Your Concise Update On Transplant Research

Advances in Transplantation

NATIONAL MARROW DONOR PROGRAM®

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Special ASH 2012 Edition

Welcome to a special edition of Advances in Transplantation, a National Marrow Donor Program® (NMDP) newsletter that summarizes the latest research in hematopoietic cell transplantation. This edition is based on the 54th American Society of Hematology Annual Meeting, held in Atlanta, Georgia. This report is not sponsored or sanctioned by, nor a part of, the Annual Meeting of the American Society of Hematology (ASH), and ASH does not endorse any uses of this report.

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Comparable survival in well-matched unrelated and related donor HCT in MDS

Allogeneic transplantation in patients with myelodysplastic syndromes (MDS) using 8/8 HLA-matched unrelated donors (URD) and 8/8 HLA-matched related donors (MRD) produces similar survival, according to results of a study presented at ASH. [1] Survival after 7/8 URD transplantation was significantly lower than survival following in 8/8 MRD and URD transplantation.

Researchers, led by Dr. Wael Saber of the Medical College of Wisconsin, Milwaukee, compared outcomes of 701 adult MDS patients (176 8/8 matched related transplants, 413 8/8 matched unrelated transplants, and 112 7/8 unrelated transplants) who underwent allogeneic HCT between 2002—2006. Median age was 53 years (range, 22-78), and 65% of patients had advanced disease at time of transplant. Outcomes were reported to CIBMTR (Center for International Blood and Marrow Transplant Research).

> "In patients with MDS, transplantation from 8/8 URD and MRD donors produces similar survival."

In multivariate analyses, 8/8 unrelated donor recipients had comparable survival and disease-free survival (DFS) rates compared to 8/8 related donor recipients: relative risk (RR) 1.24 (95% CI 0.98-1.56), and RR 1.11 (95% CI 0.89-1.39), respectively. Adjusted 3-year survival and other outcomes are shown in Table 1.

Because relapse was not significantly different among the three groups, Dr. Saber concluded that differences in outcome were largely related to excess transplant-related mortality.

Comparable survival in well-matched unrelated and related donor HCT in MDS: continued on page 5

Improved quality of life after allogeneic, autologous HCT

In the immediate post-transplant recovery period, quality of life (QoL) can be diminished for many transplant recipients. But results of a new study indicate that long-term survivors have a significantly better QoL compared to their QoL prior to transplantation. [2]

The study of 530 allogeneic and 869 autologous transplants at eight transplant centers in the Czech Republic also demonstrated that QoL increases significantly beginning at two years after allogeneic transplantation and at one year after autologous transplantation.

QoL continues to rise in both transplant groups, and at five years post transplant the QoL of allogeneic recipients reaches the QoL levels of the general population. For autologous recipients, QoL levels at five years post transplant exceed pre-transplant levels, but remain lower than general population levels.

> "Long—term survivors have significantly better QoL compared to QoL prior to transplantation."

The study used the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire, a 27-question survey measuring physical well-being, social/family well-being, emotional well-being, and functional well-being. Surveys were administered to patients prior to transplantation and at five post-transplant time points. Higher scores correspond to higher QoL, and the maximum overall combined score is 108 points. The normative general population FACT-G score is 86.6.

Median patient age was 55.2 years in the autologous group and 43.2 years in the allogeneic group, and the median follow-up was 4.5 years. In both allogeneic and autologous transplant cohorts, patients had significantly higher QoL scores at >5 years post-transplant compared to pre-transplant scores: 86.8 vs. 80.3 (allogeneic), and 79.0 vs. 73.9 (autologous)($p<0.05$).

QoL was lowest at 1-2 years in allogeneic recipients, when the proportion of patients experiencing chronic GVHD was the highest. This effect of chronic GVHD on overall FACT-G scores was due to significantly lower physical well-being scores ($p<0.001$) and functional well-being scores ($p<0.001$) in this patient group.

The study was presented in an oral session by Dr. Marek Trneny of the Charles University General Hospital, Prague. In both allogeneic and autologous patient groups, Dr. Trneny noted that improving scores were due mainly to improvements in physical well-being and functional well-being scores. Social/family and emotional well-being scores remained generally unchanged at all six time points. ■

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Also available online and in print at **marrow.org/md-guidelines**

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Pediatric HCT: Similar outcomes in single and double cord blood transplant

A multi-center, randomized, phase III trial comparing single and double umbilical cord blood (UCB) transplantation in pediatric patients has found comparable outcomes when the single UCB is of adequate size. [3] The study, conducted through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), randomized pediatric patients to receive a conventional single (n=113) or double (n=111) UCB transplant.

