

Advances

in Transplantation

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Your concise update to transplant research from the 2008 EBMT Annual Meeting

Special 2008 EBMT Annual Meeting 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 research presented at the 2008 Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT), held in Florence, Italy.

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Refining conditioning regimen improves results in AML patients

New research reported at the EBMT meeting has demonstrated that increasing the intensity of a common conditioning regimen can significantly decrease relapse rates without increasing transplant-related mortality (TRM) of patients transplanted for AML.[1]

In an oral presentation, Dr. James Russell of the Tom Baker Cancer Centre in Calgary, Alberta, outlined the improved outcomes achieved by adding 400cGy to a myeloablative regimen of IV busulfan and fludarabine for patients transplanted for both early and advanced acute myelogenous leukemia (AML).

Adding radiotherapy to a common conditioning regimen significantly reduces relapse in AML patients without increasing mortality

In this study, Dr. Russell and his colleagues added two cycles of 200cGy total-body irradiation (TBI) to a regimen of IV busulfan, fludarabine and thymoglobulin administered to 88 AML patients transplanted between 1999 and 2006 at their institution. These patients were compared to 91 matched controls who received the same conditioning regimen, but without the extra 400cGy irradiation. Dr. Russell said that he was motivated to intensify the busulfan/fludarabine/thymoglobulin regimen because while it had been proven to be generally well-tolerated, it had “a substantial relapse rate.”

Median age was 46 years (range 18-66) in TBI recipients and 42 years (range 16-65) for the non-TBI group. GVHD prophylaxis was cyclosporine A, methotrexate and thymoglobulin. There were no statistically significant differences in the TBI and non-TBI patients in disease risk categories, source of donor (related or unrelated), CMV serostatus, and ratio of female donors to male recipients.

Refining conditioning regimen improves results in AML patients: continued on page 2

Intensifying regimen lowers relapse without raising TRM

	Good-risk			High-risk		
	TBI	No TBI	p	TBI	No TBI	p
N	65	56		23	35	
3-yr. OS	77%	64%	ns	50%	28%	ns
3-yr. DFS	77%	59%	ns	45%	16%	0.04
Relapse	16%	32%	ns	34%	69%	0.004
TRM	8%	13%	ns	31%	26%	ns

Table 1. Transplant outcomes for good-risk (n=121) and high-risk (n=58) patients with AML transplanted with or without TBI.

TBI = total-body irradiation
 TRM = transplant-related mortality
 OS = overall survival
 DFS = disease-free survival

There was no significant difference in incidence of grade II-IV acute GVHD in TBI recipients (23%) and non-TBI patients (16%). Chronic GVHD was also comparable in TBI and non-TBI groups, 55% vs. 64% respectively. In good-risk patients (CR1/CR2), three-year overall survival (OS) in TBI and non-TBI patients was 77% and 64%, respectively (p=0.14). In high-risk patients, OS was 50% and 28% in TBI and non-TBI patients, respectively (p=0.07).

The main finding of the study was a Cox proportional hazard ratio (HR) for relapse, favoring TBI: HR=0.32; 95% CI: 0.17-0.6 (p=0.004). In low-risk patients, relapse was comparable, but in high-risk patients, TBI patients had significantly lower relapse, 34% vs. 69%, respectively (p=0.004). Other outcomes are shown in Table 1, which shows patients separated into good- and high-risk groups.

Dr. Russell concluded that adding 400cGy TBI to a busulfan/fludarabine/thymoglobulin conditioning regimen can significantly reduce relapse in both early and advanced AML patients without increasing TRM. ■

A majority of patients with refractory GVHD respond to MSC therapy

Response	Children (n=25)	Adults (n=30)	All patients (n=55)
Complete	16 (64%)	14 (47%)	30 (55%)
Partial	4 (16%)	4 (13%)	8 (15%)
Overall	20 (80%)	18 (60%)	38 (69%)

Table 2. Responses to MSCs of 55 transplant patients with therapy-refractory grades II-IV acute GVHD.

MSC = mesenchymal stem cell
 GVHD = graft-versus-host disease

Mesenchymal stem cells can effectively treat acute GVHD

A consortium of five European transplant centers reported that a majority of 55 patients with steroid-resistant, severe, acute GVHD achieved complete responses after being treated with mesenchymal stem cells.[2] Lead researcher Dr. Katarina Le Blanc, of the Karolinska Institute in Stockholm, Sweden, said she was inspired to administer mesenchymal stem cells to patients with GVHD because such cells are known to modulate immune responses in vitro and in vivo.

