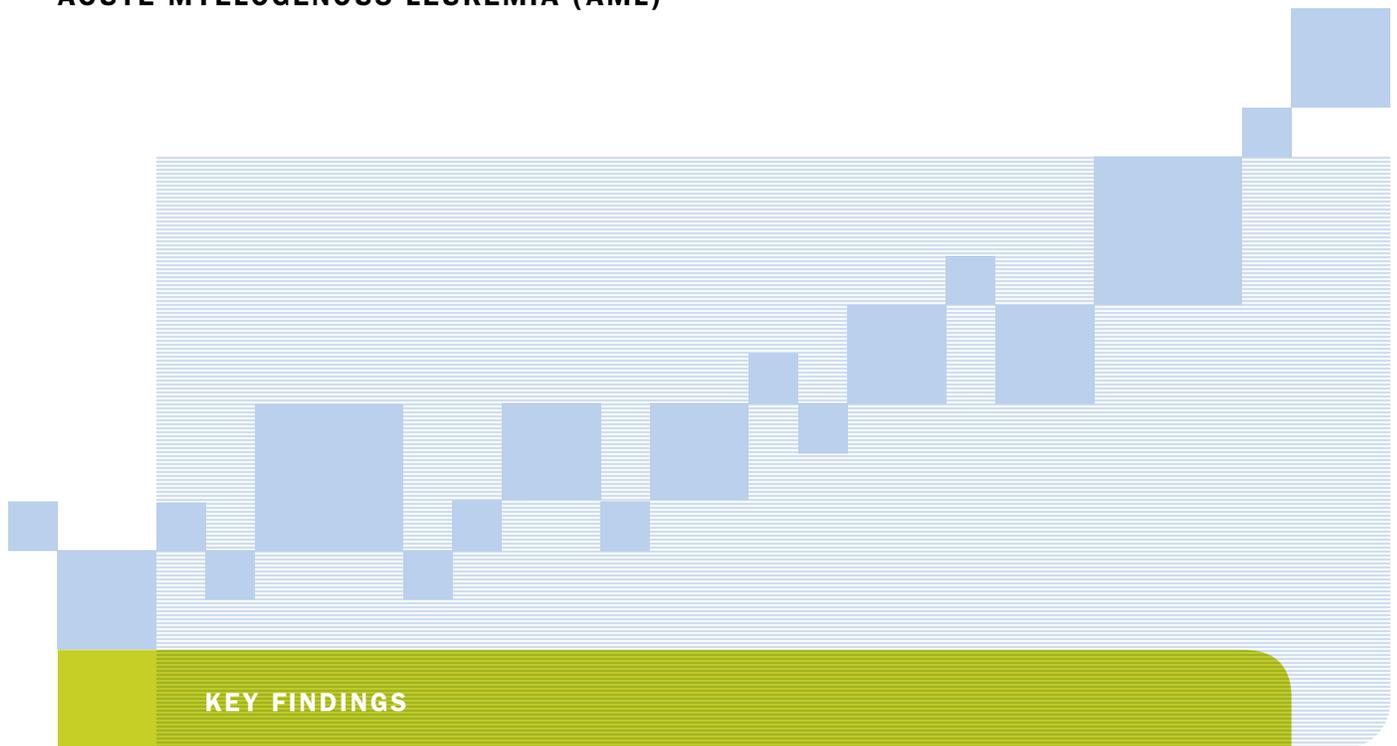


HCT in AML

TRENDS IN HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE MYELOGENOUS LEUKEMIA (AML)



KEY FINDINGS

1

Molecular markers influence therapy choices.

New classifications based on cytogenetic and molecular abnormalities in AML allow physicians to better stratify patients into risk groups and select appropriate therapies.

2

Patient eligibility is expanding.

Improved outcomes now allow for more patients to be considered for transplant, resulting in growth in transplants for older patients and those in first complete remission (CR1).

3

Survival is improving.

Allogeneic transplant outcomes have improved due to advances in clinical practice and human leukocyte antigen (HLA) typing and matching.

Advances in Research Guide Clinical Practice

This summary provides clinicians with an overview of recent trends in allogeneic transplantation for acute myelogenous leukemia (AML) in adults and how the latest research affects clinical decision-making. Worldwide, more than 7,000 allogeneic hematopoietic cell transplants (HCT) are performed annually

for AML, making it the most common and fastest growing indication for allogeneic transplantation.¹ Several factors have led to new applications of HCT to treat AML, including improved outcomes, expanded patient selection and refined risk stratification.