The study, reported in an oral presentation by Dr. John Wagner of the University of Minnesota, analyzed outcomes of 224 patients ranging in age from 1-21 years who were transplanted at 38 centers between December 2006 and February 2012. Randomization was stratified by transplant center and patient age.

> "Single UCB transplant should be the standard approach in children for whom a single unit containing ≥2.5 x 10^7 nucleated cells/kg is available"

All patients received at least one cord blood unit with ≥2.5 x 10^7 total nucleated cells/kg. If a second unit was infused, it had a cell dose of ≥1.5 x 10^7 total nucleated cells/kg. Each cord blood unit was ≥4/6 HLA-matched to the patient; use of a second cord blood unit required ≥3/6 matching.

All patients had malignant diseases, with <50% of patients in each arm diagnosed with acute lymphoblastic leukemia. Patient primary disease, disease risk, sex, age, race, ethnicity, CMV serology, performance score, and HLA-match were balanced between the two study groups.

UCB transplantation outcomes

	UCB – 1 UNIT	UCB – 2 UNITS	P-VALUE
1-year OS	66%	71%	0.12
1-year DFS	64%	68%	0.20
1-year relapse	14%	12%	0.37
Day-180 platelet recovery	72%	80%	0.06
Day-100 grade III-IV aGVHD	23%	14%	0.03
1-year cGVHD incidence	30%	32%	0.64

Table 2. Outcomes of 224 single (n=113) and double (n=111) UCB transplants in pediatric recipients. OS=overall survival, DFS=disease-free survival, aGVHD=acute GVHD, cGVHD=chronic GVHD.

Median follow-up was 25 months. Recipients of double UCB transplant had a significantly higher risk of grade III-IV acute graft-versus-host disease (GVHD), but this did not affect survival. All other outcomes shown in Table 2 were comparable between the single and double UCB transplantation groups.

Dr. Wagner concluded that single UCB transplant should be the standard approach in children for whom a single unit containing ≥2.5 x 10^7 nucleated cells/kg mismatched at zero, one or two HLA-loci is available. He also noted, however, that double UCB transplant remains a suitable alternative in the absence of an adequately dosed single UCB unit in pediatric patients with hematologic malignancies. ■

POST-TRANSPLANT CARE CME

This 45-minute case-based activity explores updated post-transplant screening recommendations for autologous and allogeneic hematopoietic cell transplant (HCT) recipients, including:

· Risk factors associated with exposures and late effects

· Guidelines for head-to-toe assessment

· Screening and vaccination schedules

Faculty: Navneet Majhail, M.D., M.S. and Linda Burns, M.D.

Access CME at **marrow.org/md-screening**

NMDP Satellite Symposium Preceding ASH
Treatment of AML and MDS in Older Patients: A Case-Based Approach

At the NMDP-sponsored satellite symposium preceding the ASH Annual Meeting, speakers focused on disease and patient-related factors affecting treatment decisions in older MDS and AML patients. They discussed research and case studies for hematopoietic cell transplantation, hypomethylating agents, and combination therapies using both approaches.

A free CME activity based on the symposium will be available spring 2013. Sign up at **marrow.org/md-AMLandMDS** to receive a notice when the activity is live.

Symposium speakers and their key points:

Gail Roboz, M.D., Weill Cornell Medical College, New York Presbyterian Hospital—*Applying novel diagnostics and therapeutics for AML in the older patient*

- Trends toward intensive regimens: induction, post-induction, transplant
- Promising results with an intensified ara-C regimen for upfront induction
- Clofarabine vs. low-dose cytarabine – doubled the response; but no survival benefit

Frederick Appelbaum, M.D., Fred Hutchinson Cancer Research Center—*Allogeneic HCT for the older patient with AML: How and when should age matter?*

- Co-morbidities are more important than age in predicting HCT outcomes
- HCT indications in AML patients age 50-70 are similar to those for patients age <50
- HCT appropriate for selected patients age >70 years

David Steensma, M.D., FACP, Dana-Farber Cancer Institute —*Drug therapy for MDS: Targets and biomarkers*
Novel therapies being tested in MDS:

- Nucleoside analogs (clofarabine, sapacitabine)
- Kinase inhibitors (rigosertib, midostaurin)
- Epigenetic modifiers (vorinostat, entinostat, panobinostat)
- Proteasome/Amino Acid recycling inhibitors (bortezomib, tosedostat)

Stephen Forman, M.D., City of Hope—*MDS and AlloHCT: Weighing risks and benefits, and the need to learn more*

- New revised IPSS scores strongly associated with prognosis
- Response to induction chemotherapy identifies better prognosis patients
- Reduced-intensity HCT applied for patients in 7th, 8th decades of life