The 55 patients had a median age of 22 years (range 0.5-64) and all but two patients were transplanted for a form of leukemia. The median dose of mesenchymal stem cells was 1.4×10^6 (range $0.4-9 \times 10^6$) cells per kg recipient weight. The bone-marrow-derived mesenchymal stem cells were obtained from HLA-identical sibling donors (n=5), haploidentical donors (n=18), and HLA-mismatched unrelated donors (n=69). Twenty-seven patients received a single infusion of mesenchymal stem cells and 28 received between two and five infusions.

Of the 55 patients, 30 (55%) achieved complete responses to the infusions of mesenchymal stem cells, and eight more patients achieved a partial response for a 69% overall response rate. Pediatric patients did better, with 16 of 25 (64%) achieving a complete response and 20 of 25 (80%) having a partial or complete response. Full results are shown in Table 2.

Because response rate was not related to donor type or HLA-match, Dr. Le Blanc concluded that mesenchymal stem cells, irrespective of the donor, are a potentially effective therapy for patients with steroid-resistant, acute GVHD and should be investigated further. ■

Early allo-transplantation an effective strategy in high-risk AML patients

Up-front hematopoietic cell transplantation as part of primary induction therapy can be an effective strategy in high-risk acute myeloid leukemia (AML) patients, according to results from a prospective trial reported at the EBMT meeting.[3] The study's lead investigator concluded that transplantation is the better choice for these patients because they are "unlikely to achieve remission using conventional chemotherapy protocols."

Dr. Uwe Platzbecker, of the Universitätsklinikum Carl Gustav Carus, Dresden, Germany, reported results from a phase II study of 40 newly diagnosed high-risk AML patients with a median age of 50 years (range 17-68). Patients were categorized as high risk due to poor-risk cytogenetics (n=26), marrow blasts >10% (n=11), or FLT3 mutation (n=3).

With a median follow-up of 17 months, the two-year probability of overall and disease-free survival is 68%.

To ensure transplantation as early as possible, tissue typing of family members and searches for unrelated donors were initiated at time of diagnosis (See Fig. 1.) Patients were transplanted after one or two cycles of induction chemotherapy and had achieved chemotherapy-induced aplasia. The median time from diagnosis to transplant was 47 days.

Patients received a reduced-intensity conditioning regimen based on fludarabine combined with either busulfan (n=4) or melphalan (n=36) followed by peripheral blood stem cells (PBSC) from related (n=12) or unrelated (n=28) donors. Twenty-six patients were not in complete remission before starting the conditioning regimen, and had a median marrow blast count of 20% (range 6-85).

Median time to neutrophil engraftment was 11 days (range 8-19) and was 15 days (range 12-32) for platelet engraftment. Complete donor chimerism and complete remission was achieved by all recipients. Grade II-IV acute GVHD occurred in 35 % of recipients and extensive chronic GVHD developed in 30%. Seven of the eight patients relapsing did so within the first year post-transplant.

Study design

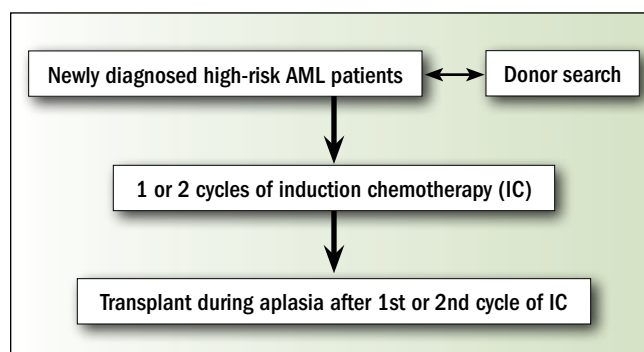
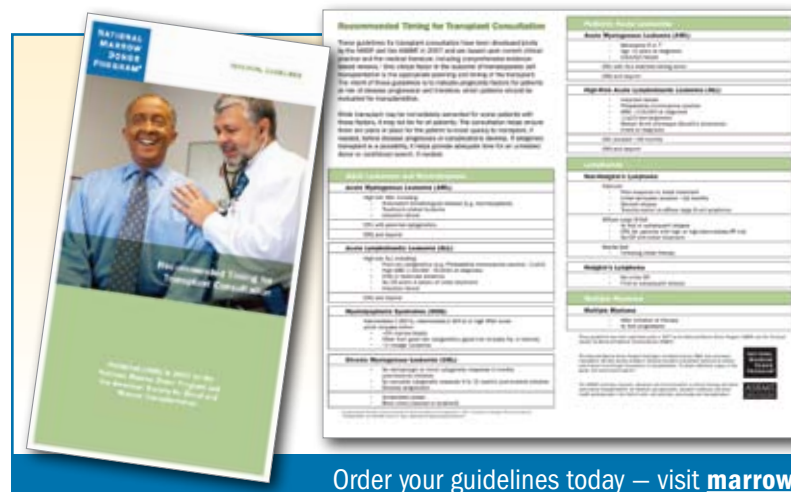


