

# Advances

Your Concise Update On Transplant Research

## in Transplantation



### Special ASH 2011 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 53rd American Society of Hematology Annual Meeting, held in San Diego, California. 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.

### In this issue:

Randomized study: marrow vs. PBSC transplantation .....	1
Reduced-intensity HCT lowers mortality without increasing relapse.....	2
Non-myeloablative HCT in patients with NHL age 65 and older.....	3
Sirolimus boosts regulatory T cells, lowers GVHD .....	3
Co-infusing haploidentical cells speeds cord blood engraftment.....	4
Long-term monitoring for late complications of HCT.....	6

## Comparable survival marrow vs. PBSC, more chronic GVHD with PBSC

Patients undergoing unrelated donor transplantation using peripheral blood stem cells (PBSC) have 2-year survival comparable to patients transplanted with bone marrow, but PBSC recipients have significantly higher rates of chronic graft-versus-host disease (cGVHD). These were the conclusions of a large-scale, prospective, randomized clinical trial comparing the two graft sources, which were presented at the Plenary Session of the American Society of Hematology (ASH). [1]

“Although PBSCs from related donors have demonstrated clinical benefits, our trial demonstrates that when these stem cells originate from unrelated donors, they are not superior to bone marrow stem cells in terms of patient survival, and they increase the risk for chronic GVHD,” said lead study author Claudio Anasetti, M.D., from the Moffitt Cancer Center in Tampa, Fla.

The study, conducted in the U.S., Canada, and Germany through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), is the first to compare outcomes by graft source in unrelated donor transplants in a prospective randomized trial. This multi-center study was conducted in the U.S. and Canada

Marrow vs. PBSC comparable survival, more cGVHD with PBSC			
OUTCOMES AT 2 YEARS	PBSC	MARROW	P-VALUE
Overall survival	52%	48%	0.37
Disease-free survival	47%	44%	0.60
Non-relapse mortality	26%	27%	0.67
Any chronic GVHD	53%	40%	0.02
Chronic extensive GVHD	46%	31%	<0.001

Table 1. Two-year outcomes of unrelated donor transplants by graft source.

# Reduced-intensity HCT lowers mortality without increasing relapse in AML

A reduced-intensity conditioning (RIC) regimen using fludarabine and fractionated total-body irradiation (TBI) can significantly lower transplant-related mortality (TRM) without raising relapse rates in adult patients with acute myeloid leukemia (AML) in first complete remission. This was the main conclusion in an ASH oral presentation of a prospective, randomized trial comparing reduced-intensity and standard-intensity transplant outcomes in 184 patients transplanted between 2004-2009 at German transplant centers. [2]

**This prospective randomized trial in patients with AML in CR1 found reduced-intensity conditioning can result in significantly lower early TRM without increasing relapse risk.**

TRM at 12 months was significantly lower in reduced-intensity transplants than in standard intensity transplants: 8% vs. 17%, respectively; ( $p=0.048$ ). In a subgroup of patients older than 40, the difference in TRM was even greater: 5% vs. 20%, respectively; ( $p=0.01$ ).

Median age of the patients in the study was 45 years (range: 18-60); 62% had intermediate-risk karyotypes and 38% had high-risk karyotypes. The 94 patients randomly assigned to the reduced-intensity arm were conditioned with a regimen of

fludarabine at 30 mg/m<sup>2</sup> for four days combined with 800 cGy fractionated TBI. These were compared to 90 patients receiving standard myeloablative pre-transplant conditioning consisting of fractionated TBI (200 cGy TBI 6 doses over 3 days, 1200 cGy total) and cyclophosphamide 60 mg/kg per day over 2 days.

The majority of patients (89%) received G-CSF-mobilized peripheral blood stem cells. Grafts from matched sibling donors were used in 60% of the patients, and 40% received unrelated donor grafts matched at 9/10 or 10/10 HLA alleles (HLA-A, B, C, DRB1, DQB1).