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3. Wagner JE, Eapen M, Carter SL, et al. No survival advantage after double umbilical cord blood (UCB) compared to single UCB transplant in children with hematological malignancy: Results of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0501) randomized trial [abstract]. Blood. 2012; 120(21): Abs. # 359.
4. de Lima M, Parmar S, Chen JJ, et al. Low dose azacitidine (AZA) reduces the incidence of chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation (HSCT) [abstract]. Blood. 2012; 120(21): Abs. # 742.
5. Majhail NS, Chitphakdithai P, Shan Y, et al. Significant and rapid improvement in survival after unrelated donor (URD) hematopoietic cell transplantation (HCT): Analysis of National Marrow Donor Program (NMDP) facilitated transplants from 2000 to 2009 [abstract]. Blood. 2012; 120(21): Abs. #234.

The National Marrow Donor Program (NMDP) is the global leader in providing marrow and umbilical cord blood transplants to patients with leukemia, lymphoma and other diseases. The nonprofit organization matches patients with donors, educates health care professionals and conducts research so more lives can be saved. The NMDP also operates Be The Match®, which provides support for patients, and enlists others in the community to join the Be The Match Registry®—the world's largest listing of potential marrow donors and donated cord blood units—contribute financially and volunteer. Learn more at marrow.org/md.

Low-dose post-transplant azacitidine can lower chronic GVHD

Low-dose azacitidine (AZA) can reduce the likelihood of developing chronic GVHD when administered to patients post transplant, according to a study presented by Dr. Marcos de Lima of Case Western Reserve University, Cleveland. [4]

In this retrospective, case-control study, 85 patients were given post-transplant AZA to prevent relapse. When the researchers began to notice very little chronic GVHD in these patients, they began comparing chronic GVHD rates in patients who received three or fewer cycles of AZA (n=48) to those who received more than three cycles (n=37).

At 2-years post transplant, the cumulative incidence of chronic GVHD in the patients receiving >3 AZA cycles was significantly lower than the incidence of chronic GVHD in the historical controls: 22% vs. 50%, respectively (p=0.02). The cumulative incidence of chronic GVHD was comparable in the patients receiving ≤3 AZA cycles and the historical controls: 51% vs. 50%, respectively (p=ns).

Median number of AZA cycles was 3 (range, 1-54), and median time on AZA for patients receiving >3 cycles was 144 days (range, 93-1329). Ninety-four percent of patients, including 230 matched controls, had acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS).

> "Cumulative incidence of cGVHD was significantly lower in the subgroup that received >3 AZA cycles post transplant."

The historical control group and the two AZA cohorts were matched for age (median age range, 52-60 years), underwent allogeneic HCT within the same time period, and received comparable GVHD prophylaxis. However, significantly more patients in the AZA cohorts had active disease at time of transplant.

Median follow-up was 25 months (range, 1-99) in the AZA group, and 31 months (range, 1.5-117) in the control group. Median AZA dose was 32 mg/m^2 (range, 8-40), and AZA administration started a median of 45 days post transplant (range, 17-149). In his oral presentation, Dr. de Lima noted that the effect of AZA on acute GVHD was not studied because AZA administration typically began after most cases of acute GVHD had already occurred, had resolved, or improved.

Dr. de Lima concluded that low-dose AZA appears to reduce the likelihood of developing chronic GVHD, and noted that his research group is conducting an ongoing randomized study of whether this effect is associated with preservation or improvement of the graft-versus-leukemia effect. ■

Comparable survival in well-matched unrelated and related donor HCT in MDS: continued from page 1

Adjusted 3-year survival and other outcomes

	MRD	8/8 URD	7/8 URD	8/8 URD VS. MRD P-VALUE	7/8 URD VS. MRD P-VALUE
TRM	30%	41%	42%	0.01	0.03
Relapse	32%	24%	27%	0.058	0.30
Survival	47%	38%	31%	0.04	0.003
DFS	40%	35%	29%	0.22	0.04

Table 1. Adjusted three-year transplant outcomes. TRM=transplant-related mortality, DFS=disease-free survival, MRD=matched related donor, MUD=matched unrelated donor.

The 100-day incidence of IBMTR grades B-D acute graft-versus-host disease (GVHD) was significantly lower in the MRD group than in 8/8 URD and 7/8 URD group: 42%, 54%, and 57%, respectively (p=0.009). Three-year cumulative incidence of chronic GVHD were similar among the MRD, 8/8 URD, and 7/8 URD groups: 51%, 49%, and 41%, respectively (p=0.25).