Figure 1. Donor searches were initiated at time of diagnosis, resulting in a median time to transplant of 47 days.

With a median follow-up of 17 months (range 1-91) the two-year probability of overall and disease-free survival is 68%. Dr. Platzbecker concluded that early allogeneic PBSC transplantation can be an effective strategy in patients with newly diagnosed high-risk AML, who are unlikely to achieve remission with conventional chemotherapy protocols. ■



Transplant timing matters; a new resource can help

Research shows that patients transplanted at the optimal time in their disease have better outcomes. The NMDP/ASBMT evidence-based clinical guidelines; provide a quick reference to determine patient eligibility and timing for transplant consultation.

These guidelines are part of the NMDP *Quick Reference Guidelines*, a toolkit that also includes post-transplant care information aimed at recognizing complications early, while therapeutic options are more effective.

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Novel delivery of anti-fungal drug may improve transplant outcomes

Immunosuppressed transplant recipients are at risk of invasive *Aspergillus* (IA) infections, with the lungs being the most common infection site. Prophylactic administration of an inhaled form of the anti-fungal drug amphotericin B is especially effective in reducing IA, according to a study presented at the EBMT meeting.[4]

Led by Dr. Anne Nihtinen, researchers at the Helsinki University Central Hospital compared the outcomes of allogeneic transplant patients during two time periods at their institution. One group was transplanted between 1996 and 2000 (Period I) without any anti-fungal prophylaxis and the other group of patients was transplanted between 2001 and 2005 (Period II) with an inhaled formulation of amphotericin B (25 mg daily, dissolved in sterile water and nebulized).

Inhaled amphotericin B was only given to patients who developed acute GVHD and subsequently treated with high-dose methylprednisolone (10mg/kg). None of the 95 patients in Period II receiving inhaled amphotericin B interrupted the treatment due to side effects. Treatment lasted for a median of 81 days (range 2-284).

Table 3, from the researchers' poster presentation, shows that the incidence of IA was significantly reduced in patients receiving prophylactic inhaled amphotericin B as compared to patients receiving no prophylactic medication (2.5% vs. 6.6%, respectively; $p=0.021$).

The five-year overall survival (OS) was also significantly better in the inhaled amphotericin B group of patients (60% vs. 47%, respectively; $p<0.001$).

Transplant outcomes using inhaled amphotericin B

	Period I (no IA prophylaxis) n=258	Period II (IA prophylaxis) n=354	p-value
IA	17 (6.6%)	9 (2.5%)	$p=0.021$
5-year OS	47%	60%	$p<0.001$

Table 3. Transplant outcomes of patients with or without IA prophylaxis.

OS = overall survival, IA = invasive *Aspergillus*

The researchers note that there might be other contributing factors to account for the differences in the two groups, including a general trend for better outcomes in transplants performed in more recent time periods. However, the researchers noted that cutting the incidence of IA in half most likely also contributed to the better OS in the group treated with inhaled amphotericin B. ■

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Myeloablative, reduced-intensity regimens comparable

Reduced-intensity conditioning regimens prior to allogeneic transplantation are frequently preferred for older patients and patients with comorbidities. Although these less intense regimens can reduce the incidence of transplant-related mortality (TRM), they can lead to higher relapse rates. Two studies presented at the EBMT annual meeting show that these two factors — TRM and relapse — affect outcomes approximately equally, resulting in comparable long-term survival for both myeloablative and reduced-intensity regimens.