Lead researcher Dr. Martin Bornhauser of the University Hospital, Dresden, Germany, reported that at a median follow-up of 27 months (range: 4-81), 3-year overall survival was comparable in the reduced-intensity and standard intensity patients: 62% vs. 59%, respectively; ( $p=0.28$ ). Disease-free survival were also similar: 60% vs. 56%, respectively; ( $p=0.44$ ). There was also no significant difference in the cumulative incidence of grade II-IV acute GVHD at day 100: 16% vs. 23%, respectively; ( $p=0.15$ ).

Although reduced-intensity conditioning transplantation is most often used in older patients, Dr. Bornhauser said that these results suggest that this fludarabine and TBI regimen “can be regarded as a valid alternative to standard intensity conditioning even in younger patients with AML transplanted in first remission.” ■

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# Comparable HCT outcomes for NHL in two older patient groups

Non-myeloablative hematopoietic cell transplantation (HCT) in patients  $\geq 65$  years with non-Hodgkin lymphoma (NHL) have comparable outcomes to those of NHL patients transplanted between the ages of 55-64, according to a study presented at an ASH oral session. [4]

In his presentation, lead author Dr. Brian McClune from the University of Minnesota Medical Center noted that these comparable outcomes occurred despite the more frequent aggressive NHL histologies of the patients in the  $\geq 65$  cohort. “Despite higher risk characteristics, three-year survival still approached 40% for even the oldest groups, making HCT a worthwhile option for these patients.”

This large-scale retrospective study analyzed HCT outcomes reported to the CIBMTR (Center for International Blood and Marrow Transplant Research) of 1,248 patients with aggressive (n=668) and indolent (n=580) NHL and transplanted between 2001-2007. All patients received either non-myeloablative or reduced-intensity conditioning (RIC) prior to allogeneic transplantation.

The study stratified transplant recipients into three age cohorts: 40-54, 55-64, and  $\geq 65$  years. Most clinical characteristics did not significantly vary among the three age cohorts. However, patients in the  $\geq 65$  cohort had more aggressive NHL histologies compared to the 40-54 and 55-64 cohorts: 67% vs. 49% vs. 57%, respectively (p=0.0008). In addition, fewer patients  $\geq 65$  years had prior autologous transplants than those in the 40-54 and 55-64 cohorts: 9% vs. 26% vs. 24%, respectively (p=0.002).

As shown in Table 3, three-year progression-free survival (PFS) and overall survival (OS) were significantly reduced in the two older cohorts, but there were no differences between those aged 55-64 and  $\geq 65$  years.

Comparable HCT survival in two older patient groups				
	40-54 YRS (N=614)	55-64 YRS (N=552)	$\geq 65$ YRS (N=82)	P-VALUE
Relapse, 3 yrs	28%	33%	33%	0.22
PFS, 3 yrs	44%	32%	27%	<0.0001
OS, 3 yrs	54%	40%	39%	<0.0001

Table 3. Univariate probabilities of patients receiving HCT for NHL.

In a multivariate analysis, age had no significant independent impact on the incidence of acute (p=0.91) or chronic GVHD (p=0.66), or on relapse (p=0.06). However, older age  $\geq 55$  years, lower Karnofsky performance status, and HLA match disparity were all significantly associated with higher transplant-related mortality, and lower PFS and OS.

Dr. McClune concluded that patients  $\geq 55$  receiving non-myeloablative HCT for NHL have only modestly worse outcomes than patients age 40-54—with no further decrement in those  $\geq 65$  years. In conclusion, Dr. McClune noted that these transplant results compare favorably to chemotherapy alone and that “reduced-intensity or non-myeloablative transplantation has a role in the treatment of those with a good performance status, well-controlled disease, and a well-matched related or unrelated donor.” ■

# Sirolimus reduces GVHD by boosting regulatory T cell recovery

A prospective, randomized phase II trial comparing sirolimus/tacrolimus to methotrexate/tacrolimus has shown that the regimen containing sirolimus selectively boosts immunosuppressive regulatory T cells post transplant and significantly reduces both acute and chronic GVHD. The results, presented in an ASH oral session, also showed no difference in patient-reported quality of life (QOL) between the two regimens. [5]

The trial enrolled 74 patients, 37 in each arm; median age of the patients was 49 years (range, 23-69). Age, diagnosis, disease risk and stem cell source (related or unrelated donor) were balanced across the two study arms.

