

Advances

in Transplantation

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Your concise update to transplant research from the BMT Tandem 2009 Meetings

Special BMT Tandem Meetings 2009 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 2009 BMT Tandem Meetings held in Tampa, Florida. The BMT Tandem Meetings are jointly sponsored by the Center for International Blood and Marrow Transplant Research (CIBMTR) and the American Society for Blood and Marrow Transplantation (ASBMT).

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Partially matched cord blood units are suitable graft source for children

Partially matched cord blood units (CBUs) from unrelated donors is a suitable alternative to matched cord blood or bone marrow, according to results from a study of 314 pediatric cord blood transplants [1]. In an oral presentation at the BMT Tandem Meetings, lead researcher Dr. Vinod Prasad, from Duke University Medical Center, said that using partially matched cord blood will make transplant accessible to many more patients, in particular those of ethnic and racial minorities.

Dr. Prasad said that he and his colleagues undertook the study to determine if the reluctance of some transplant physicians to use single 4/6 matched CBUs was justified or not. The results of the study, noted Dr. Prasad in his presentation, showed that a single 4/6 CBU “should be seriously considered for patients lacking other donors if the cryopreserved cell dose is more than 2.5×10^7 cells/kg.”

“The use of 4/6 matched units will make transplant accessible to many more patients, in particular those of ethnic and racial minorities.”

The researchers retrospectively studied the outcomes of 314 consecutive pediatric cord blood transplants using myeloablative conditioning between 1993 and 2007 at Duke University. Patients were a median age of 6.1 years (range 0.5-21 years). Sixty-one percent had malignant diseases (n=192) and 39% had non-malignant diseases (n=122). Median follow-up was 6.9 years.

Patients received a post-thaw median dose of 4.80×10^7 cells/kg (range 0.54-27.40). Cord blood units were tissue typed using low resolution for HLA-A and -B and high resolution at -DRB1. All cords had one or two HLA mismatches: 51% were mismatched

4/6 cord blood outcomes in pediatric patients

Years post-transplant	OS
1 year	54.8%
3 years	46.6%
5 years	44.5%
10 years	43.8%

Table 1. Overall survival (OS) at four time points of 314 consecutive pediatric patients transplanted with single 4/6 matched cord blood units.

Transplant outcomes using marrow, PBSC

Outcome	PBSC	Marrow	p-value
Grade II-IV acute GVHD at 100 days	53%	49%	NS
Chronic GVHD at 3 years	58%	33%	<0.001
TRM at 3 years	20%	24%	NS
Overall survival at 3 years	49%	49%	NS

Table 2. Outcomes of unrelated donor transplantation in patients <18 years old with acute leukemia. PBSC=Peripheral blood stem cell, GVHD=Graft-versus-host disease, TRM=Transplant-related mortality.

Partially matched cords are suitable for children: continued from page 1

at one and 49% at two class I HLA loci.

The incidence and severity of acute and chronic graft-versus-host disease (GVHD) was low, according to Dr. Prasad. Cumulative incidence of grade III-IV acute GVHD at day 100 was 13.6%, and 1-year cumulative incidence of chronic GVHD was 13.7%.

Overall survival is shown in Table 1.

In a multivariate analysis, 1-year and long-term overall survival were better in boys, those receiving a pre-cryopreserved total cell dose of $>2.5 \times 10^7/\text{kg}$, and 0 or 1 compared to 2 HLA-B mismatches.

“Our study found that using cord blood can be effective, without increased complications, and can provide more matches for patients, including ethnic minorities,” said Dr. Prasad. ■

Comparing PBSC and marrow outcomes in pediatric transplantation for acute leukemia

Peripheral blood stem cell (PBSC) use in pediatric transplantation declined following a 2004 study showing lower survival in PBSC recipients compared to marrow recipients [3]. That study examined transplants using HLA-identical sibling donors, prompting a group of researchers to wonder whether the same trend would hold if unrelated donors were used.

Dr. Olle Ringdén, from the Karolinska Institutet, Stockholm, Sweden, and colleagues studied the outcomes of 495 unrelated donor transplants in pediatric patients with acute leukemia. In an oral presentation of the study, Dr. Ringdén reported data showing that PBSC and marrow transplants have comparable survival in this patient cohort [2].

The study included 110 PBSC transplants and 385 bone marrow transplants in patients <18 years old undergoing transplantation between 2000-2006 and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Group for Blood and Marrow Transplantation (EBMT). Of the marrow recipients, 186 were allele-matched and 199 were mismatched at HLA-A, -B, -C, or -DRB1; of the PBSC recipients, 60 were matched and 50 were mismatched.

