

Advances

Your Concise Update On Transplant Research

in Transplantation



Special CIBMTR Edition

This commemorative edition of *Advances in Transplantation* highlights the important research contributions of the CIBMTR (Center for International Blood and Marrow Transplant Research). The CIBMTR, in collaboration with the Medical College of Wisconsin, is the research arm of the National Marrow Donor Program (NMDP).

This issue summarizes 12 practice-changing research studies published by the CIBMTR.

About CIBMTR

For 40 years, the CIBMTR (with predecessor IBMTR) has collaborated with a global scientific community dedicated to advancing hematopoietic cell transplantation and cellular therapy.

This collaboration involves more than 500 transplant centers in the United States and throughout the world, which has advanced the transplant field by:

- Leading and conducting observational and prospective studies – more than 250 active studies underway
- Collecting and maintaining outcomes data
- Providing researchers access to outcomes data
- Providing access to research repository samples
- Providing statistical expertise to researchers
- Providing guidelines and training

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Dear Reader,

We would like to welcome you to this special edition of *Advances in Transplantation*, which features just 12 of more than 700 publications from the CIBMTR (Center for International Blood and Marrow Transplant Research). The CIBMTR, in collaboration with the Medical College of Wisconsin, is the research arm of the National Marrow Donor Program (NMDP).

In recognition of CIBMTR's 40th anniversary, we acknowledge the tremendous progress that has been made in the field of hematopoietic cell transplantation. Because CIBMTR collects data from more than 500 transplant centers around the world, we offer researchers a database containing outcome data on more than 350,000 transplant recipients, many with follow-up of a decade or more. But this is only possible because of the remarkable collaboration of researchers in the transplant field.

Importantly, this research has made a difference. These practice-changing findings (some of which you will read here) have contributed to the tremendous advances in survival and quality of life for thousands of patients around the world.

As we look to the next phase of discovery, we are continually reminded of the patients who count on us to discover and apply the best therapies that research has identified, and to never let up in our efforts to improve those therapies.

We invite you to turn the page and learn more about CIBMTR research, and also invite you to make a connection yourself with the CIBMTR to further our shared mission to increase survival and enrich the quality of life of transplant recipients.

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Unrelated cord blood transplantation in adults with acute leukemia

STUDY TYPE: Retrospective, using outcome data reported to the CIBMTR and three other registries from 216 transplant centers, plus high-resolution HLA data from specimens in the NMDP research sample repository [1]

PATIENTS AND METHODS: 1,525 patients age ≥ 16 years with acute leukemias transplanted between 2002 and 2006:

- 165 received umbilical cord blood (UCB)
- 888 received peripheral blood progenitor cells (PBPCs)
- 472 received bone marrow (BM)

STUDY DETAILS:

- UCB units were matched at HLA-A and HLA-B at antigen level, and HLA-DRB1 at allele level (n=10), or mismatched at one (n=40) or two (n=115) antigens
- PBPCs and bone-marrow grafts from unrelated adult donors were matched for allele-level HLA-A, HLA-B, HLA-C, and

HLA-DRB1 (n=632 and n=332, respectively), or mismatched at one locus (n=256 and n=140, respectively)

- UCB recipients received a single unit containing a minimum of 2.5×10^7 nucleated cells/kg body weight

RESULTS: Transplant-related mortality was higher after UCB transplantation than after 8/8 allele-matched PBPC (HR: 1.62; 95% CI: 1.18-2.23; p=0.003) or bone marrow transplantation (HR: 1.69; 95% CI: 1.19-2.39; p=0.003). However, this did not result in a difference in leukemia-free survival (LFS), as shown in Table 1.

CLINICAL RELEVANCE:

These data support the use of UCB for adults with acute leukemia when there is no HLA-matched unrelated adult donor available, and when a transplant is needed urgently.

1. Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol.* 2010; 11(7): 653-660.

Multivariate analysis		
LEUKEMIA-FREE SURVIVAL	HR FOR RELAPSE OR DEATH (95% CI)	P-VALUE
4-6/6 matched UCB	1.00	
4-6/6 matched UCB vs. 8/8 matched BM	1.15 (0.90–1.47)	0.25
4-6/6 matched UCB vs. 7/8 matched BM	0.93 (0.69–1.24)	0.63
4-6/6 matched UCB vs. 8/8 matched PBPC	1.12 (0.89–1.39)	0.18
4-6/6 matched UCB vs. 7/8 matched PBPC	0.91 (0.71–1.17)	0.46

Table 1. Multivariate analysis of leukemia-free survival by stem cell source. Overall p-value=0.09. HR=Hazard ratio, CI=Confidence interval.

