review and meta-analysis. Biol Blood Marrow Transplant. 2015; Epub October 31.
9. Sorror ML, Logan BR, Zhu X, et al. Prospective validation of the predictive power of the hematopoietic cell transplantation comorbidity index: A Center for International Blood and Marrow Transplant Research study. Biol Blood Marrow Transplant. 2015; 21(8): 1479-1487.
10. National Marrow Donor Program/Be The Match 2015 fiscal year reports.
11. Ossenkoppele G, Löwenberg B. How I treat the older patient with acute myeloid leukemia. Blood. 2015; 124(5): 767-774.
12. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015; 373(12) 1136-1152.
13. Cornelissen JJ, Versluis J, Passweg JR, et al. Comparative therapeutic value of post-remission approaches in patients with acute myeloid leukemia aged 40-60 years. Leukemia. 2015; 29(5), 1041-1050.
14. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation; Center for International Blood and Marrow Transplant Research (CIBMTR), American Society for Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplantation (EBMT), Asia-Pacific Blood and Marrow Transplantation Group (APBMT), Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), East Mediterranean Blood and Marrow Transplantation Group (EMBMT) and Sociedade Brasileira de Transplante de Medula Ossea (SBTMO). Biol Blood Marrow Transplant. 2012; 18(3): 348-371.
15. 2015 CIBMTR analysis of NMDP/Be The Match-facilitated transplants.
16. Schetelig J, Bornhäuser M, Schmid C, et al. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: A report from the Cooperative German Transplant Study Group. J Clin Oncol. 2008; 26(32): 5183-5191.
17. Peffault de Latour R, Brunstein CG, Porcher R, et al. Similar overall survival using sibling, unrelated donor, and cord blood grafts after reduced-intensity conditioning for older patients with acute myelogenous leukemia. Biol Blood Marrow Transplant. 2013; 19(9): 1355-1360.

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.
Learn more at **BeTheMatchClinical.org**

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