Median follow-up was two years in both patient groups. There were no significant differences in patient and disease characteristics, conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, or donor-recipient HLA disparity by graft type.

As expected, neutrophil engraftment was significantly faster in the PBSC group than in the marrow group at 14 days post transplant: 31% vs. 10%, respectively ($p < 0.001$). But both groups had comparable neutrophil engraftment by day 28: 94% vs. 91%, respectively ($p = 0.391$). Platelet recovery at day 60 was significantly better after PBSC transplants: 86% vs. 76% ($p = 0.022$).

Comparing PBSC and marrow outcomes: continued on page 3

Major outcomes are shown in Table 2. Dr. Ringdén noted that PBSC patients had a significantly greater risk of developing chronic GVHD (Hazard ratio: 2.36, $p < 0.001$). This was not unexpected, noted Dr. Ringdén, as previous studies have demonstrated similar findings.

But the overall results of the study were surprising, noted Dr. Ringdén, because a previous analysis of CIBMTR data found lower survival in pediatric transplantation using PBSC compared to marrow [3]. This 2004 study examined transplants using HLA-identical siblings, and led to a decline in the use of PBSC to transplant pediatric patients.

Dr. Ringdén ended his oral presentation by noting that larger studies are needed to ultimately determine whether PBSC transplants are advisable in children, and whether the donor source (related or unrelated donor) is clinically relevant. ■

ATG may lower rates of acute and extensive chronic GVHD

Including antithymocyte globulin (ATG) in a myeloablative conditioning regimen can significantly reduce the incidence of both acute and chronic graft-versus-host disease (GVHD), according to a study of 171 adult patients [4].

The effect in chronic GVHD was marked: 33% of patients conditioned without ATG experienced extensive chronic GVHD, while those receiving ATG had a 5% incidence ($p = 0.001$).

The study, led by Dr. Mohamad Mohty of the University Hospital Center, Nantes, France, examined outcomes of 171 adult patients with acute leukemia and myelodysplastic syndromes. All patients received grafts from unrelated donors; 81% were 10/10 HLA matched, and 19% were mismatched at one or more alleles.

All patients were conditioned using a myeloablative regimen: 51 patients (30%) received rabbit-derived ATG, and 120 patients (70%) did not.

Patient and donor characteristics were comparable between the two patient cohorts, with the exception of the no-ATG group, which had a significantly higher percentage of allelic differences between recipient and donor (33% vs. 13%; $p = 0.002$).

Table 3 shows patient outcomes at a median follow-up of 30.3 months (range 2.6-68.1). Patients receiving ATG had a significantly lower incidence of grade III-IV acute GVHD and extensive chronic GVHD. All other major transplant outcomes shown in Table 3 were not statistically different in the ATG and non-ATG patient groups.

A multivariate analysis revealed that an increased risk of grade III-IV acute GVHD was significantly associated with an HLA allelic mismatch (Relative Risk=2.80) and the non-use of ATG (RR=2.4). The analysis also showed that non-use of ATG was the unique parameter associated with an increased risk of extensive chronic GVHD (RR=6.9).

Dr. Mohty concluded that there is a global long-term beneficial effect of ATG when used as part of a myeloablative regimen prior to unrelated donor transplant, and that this effect is more pronounced when HLA mismatched donors are used.

ATG can lower rates of acute, extensive chronic GVHD

Outcome	No ATG	ATG	p-value
Grade III-IV acute GVHD	32%	18%	0.04
Extensive chronic GVHD	33%	5%	0.001
Limited chronic GVHD	18%	33%	NS
Non-relapse mortality	29%	30%	NS
Infection-related mortality	27%	23%	NS
Overall survival at 2 years	53.6%	54.3%	NS
Leukemia-free survival	48.8%	41.3%	NS

Table 3. Outcomes of myeloablative transplantation with or without ATG. ATG=Antithymocyte globulin, GVHD=Graft-versus-host disease, NS=not significant. ■

NMDP guidelines: Long-term care and screening for chronic GVHD

Order this two-part guide with recommendations to help you care for patients post transplant. NMDP *Quick Reference Guidelines* contain:

- Long-term screening guidelines
- Screening for chronic GVHD includes photo atlas



Order online: marrow.org/md-guidelines

Sirolimus-based GVHD prophylaxis in pediatric ALL

A pilot study of sirolimus-based GVHD prophylaxis has shown that the agent can result in favorable overall survival (77% at two years) in pediatric patients transplanted for acute lymphoblastic leukemia (ALL) [6].

Lead researcher Dr. Michael Pulsipher, from the University of Utah, Salt Lake City, also noted that the patients had low rates of hepatic veno-occlusive disease (VOD) and of relapse.