Effect of T-cell-epitope matching at HLA-DPB1 in unrelated-donor HCT

STUDY TYPE: Retrospective study to test a system for classifying permissive and non-permissive HLA-DPB1 mismatches in unrelated donor marrow and peripheral blood stem cells (PBSC) transplants [2]

PATIENTS AND METHODS: 8,539 transplant recipients between 1993-2007: 5,428 (64%) HLA 10/10 allele matched, 3,111 (36%) HLA 9/10 allele matched

STUDY DETAILS:

- 1,719 (20%) HLA-DPB1 matches
- 2,670 (31%) non-permissive HLA-DPB1 mismatches
- 4,150 (49%) permissive HLA-DPB1 mismatches

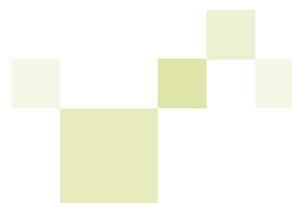
RESULTS:

- In both 9/10 and 10/10 cohorts, non-permissive DPB1 mismatches were associated with significantly increased risk of non-relapse mortality and severe (Grade III-IV) acute GVHD
- HLA 9/10-matched transplants with permissive HLA-DPB1 mismatches had comparable outcomes to 10/10 matched transplants with non-permissive DPB1 mismatches

CLINICAL RELEVANCE:

To lower the risk of non-relapse mortality after unrelated-donor HCT, a non-permissive T-cell epitope mismatch at HLA-DPB1 should be avoided if possible.

2. Fleischhauer K, Shaw BE, Gooley T, et al. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study. *Lancet Oncol.* 2012; published online Feb. 15.



Reduced-intensity HCT better than chemotherapy in older AML patients

STUDY TYPE: Retrospective, using data from CIBMTR and CALGB [3]

PATIENTS AND METHODS: 190 patients age 60-70 years with acute myelogenous leukemia (AML) in first remission for a minimum of four months

STUDY DETAILS: Researchers compared outcomes of 94 patients who underwent reduced-intensity allogeneic HCT between 1999-2005 with outcomes of 96 patients treated with chemotherapy alone on CALGB protocols 9720 and 10201 between 1998-2006.

RESULTS: Compared to chemotherapy-only patients, recipients with AML receiving HCT had significantly:

- Lower risk of relapse at 3 years (32% vs. 81%, $p < 0.001$)
- Higher 3-year non-relapse mortality (36% vs. 4%, $p < 0.001$)
- Higher 3-year leukemia-free survival (32% vs. 15%, $p = 0.001$)

Three-year overall survival was not statistically different in the two groups.

CLINICAL RELEVANCE:

Reduced-intensity conditioning allogeneic HCT in patients age 60-70 with AML in CR1 reduces relapse and improves leukemia-free survival compared to chemotherapy.

3. Farag SS, Maharry K, Zhang M-J, et al. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60-70 years with acute myelogenous leukemia in first remission. *Biol Blood Marrow Transplant.* 2011; 17(12): 1796-1803.

Effect of race and gender on access to HCT

STUDY TYPE: Population study/analysis [4]

PATIENTS AND METHODS: This study compared:

- The annual incidence of leukemia, lymphoma and multiple myeloma in the U.S. in people <70 years using SEER data and U.S. Census Reports
- The annual incidence of autologous and allogeneic (related and unrelated) transplants performed for these diseases using CIBMTR data

STUDY DETAILS: Researchers analyzed data from 1997-2002 and used logistic regression to calculate the age-adjusted odds ratio of undergoing transplantation for Caucasians vs. African Americans, and men vs. women.

RESULTS:

- Caucasians had a significantly higher likelihood of undergoing transplant than African Americans [Odds Ratio (OR): 1.40 (95%CI: 1.34-1.46); $p < 0.0001$]
- African Americans have lower rates of both allogeneic and autologous transplantation; consequently, the difference in transplant rates cannot be fully explained by donor availability
- Men were more likely than women to undergo transplantation [OR=1.07 (1.05-1.1) $p < 0.0001$], but this difference was significant only for autologous transplantation [OR: 1.10 (1.07-1.13); $p < 0.0001$]

CLINICAL RELEVANCE:

While waiting for further research to better understand disparate access to transplantation, the medical community should work at all levels to eliminate these disparities.