Refined Patient Selection

Molecular Markers Influence Therapy Choices

In 2008, the World Health Organization (WHO) re-classified AML into eight distinct categories with 25 sub-classifications based on the underlying cytogenetic and molecular genetic abnormalities that characterize AML.²

Based on these WHO classifications, clinicians are now better able to refine risk stratification of patients with AML into prognostic risk groups and selecting those patients most likely to benefit from allogeneic HCT.³

Survival Benefit of HCT in Intermediate-Risk AML in CR1

A 2009 meta-analysis demonstrated the survival benefit of allogeneic HCT for intermediate-risk AML in first complete remission (CR1) over chemotherapy and autologous transplantation (see Table 1). Based on this research, transplant consultation guidelines have recently been updated (see Table 2).

Relapse-Free Survival Benefit of Allogeneic Transplant in Patients with AML				
CYTOGENETIC RISK	# OF TRIALS	HAZARD RATIO (95% CI)	P-VALUE	ALLOGENEIC BENEFIT
Good-risk	10	1.06 (0.80–1.42)	0.68	No
Intermediate-risk	14	0.76 (0.68–0.85)	<0.01	Yes
Poor-risk	14	0.69 (0.57–0.84)	<0.01	Yes

Table 1. Allogeneic HCT in patients with intermediate- and poor-risk AML in CR1 have significantly better relapse-free survival compared to consolidation chemotherapy and autologous transplantation.⁴

Transplant Guidelines Updated

Based on the new research, transplant consultation guidelines from the National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) were updated to recommend that intermediate-risk AML patients in CR1 be referred for transplant consultation (see Table 2).

The intent of these guidelines, based on evidence-based reviews, is to identify patients at risk of disease progression and, therefore, which patients should be evaluated for transplantation.⁴

Recommended Timing for Transplant Consultation
ADULT ACUTE MYELOGENOUS LEUKEMIA
High-risk AML including:
• Antecedent hematological disease (e.g., myelodysplasia (MDS))
• Treatment-related leukemia
• Induction failure
CR1 with intermediate- or poor-risk cytogenetics or molecular markers
AML after relapse
CR2 and beyond

Table 2. Excerpt from NMDP/ASBMT guidelines, which recommend transplant consultation for adult AML patients with: 1) high-risk disease, 2) CR1 with intermediate or poor-risk cytogenetics or molecular markers, and 3) CR2 and beyond.⁵



Increased Use in Older Patients

Reduced-Intensity HCT Expands Eligibility

Reduced-intensity conditioning regimens have expanded HCT to older patients and those with comorbidities unable to undergo myeloablative HCT. Studies show that reduced-intensity HCT can have comparable outcomes to myeloablative transplants using both related and unrelated donors.^{6,7,8,9}

Effect of Age on Survival

A multicenter study of 545 adults age 40–79 years with AML undergoing reduced-intensity transplantation did not identify age as a significant factor affecting overall survival.¹⁰ Other clinical studies have also shown that HCT can be appropriate therapy for older patients with AML.^{6,9}

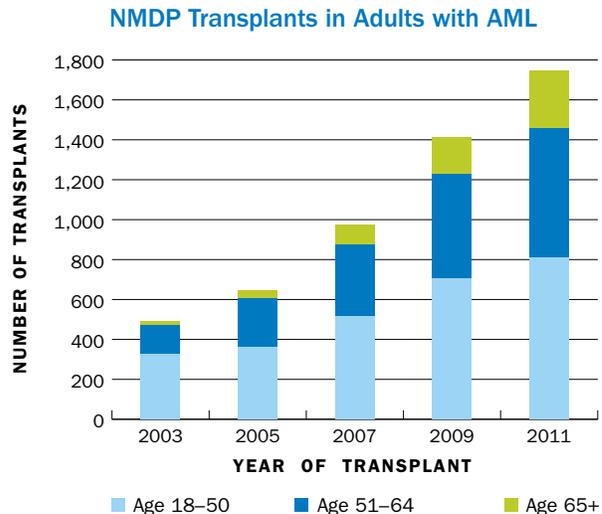


Figure 1. Distribution of unrelated donor transplants, by age, 2003–2011 for AML facilitated by the NMDP.¹¹

Improved Survival

Several factors have led to the steady improvement in overall survival after HCT, including:

Clinical Practice Advances

- Improved ability to manage post-transplant complications¹²
- Preparative regimens, such as reduced-intensity conditioning, tailored to the patient’s disease and condition⁵

HLA Matching Advances

- DNA-based patient and donor tissue typing^{13,14}
- Identification of which HLA loci are most significant to outcomes^{13–15}

Several recently published studies show that unrelated donor transplant outcomes in AML are now comparable to related donor transplant results.^{7,16–18} Table 3 shows the improvement over time for unrelated transplants facilitated by the NMDP.¹⁹ These improved outcomes have been achieved even as a greater number of older patients are being transplanted.