Median percent of regulatory T cells (Tregs) among blood CD4 T cells was significantly higher in the sirolimus patients than in the methotrexate patients at day 30 post transplant (16.3 vs. 9.9, respectively, p<0.0001) and at day 90 post transplant (14.6 vs. 9.7, respectively, p=0.0009).

The cumulative incidence of Grade II-IV acute GVHD at day 100 for the sirolimus and methotrexate patients was 43% and 89%,

respectively, (p<0.0001). Incidence of Grade III-IV acute GVHD at day 100 was comparable in the sirolimus and methotrexate groups (16% vs. 13%, respectively, (p=0.16)) as was the incidence of any grade chronic GVHD (51% vs. 67%, respectively, (p=0.56).

However, the difference in the cumulative incidence of moderate to severe chronic GVHD between the two groups was “striking,” according to lead author Dr. Joseph Pidala. Only 20% of sirolimus patients experienced moderate to severe chronic GVHD, compared to 63% of the methotrexate patients (p=0.013).

Two-year overall survival did not differ between the sirolimus and the methotrexate patients: 62% vs. 63%, respectively, (p=0.655). A transplant-specific QOL assessment (FACT-BMT) administered at day 30 or 90 post transplant did not detect any significant differences in any domain or summary score.

In conclusion, Dr. Pidala said that these results provide evidence that the combination of sirolimus and tacrolimus, “favors Treg recovery and more effectively prevents acute GVHD and moderate to severe chronic GVHD after allogeneic HCT.” ■

# Co-infusing haploidentical cells speeds UCB engraftment

Time to engraftment is typically longer after umbilical cord blood (UCB) transplantation than it is after bone marrow or peripheral blood stem cell transplantation, and UCB recipients therefore have a higher risk of infection and other complications. Results presented at an ASH oral session demonstrate that co-infusion of CD34+ stem cells from a haploidentical donor can speed UCB engraftment and reduce the duration of post-transplant pancytopenia. [6]

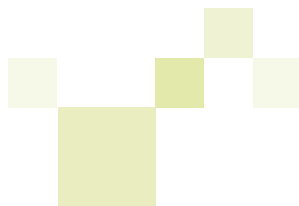
In his presentation, Dr. Koen Van Besien noted that earlier studies and pre-clinical trials have suggested that haploidentical cells can protect transplant recipients from infections in the early post-transplant period while the UCB cells eventually reconstitute the recipient's immune system. [7]

This prospective study examined outcomes after reduced-intensity conditioning allogeneic transplantation in 45 adults (median age 50 years) with high-risk hematological malignancies. Haploidentical donors were HLA-mismatched relatives, and the median infused UCB dose was  $1.55 \times 10^7$  (range, 1.24-2.09) nucleated cells/kg patient weight.

Cumulative incidence of neutrophil recovery at day 50 was 95% (95% Confidence interval (CI), 87-100%) with a median time to engraftment of 11 days (Inter-quartile range (IQR), 9-15 days). Cumulative incidence of platelet recovery at day 100 was 83% (95% CI, 69-97%) with median time to platelet engraftment of 19 days (IQR 15-33 days). Dr. Van Besien noted that these engraftment rates were, "considerably reduced compared with literature reports." At a median follow-up of 330 days (range, 64-1259), one-year overall survival was 55% and progression-free survival was 42%.

Dr. Van Besien, also noted that when paired with haploidentical stem cell infusions, UCB cell dose did not affect time to hematopoietic recovery. This can potentially lead to the use of smaller UCB units, which would increase the pool of UCB units available for transplantation. ■

[Note: Dr. Liu is the lead author of the abstract (see reference #6), but Dr. Van Besien presented the results at the oral session.]



## References

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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](http://marrow.org/md).

between January 2004 and September 2009, and enrolled 278 patients randomized to receive marrow and 273 randomized to receive PBSC.

A majority of patients (90%) were adults over age 20. Primary disease (AML, ALL, CML, MDS, CMML, and MF), disease risk, gender, age, race, and other pre-transplant factors were well balanced between the two groups. The most common indication was AML (47%); 28% of patients had high-risk disease, and 71% received tacrolimus plus methotrexate for GVHD prophylaxis. All patients received myeloablative conditioning regimens, with 48% receiving cyclophosphamide plus total body irradiation.