4. Joshua TV, Rizzo JD, Zhang M-J, et al. Access to hematopoietic stem cell transplantation: effect of race and gender. *Cancer.* 2010; 116(14): 3469-3476.

Reduced-intensity HCT for AML/MDS not affected by age

STUDY TYPE: Retrospective, using CIBMTR outcomes database [5]

PATIENTS AND METHODS: 1,080 patients >40 years with acute myelogenous leukemia (AML) in first complete remission (n=545) and myelodysplastic syndromes (MDS, n=535) undergoing reduced-intensity hematopoietic cell transplantation between 1995-2005.

STUDY DETAILS: Outcomes analyzed included neutrophil recovery, incidence of acute or chronic GVHD, relapse, non-relapse mortality, disease-free survival, and overall survival.

RESULTS: A multivariate analysis found no significant impact of age on non-relapse mortality, relapse, disease-free survival or overall survival. Two-year overall survival by disease and age is shown in Table 2.

No impact of age on overall survival				
AGE RANGE (YRS):	40-54	55-59	60-64	≥65
AML (p=0.06)	44%	50%	34%	36%
MDS (p=0.37)	42%	35%	45%	38%

Table 2. Two-year overall survival by disease and age

CLINICAL RELEVANCE:

Older age alone should not be considered a contraindication to hematopoietic cell transplantation.

5. 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.

Solid cancers after allogeneic HCT

STUDY TYPE: Longitudinal study of transplant outcomes tracked by CIBMTR and the Fred Hutchinson Cancer Research Center (FHCRC) [6]

PATIENTS AND METHODS: 28,874 marrow transplant patients: 23,542 transplanted at CIBMTR centers between 1964-1994, and 5,332 transplanted at FHCRC between 1969-1996

STUDY DETAILS:

- Median patient age was 27 years (range, 0.08-72.41)
- 74% of patients were transplanted for a leukemia
- 76% of transplants used an HLA-identical sibling donor

This study is an update of a previous analysis of 19,229 patients, with results published in 1997. [7]

RESULTS:

- HCT recipients developed new solid cancers at twice the rate expected based on general population rates (observed-to-expected ratio 2.1; 95% CI: 1.8-2.5)
- Among patients irradiated at ages under 30 years, the relative risk of developing a non-squamous cell carcinoma was 9 times that of non-irradiated patients

CLINICAL RELEVANCE:

Allogeneic transplant survivors, particularly those irradiated at young ages, face increased risks of solid cancers and should receive lifelong surveillance.

6. Rizzo JD, Curtis RE, Socié G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. *Blood*. 2009; 113(5): 1175-1183.
7. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. *N Engl J Med*. 1997; 336(13): 897-904.

Secondary solid cancers after allogeneic HCT using Bu/Cy conditioning

STUDY TYPE: Retrospective, using CIBMTR outcomes database [8]

PATIENTS AND METHODS: 4,318 patients undergoing a first allogeneic HCT between 1986-2005, and conditioned using high-dose busulfan-cyclophosphamide (Bu-Cy) regimens. Patient cohort represented 22,041 person-years at risk.

STUDY DETAILS:

- Acute myelogenous leukemia (AML) in first complete remission (n=1,742)
- Chronic myeloid leukemia (CML) in first chronic phase (n=2,576)

RESULTS: At a median of 6 years after transplant, 66 solid cancers were reported. Transplant recipients had 1.4 times higher than expected rate of invasive solid cancers compared to incidence in the general population (95% CI: 1.08-1.79, p=0.01). Cumulative incidence of solid cancers at 5 and 10 years post-transplant:

- 0.6% and 1.2%, respectively, among AML patients
- 0.9% and 2.4%, respectively, among CML patients

CLINICAL RELEVANCE:

Recipients of allogeneic HCT using Bu-Cy conditioning are at risk for developing solid cancers, a risk that increases with time, and so lifelong cancer surveillance is warranted in this population.

8. Majhail NS, Brazauskas R, Rizzo JD, et al. Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. *Blood*. 2011; 117(1): 316-322.