In conclusion, Dr. Saber said that clinicians should not automatically defer transplantation if a 7/8 unrelated donor is the only donor available. Rather, he said that physicians and patients must decide whether a less-than-perfect match might still be beneficial compared to non-transplant treatment options.

ACCESS MDS RESOURCES

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

- Clinical resources, including new MDS Clinical fact sheet
- Education
- Latest research to help guide decision-making

Visit **marrow.org/md-MDS**

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Significant improvement in survival over time in unrelated donor HCT

A long-term, retrospective cohort study of 15,040 patients undergoing unrelated donor hematopoietic cell transplantation (HCT) between 2000-2009 has documented significant improvements in overall survival over time. [5]

The study, presented at an ASH oral session, found that in every age group, both one- and three-year survival was significantly higher in HCT recipients transplanted between 2005-2009 compared to those transplanted between 2000-2004. Figures 1 and 2 show three-year survival in malignant diseases for recipients age 18-59 years and <18 years, respectively.

Several factors have likely contributed to this dramatic improvement in survival over time, noted Dr. Navneet Majhail, lead author of the study and medical director at the National Marrow Donor Program (NMDP). These include increased use of HLA 8/8 matched donors, better supportive care, less intensive conditioning regimens, and new medications to treat post-transplant complications.

> "Overall survival was 12—13% better at one year for patients transplanted in the more recent era for all three age groups."

The study also showed that three-year transplant-related mortality (TRM) declined significantly over time in both pediatric and adult patient groups. TRM decreased between 2000-2004 and 2005-2009 in pediatric patients (28% vs. 21%, respectively; p<0.001) and in adult patients (37% vs. 28%, respectively; p<0.001). In patients 60 years and older, TRM did not differ significantly between the early and later transplant periods: 34% vs. 31%, respectively (p=0.20).

This study examined unrelated donor transplants facilitated by the NMDP including all age groups, all diagnoses, and all conditioning regimens. Bone marrow and peripheral blood stem cell (PBSC) transplants were included; umbilical cord blood transplants were excluded.

"These data confirm that physicians working with patients who are fighting a blood cancer should consider unrelated transplantation as a standard therapy," said Dr. Majhail. ■

Improvement over time, three-year survival—adult HCT

MALIGNANT DISEASES, AGE 18-59 YEARS

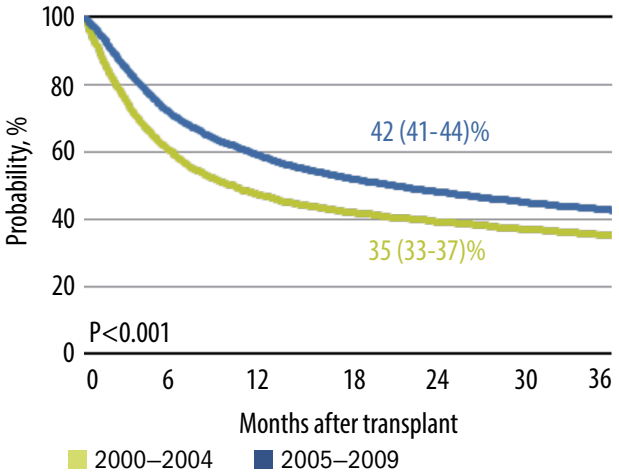

Figure 1. Three-year overall survival in patients age 18 - 59 years transplanted for malignant diseases in 2000–2004 (n=3,808) and 2005–2009 (n=5,745).

Improvement over time, three-year survival—pediatric HCT

MALIGNANT DISEASES, AGE <18 YEARS

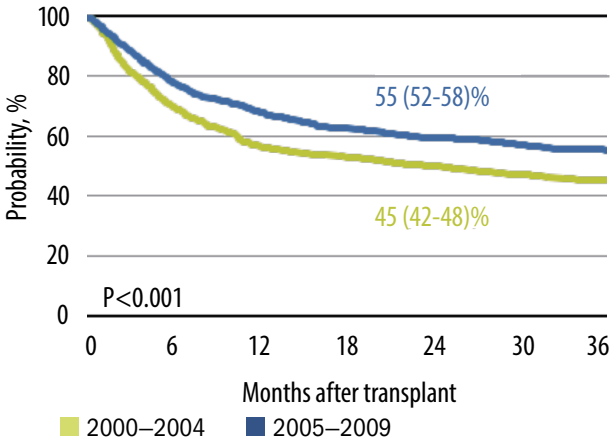

Figure 2. Three-year overall survival in patients age <18 years transplanted for malignant diseases in 2000–2004 (n=906) and 2005–2009 (n=1,017).

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