Dr. Pulsipher hypothesized that daily administration of sirolimus would improve outcomes by reducing residual disease. He based this hypothesis on published data showing that sirolimus has an anti-leukemic effect resulting from its ability to induce apoptosis in ALL blast cells [7].

The sirolimus was started on the day of transplant, and combined with a tacrolimus/methotrexate GVHD prophylaxis. The sirolimus was tapered over a period of one month starting at six months post transplant. Conditioning was 1200cGy total body irradiation, thiotepa and cyclophosphamide. Graft sources were matched related donors in 26, cord blood in 28, and unrelated donors in 5.

Of the 59 patients enrolled, 47 had pre-B cell ALL, 11 had T-cell ALL, and 1 had mixed-lineage leukemia. Eighteen patients were high-risk in CR1, 14 were in high-risk CR2, 16 were in intermediate-risk CR2, and 11 were in CR3. Median age of patients was 9 years (range 1-22).

At a median follow-up of 25 months (range 5-63), grade II-IV acute GVHD occurred in 42% of patients. The incidence of grade III-IV acute GVHD was 23%. Overall incidence of chronic GVHD was 33%, with 12 patients (23%) experiencing extensive chronic GVHD. Thirty-five of 52 evaluable patients (67%) did not develop any chronic GVHD. Two-year event-free survival is shown in Table 4.

Higher-than-expected rates of survival using sirolimus

ALL Risk Group	HR CR1	HR CR2	IR CR2	CR3
2 year EFS	85%	57%	85%	48%

Table 4. Two-year event-free survival (EFS) in 59 ALL patients. HR=high risk, IR=intermediate risk, CR=complete remission.

Fatal VOD developed in two patients, and three patients had mild or moderate VOD that successfully resolved. This 8% rate of VOD is similar to the anticipated rate in children, according to Dr. Pulsipher, which suggests that a sirolimus/methotrexate regimen does not increase the risk of VOD in children. He also noted that the rates of non-relapse mortality and relapse, 10% and 26%, respectively, were also lower than expected for this patient population. ■

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Dear Health Care Professional:

As patient eligibility expands and outcomes improve, the number of unrelated transplants is growing. So too does the need for additional committed donors. In response, the National Marrow Donor Program® (NMDP) recently introduced Be The MatchSM, the new name of our adult donor and cord blood registry.

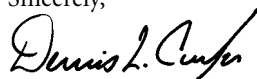
Our mission is to help every patient in need of a transplant. To date, we've facilitated more than 35,000 unrelated donor transplants, with 5,000 transplants in the past 13 months alone. To enable us to help even more patients, Be The Match will grow our registry through public awareness building activities that will appeal to those most likely to join the registry, donate cord blood, and stay committed and available.

Patient Questions

Your patients may start asking you about Be The Match. You and your patients can find the answers you need at marrow.org or by contacting our Office of Patient Advocacy at (888) 999-6743 or patientinfo@nmdp.org.

National Marrow Donor Program will remain the name of the overall organization that operates the Be The Match RegistrySM. You and your patients can continue to turn to the NMDP for clinical decision-making resources, education and support.

Sincerely,



Dennis Confer, M.D.

Chief Medical Officer

National Marrow Donor Program

See Be The Match in action:

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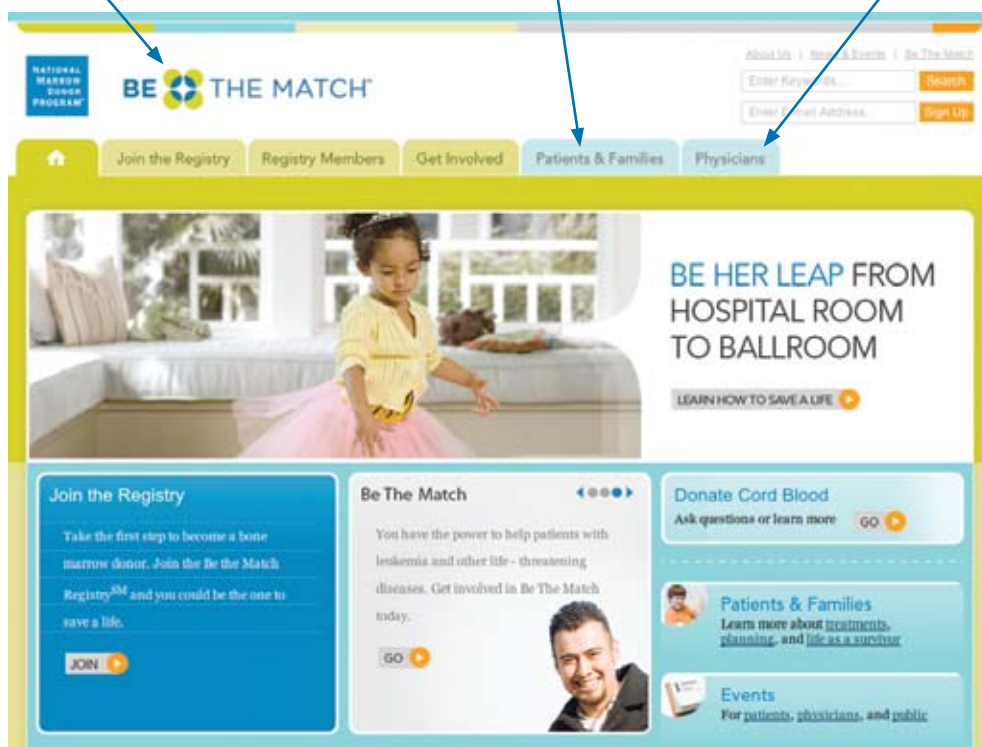
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Reduced-intensity transplantation to treat sickle cell disease