Comparable outcomes after matched related, unrelated HCT

STUDY TYPE: Comparative effectiveness cohort study using CIBMTR outcomes database, and high-resolution HLA data from specimens in the NMDP research sample repository [9]

PATIENTS AND METHODS: 2,223 adult acute myelogenous leukemia (AML) patients who underwent allogeneic HCT between 2002 and 2006

STUDY DETAILS:

- Matched related (MRD, n=624)
- 8/8 matched unrelated (URD, n=1,193)
- 7/8 matched unrelated (URD, n=406)

RESULTS:

- 100-day cumulative incidence of grade II-IV acute GVHD was significantly lower in MRD recipients than in 8/8 URD and 7/8 URD HCT recipients (33%, 51%, and 53%, respectively; p<.001)
- In multivariate analysis, 8/8 URD HCT recipients had a similar survival rate compared to MRD HCT recipients (Relative risk (RR): 1.03; p=0.62)

- 7/8 URD HCT recipients had higher early mortality than MRD HCT recipients (RR: 1.40; p<.001), but after six months, their survival rates were similar (RR: 0.88; p=0.30)

CLINICAL RELEVANCE:

Transplantation from URD and MRD donors produces similar survival for patients with AML.

9. Saber W, Opie S, Rizzo JD, et al. Outcomes after matched unrelated donor vs. identical sibling hematopoietic cell transplantation (HCT) in adults with acute myelogenous leukemia (AML). *Blood*. 2012; published online Feb 10.

CIBMTR SUMMARY SLIDE SET

Download the CIBMTR annual slide set:

- Based on data from >500 centers worldwide
- Summarizes current uses and outcomes of allo- and auto-HCT

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HCT outcomes comparable: umbilical cord blood vs. bone marrow in pediatric acute leukemia

STUDY TYPE: Retrospective, using data from CIBMTR and the New York Blood Center's National Cord Blood Program [10]

PATIENTS AND METHODS: Children (<16 years) with acute leukemia transplanted in the United States between 1995-2003 using unrelated donor umbilical cord blood (UCB) (n=503) or bone marrow (n=282)

STUDY DETAILS: The study compared 5-year leukemia-free survival (LFS) between cord blood and bone marrow transplant recipients. Graft sources were:

- UCB: HLA-matched (n=35) or HLA-mismatched at one (n=201) or two antigens (n=267)
- Bone marrow: 8/8 allele-level matched (n=116) or 7/8 matched (n=166)

RESULTS: Five-year LFS was highest with UCB and was comparable between allele-matched bone marrow transplants and umbilical cord blood mismatched for either one or two antigens. Relapse rates were lower in two-antigen HLA-mismatched UCB transplants compared to allele-matched bone marrow transplants (Relative risk: 0.54, p=0.0045).

CLINICAL RELEVANCE:

These data support the use of HLA-matched and one- or two-antigen HLA-mismatched umbilical cord blood in children with acute leukemia who need transplantation.

10. Eapen M, Rubinstein P, Zhang M-J, et al. Outcomes of transplantation of unrelated umbilical cord blood and bone marrow in children with acute leukemia: a comparison study. *Lancet*. 2007; 369(9577): 1947-1954.

HLA-C matching improves outcomes in cord blood transplantation

STUDY TYPE: Retrospective, using CIBMTR outcomes data on single-unit cord blood transplants between 1996-2008 [11]

PATIENTS AND METHODS: 803 patients, with a median age of 10 years (range, 1-62). Sixty-nine percent of study subjects were ≤16 years at transplantation

STUDY DETAILS: Diseases transplanted were leukemia (n=727) and myelodysplastic syndromes (MDS) (n=76). HLA typing was done with molecular techniques with a minimum of intermediate resolution for HLA-A, -B, and -C, and at the allele-level for HLA-DRB1.

RESULTS: Transplant-related mortality (TRM) was significantly higher after transplants mismatched at HLA-C compared to those matched at HLA-A, -B, -C and -DRB1 (HR: 3.97; 95% CI 1.27-12.40; p=0.018). TRM was also significantly higher after transplants with a mismatch at HLA-C and another locus compared to transplants matched at HLA-C with a single mismatch at HLA-A, -B, or -DRB1 (HR: 1.70, 1.06-2.74; p=0.029).

CLINICAL RELEVANCE:

To minimize mortality risk, matching at HLA-C should be sought for units that are matched at HLA-A, -B, or -DRB1 and for units with a single locus mismatch at HLA-A, -B, or -DRB1.

11. Eapen M, Klein JP, Sanz GF, et al. Effect of donor-recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. *Lancet Oncol*. 2011; 12(13): 1214-1221.

Recommended screening and preventive practices for long-term HCT survivors

STUDY TYPE: Consensus report [12]

PATIENTS AND METHODS: Literature review and analysis

STUDY DETAILS: An internationally diverse group of transplant experts convened in 2011 to review the contemporary literature and update the 2006 guidelines on screening and prevention of late complications in HCT recipients.