After a median follow up of 36 months, there were no significant differences in 2-year overall survival between PBSC and marrow transplants: 52% vs. 48%, respectively ( $p=0.37$ ). Subset analyses also showed no survival differences according to graft sources in patients with low- or high-risk malignancies or in those who received HLA-matched or mismatched grafts. As shown in Table 1 [page 1], rates of disease-free survival and non-relapse mortality were also comparable in both patient groups.

However, there was a significantly higher incidence of overall chronic GVHD in the PBSC recipients than in marrow recipients: 53% vs. 40%, respectively ( $p=0.02$ ). In addition, PBSC recipients experienced more extensive chronic GVHD compared to marrow recipients: 46% vs. 31%, respectively ( $p<0.001$ ).

These results do not necessarily mean that bone marrow should become the unequivocal stem cell source for all unrelated donor

transplants, said Dr. Anasetti, who noted that in this study PBSC engrafted significantly faster than bone marrow. Median time to neutrophil engraftment was 5 days faster and platelet engraftment was 7 days faster in PBSC recipients than in marrow recipients ( $p<0.001$  in both instances). Death due to graft rejection was also significantly lower in PBSC recipients compared to marrow recipients: 0% vs. 8%, respectively ( $p=0.002$ ).

For those reasons, Dr. Anasetti said that PBSC may still be the preferred source of stem cells for some patients, such as those at risk for graft failure. PBSC transplants may also be preferred for patients who require faster engraftment because they have been heavily pre-treated and have systemic infections, he said.

Dr. Anasetti noted that approximately 75% of unrelated adult donor transplants currently use PBSC, and that it's unclear whether these study results will affect how transplant physicians select stem cells for their patients. "We also have to honor patient and donor preferences," he said.

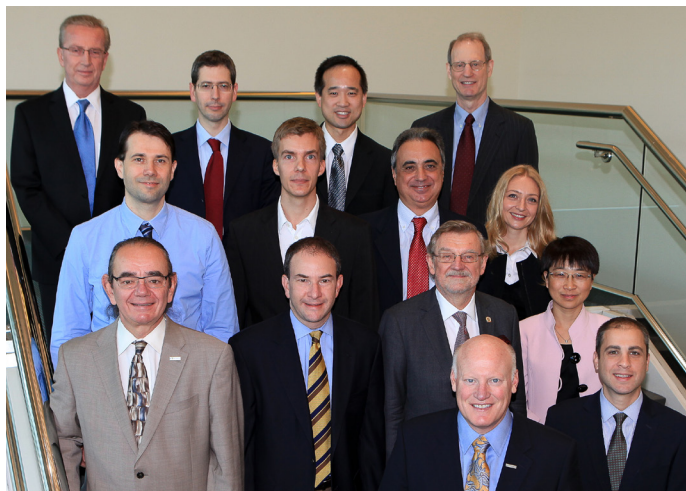
In conclusion, Dr. Anasetti noted that future research should focus on ways to prevent acute and chronic GVHD with either stem cell source and to lower the incidence of graft failure when using bone marrow. ■

#### Award-winning abstract:

Dr. Anasetti was one of 10 researchers recognized by the NMDP and ASH at the 2011 ASH Annual Meeting. (See below for other award winners.)

## Medical researchers honored for outstanding research

To recognize the critical contributions of researchers, the NMDP provided Best ASH Abstract Awards in 10 categories (view the categories at [marrow.org/ASH](http://marrow.org/ASH)) at the 2011 ASH Annual Meeting in San Diego.



Pictured above, left to right, top to bottom:

Claudio Anasetti, M.D.; Luca Malcovati, M.D.; Mark Y. Chiang, M.D.; J. Evan Sadler, M.D.  
Jens Lohr, M.D.; Pekka Jaako; Riccardo Saccardi, M.D.; Tanja A. Gruber, M.D., Ph.D.  
Dennis Confer, M.D.; David Jacobsohn, M.D.; Armand Keating, M.D.; Can-Lan Sun, Ph.D.  
Jeffery Chell, M.D.; Saro Armenian, D.O., M.P.H.