Improved Survival Over Time—AML		
YEAR OF HCT	NUMBER OF CASES	ONE-YEAR SURVIVAL
2008–2010	2,837	58%
2004–2007	2,362	52%
1999–2003	1,287	41%
1987–1998	919	26%

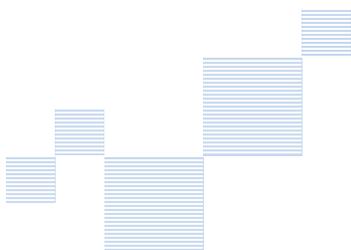
Table 3. One-year survival of adults with AML after unrelated HCT is significantly better for patients transplanted during 2004–2007 and 2008–2010 ($p < 0.001$) compared to patients transplanted during 1987–1998 and 1999–2003 ($p < 0.001$).²⁰

ACCESS AML RESOURCES

When considering transplant as a treatment for patients with AML, quickly access:

- clinical resources
- education
- latest research to help guide decision-making

Visit marrow.org/md-AML



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CLINICAL ACTION POINTS

1

Use molecular markers to stratify patients with AML into prognostic risk groups and identify those most likely to benefit from allogeneic HCT.

2

Recommend transplant consultation for patients in CR1 with intermediate- or poor-risk AML.

3

Review current protocols and consider HCT as a treatment option for older patients with AML.

References:

1. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic Stem Cell Transplantation: A Global Perspective. *JAMA*. 2010; 303(16): 1617-1624.
2. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the WHO Classification of Myeloid Neoplasms and Acute Leukemia: rationale and important changes. *Blood*. 2009; 114(5): 937-951.
3. Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010; 115(3): 453-474.
4. 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.
5. NMDP/ASBMT Recommended Timing for Transplant Consultation, 2011. <http://www.marlow.org/md-guidelines>
6. Ringdén O, Labopin M, Ehninger G, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol*. 2009; 27(27): 4570-4577.
7. Hegenbart U, Niederwieser D, Sandmaier B, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol*. 2006; 24(3): 444-453.
8. Mielcarek M, Storer BE, Sandmaier BM, et al. Comparable outcomes after nonmyeloablative hematopoietic cell transplantation with unrelated and related donors. *Biol Blood Marrow Transplant*. 2007; 13(12): 1499-1507.
9. Oran B, Giralt S, Saliba R, et al. Allogeneic hematopoietic stem cell transplantation for the treatment of high-risk acute myelogenous leukemia and myelodysplastic syndrome using reduced-intensity conditioning with fludarabine and melphalan. *Biol Blood Marrow Transplant*. 2007; 13(4): 454-462.
10. 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.
11. NMDP 2011 fiscal year reports.
12. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009; 15 (10): 1143-1238.
13. Spellman S, Setterholm M, Maiers M, et al. Advances in the selection of HLA-compatible donors: refinements in HLA typing and matching over the first 20 years of the National Marrow Donor Program Registry. *Biol Blood Marrow Transplant*. 2008; 14(9, Suppl. 3): 37-44.
14. 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.
15. Petersdorf EW, Gooley T, Malkki M, Horowitz M. Clinical significance of donor-recipient HLA matching on survival after myeloablative hematopoietic cell transplantation from unrelated donors. *Tissue Antigens*. 2007; 69(Suppl. 1):25-30.
16. Moore J, Nivison-Smith I, Goh K, et al. Equivalent survival for sibling and unrelated donor allogeneic stem cell transplantation for acute myelogenous leukemia. *Biol Blood Marrow Transplant*. 2007; 13(5): 601-607.
17. 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.
18. Chang CK, Storer BE, Scott BL, et al. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorder. *Blood*. 2007; 110(4): 1379-1387.
19. Karanes C, Nelson GO, Chitphakdithai P, et al. Twenty years of unrelated donor hematopoietic cell transplantation for adult recipients facilitated by the National Marrow Donor Program. *Biol Blood Marrow Transplant*. 2008; 14(9, Suppl. 3): 8-15.
20. CIBMTR Analysis of NMDP Facilitated Transplants 2012.

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