A pilot study of reduced-intensity allogeneic transplantation in sickle cell disease (SCD) has resulted in excellent survival, according to lead researcher Dr. Monica Bhatia of Columbia University. In this study, all 14 pediatric patients are alive after a median follow-up of 496 days [8].

Reduced-intensity conditioning regimens are an attractive option for SCD patients, noted Dr. Bhatia, because of the need to minimize transplant-related toxicity as much as possible for this generally chronic, very debilitating disease.

The researchers enrolled only patients experiencing debilitating SCD symptoms (i.e., cerebrovascular episodes, splenic sequestration, acute chest syndrome) suggestive of poor sickle cell disease prognosis. Six patients received HLA-matched related bone marrow, and eight received umbilical cord blood grafts (two related, six unrelated donors).

Median nucleated cell doses were $5.4 \times 10^8/\text{kg}$ and $4.1 \times 10^7/\text{kg}$ for marrow and cord blood grafts, respectively. The reduced-intensity regimen utilized IV busulfan, fludarabine, and alemtuzumab. Median age of patients was 6.1 years (range 1.5-16).

Dr. Bhatia reported in an oral presentation that median neutrophil and platelet recovery was day 27 and day 43, respectively. Four out of 13 evaluable patients (31%) experienced grade II-IV acute GVHD, and one of nine (11%) evaluable patients experienced chronic extensive GVHD.

Overall survival is 100% (longest follow-up of 1491 days) and no patients experienced further sequelae of SCD. Dr. Bhatia concluded that while the short-term results of her study are exciting, the long-term toxicities of the reduced-intensity regimen remain unknown and need to be evaluated in a larger cohort with a longer follow-up. ■

Choosing the right CLL patients to undergo allogeneic transplantation

Many patients with chronic lymphocytic leukemia (CLL) have an indolent disease course and are therefore not candidates for allogeneic transplantation. However, some CLL patients will be at high risk for disease progression, with consequent short survival, and can benefit from early allogeneic transplantation.

Identifying which CLL patients can benefit most from early identification and transplantation was the topic of a scientific session by Dr. John Gribben, of St. Bartholomew's and The Royal London Hospital [9]. Dr. Gribben introduced the guidelines for allogeneic transplantation in CLL developed by the European Group for Blood and Marrow Transplantation (EBMT) [10].

EBMT Guidelines for Transplantation in CLL

- Allogeneic HCT is a reasonable treatment option in poor-risk CLL, including:
 - Fludarabine resistance — non-response or early relapse (<12 months) after purine analogue-based therapy
 - Relapse <24 months after purine analogue combinations or autologous HCT (+ high-risk genetics)
 - p53 mutation with treatment indication
- Autologous HCT indicated in clinical trial only

Dr. Gribben also reported on an EBMT study of 374 B-cell CLL patients undergoing allogeneic transplantation with HLA-matched sibling donors (n=202), mismatched related donors (n=2), and matched and mismatched unrelated donors (n=170).

Most patients were in complete (13%) or partial (43%) remission, but 28% had active disease progression at time of conditioning. Median age was 53 years (range 24-69), and the median time from diagnosis to transplant was 53 months (range 3-308). Reduced-intensity conditioning was used in 292 (78%) patients, and 82 (22%) received standard conditioning.

Three-year overall survival was 56%, with patients in complete remission at time of conditioning having significantly better survival (80%) than patients in partial remission (63%) and those not in remission (43.5%) ($p < 0.00001$). ■