#### Award winners:

- Claudio Anasetti, M.D.,  
H. Lee Moffitt Cancer Center & Research Institute
- Saro Armenian, D.O., M.P.H.,  
City of Hope
- Mark Y. Chiang, M.D., Ph.D.,  
University of Michigan
- Tanja A. Gruber, M.D., Ph.D.,  
St. Jude Children's Research Hospital
- Pekka Jaako,  
Lund University
- David Jacobsohn, M.D.,  
Children's National Medical Center
- Jens Lohr, M.D., Ph.D.,  
Dana-Farber Cancer Institute
- Luca Malcovati, M.D.,  
Fondazione IRCCS Policlinico San Matteo  
& University of Pavia
- Riccardo Saccardi, M.D.,  
Eurocord Registry
- Can-Lan Sun, Ph.D.,  
City of Hope

## Long-term monitoring for late complications of HCT

Two research studies presented at the ASH Annual Meeting underscore the importance of long-term monitoring of hematopoietic cell transplantation (HCT) recipients, who face a higher risk of several adverse health conditions even decades after transplantation.

In an oral presentation, Dr. Can-Lan Sun reported on the incidence of adverse chronic physical and psychological health conditions in 366 HCT recipients who have been periodically surveyed for 10 years or more in the Bone Marrow Transplant Survivor Study (BMTSS). [8] These HCT recipients were compared to a control group of their siblings (n=309).

The mean age at transplant was 22 years (range, 0.4-59.8) and at the time the most recent health survey was conducted the mean age was 37 years (range, 11-72). Stem cell source was allogeneic in 73% of recipients (65% related, 8% unrelated donor) and autologous in 27%.

At least one chronic adverse health condition was reported by 74% of HCT survivors, compared with 29% of siblings ( $p<0.001$ ). Twenty-five percent of HCT survivors reported severe or life-threatening conditions—including myocardial infarction, stroke, blindness, diabetes, and musculoskeletal problems—compared to 8% of the siblings ( $p<0.001$ ).

Dr. Sun, of the City of Hope, Duarte, Calif., also reported that the prevalence of anxiety and depression as measured by the Brief Symptom Inventory (BSI) questionnaire were comparable between HCT recipients and the sibling controls. However, the BSI revealed that HCT recipients were 2.7 times more likely to report somatic distress ( $p<0.001$ ).

Dr. Sun concluded that physical and emotional morbidity in long-term HCT survivors requires extensive post-transplant monitoring, even many years after HCT.

In a second oral presentation, Dr. Saro Armenian focused on long-term cardiovascular complications that can affect HCT survivors. [9]

Dr. Armenian reported the results of a retrospective cohort study of 2041 consecutive patients who underwent HCT at City of Hope between 1995-2004 and who were alive at least one year post transplant. Median age was 44.1 years (range, 0.6-78.9), and 41% underwent allogeneic transplantation.

After 12,551 person-years of follow-up, the 10-year cumulative incidence of the cardiac risk factors dyslipidemia, hypertension, and diabetes was 43.5%, 36.1%, and 16.8%, respectively. Allogeneic recipients with a clinical history of chronic GVHD were at significantly higher risk to develop each of these cardiac risks compared to autologous transplant recipients. HCT recipients with multiple (2 or more) cardiac risk factors were significantly more likely to have cardiovascular disease compared to recipients with 0 or 1 cardiac risk factor (RR: 1.8; 95% CI: 1.1-3.3,  $p=0.04$ ).

In summary, Dr. Armenian noted that these results provide the rationale for “close monitoring and aggressive interventions for this high-risk population in order to reduce cardiovascular morbidity and mortality.” ■

### Award-winning abstracts:

Drs. Sun and Armenian were two of 10 researchers recognized by the NMDP and ASH at the 2011 ASH Annual Meeting. The awards honored outstanding research in hematology/oncology and went to the highest-scoring abstracts in 10 scientific categories. (See article on page 5 for other award winners.)

### POST-TRANSPLANT CARE APP

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