RESULTS: This report lists specific recommendations for screening and prevention of late complications in transplant recipients, organized by the organs and tissues that can be affected by HCT. The guidelines also include recommendations for post-transplant vaccinations and recommendations for patients with specific

exposures/risk factors (e.g., TBI, chronic GVHD, pediatric recipients).

CLINICAL RELEVANCE:

Because of the HCT recipient's risk of developing long-term complications due to pre-, peri-, and post-transplant exposures, these guidelines offer a systematic follow-up plan for caring for HCT recipients.

12. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012; 18(3): 348-371.

POST-TRANSPLANT CARE APP

The free **Transplant Guidelines** app provides quick access to recommended:

- Screening/prevention practices
- Screening for GVHD
- Vaccination schedule

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High-resolution donor-recipient HLA matching improves HCT outcomes

STUDY TYPE: Retrospective, using multivariate proportional hazards models to determine association between number and type of HLA mismatches and transplant outcomes [13]

PATIENTS AND METHODS: 3,857 patients transplanted between 1988-2003 using NMDP donors and myeloablative conditioning

STUDY DETAILS:

- 78% received T-cell replete grafts
- 78% received calcineurin inhibitor-based GVHD prophylaxis
- 94% received bone marrow
- Median follow-up: 6 years

RESULTS:

- Mismatching at a single HLA-A, -B, -C, or -DRB1 locus (7/8 match) was associated with lower survival and disease-free survival compare with 8/8 HLA-matched pairs

- A single mismatch detected by low- or high-resolution DNA testing at HLA-A, -B, -C or -DRB1 (7/8 match) was associated with significantly higher mortality (relative risk, 1.25; 95% CI, 1.13-1.38; $p < 0.001$) compared to 8/8 matched pairs
- More advanced disease before HCT is associated with a greater absolute impact on survival than increasing HLA disparity (see Figure 1)

CLINICAL RELEVANCE:

Expedient transplantation with the best available donor, even if mismatched, may offer the best chance for survival.

13. 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

PROBABILITY OF OVERALL SURVIVAL BY HLA MATCHING:

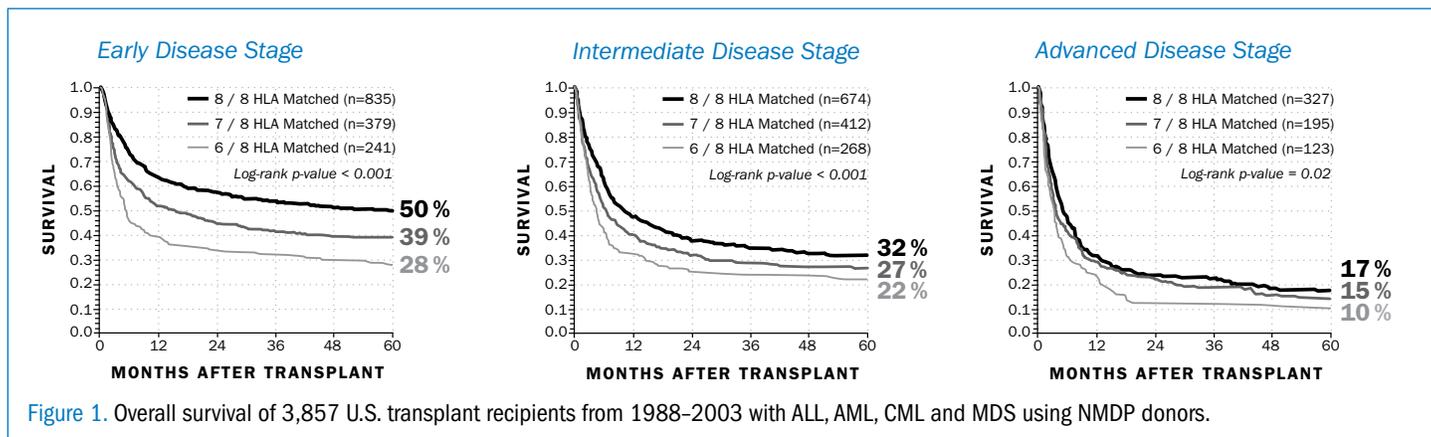


Figure 1. Overall survival of 3,857 U.S. transplant recipients from 1988-2003 with ALL, AML, CML and MDS using NMDP donors.

This research was originally published in *Blood*. Lee SJ, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007; Vol 110: 4576-4583. (c) the American Society of Hematology.

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