The Acute Leukemia Working Party of the EBMT reported on the outcomes of 2,084 adult patients with AML in 2nd to 3rd remission transplanted using unrelated donors with either reduced-intensity (n=488) or myeloablative (n=1,596) conditioning regimens.[5]

In patients younger than 50 years, the study found significantly higher rates of relapse at two years in the reduced-intensity patients than in the myeloablative patients (51% vs. 31%, respectively; $p=0.006$). However, the higher relapse rate in reduced-intensity patients did not significantly affect TRM (36% vs. 26%) and leukemia-free survival (LFS) (44% vs. 36%) in myeloablative patients and reduced-intensity patients, respectively ($p=ns$).

Reduced-intensity transplantation can lead to a better quality of life for patients

In patients older than 50 years, the study found a significantly higher relapse rate in the reduced-intensity patients than in the myeloablative patients (47% vs. 18%, respectively; $p=0.009$). However, despite the differences in relapse rates, the study also found comparable rates of TRM and LFS regardless of which conditioning regimen was used.

The study, presented at the meeting by Dr. Olle Ringdén of the Karolinska University Hospital, Stockholm, Sweden, also showed no significant difference in grade II-IV acute GVHD in reduced-intensity and myeloablative groups. In patients younger than 50 years, 36% and 31% experienced grade

II-IV acute GVHD using myeloablative and reduced-intensity regimens, respectively ($p=0.22$). In patients older than 50 years, 29% experienced grade II-IV acute GVHD, regardless of conditioning regimen ($p=0.92$).

Better quality of life

A second study presented at the EBMT meeting also showed comparable survival following myeloablative and reduced-intensity transplantation. It also suggested that reduced-intensity recipients may experience a better quality of life due to a shorter duration of immune suppression therapy. In this study of 111 adults transplanted for hematological malignancies, patients receiving reduced-intensity conditioning experienced significantly shorter duration of immunosuppressive therapy than patients receiving myeloablative conditioning.[6]

The study, led by Dr. Avichai Shimoni of the Chaim Sheba Medical Center in Tel-Hashomer, Israel, compared the outcomes of 50 patients undergoing reduced-intensity transplantation to 61 patients undergoing myeloablative transplantation. The median age was significantly higher in the reduced-intensity group (49 years, range 16-65) than in the myeloablative group (36 years, range 18-65).

After a median follow-up of 6.2 years, overall survival is 44% in the reduced-intensity group and 45% in the myeloablative group ($p=ns$). Cumulative incidence of chronic GVHD was similar in the two groups (51%, reduced-intensity vs. 66%, myeloablative; $p=ns$), but the reduced-intensity patients had a significantly shorter duration of immunosuppressive therapy.

Only two of 25 long-term survivors in the reduced-intensity group were still taking immunosuppressive drugs at last follow-up compared to 11 of 23 survivors in the myeloablative group. Median duration of immunosuppressive therapy was also shorter in the reduced-intensity group (18 months vs. 45 months; $p<0.01$). Dr. Shimoni concluded that while both conditioning regimens can achieve comparable survival, reduced-intensity transplantation can lead to a better quality of life for patients. ■

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PET scans are useful prognostic tools in lymphoma patients

A study of 82 adults with Hodgkin lymphoma (HL) or aggressive non-Hodgkin lymphoma (NHL) has demonstrated the predictive value of positron emission tomography (PET) scans prior to reduced-intensity allogeneic transplantation.

The retrospective study, led by Dr. Anna Dodero, examined the outcome of 82 consecutive lymphoma patients undergoing reduced-intensity transplantation between 2000 and 2007 at the Istituto Nazionale dei Tumori in Milan, Italy.[7]

In an oral presentation, Dr. Dodero noted that positive PET scans — i.e., those detecting the uptake of a radioactive tracer by malignant lymph cells — are associated with poorer outcomes in HL and aggressive NHL patients undergoing chemotherapy or autologous transplantation. In this study, Dr. Dodero and colleagues set out to determine if full-body PET scans could have prognostic value in patients undergoing reduced-intensity allogeneic transplants.

The median age of patients was 36 years (range 17-68). Thirty-eight patients had NHL, and 44 had HL. HLA-identical sibling donor grafts were used in 47 patients, haploidentical donor grafts in 16 patients, and unrelated donor grafts in 19 patients.

Sixty-eight patients (83%) had failed previous autografts, and the median number of prior regimens was three (range 1-6). PET scans were interpreted by a double-blinded nuclear medicine physician.

Our study shows a better progression-free survival and overall survival for patients being PET negative before allogeneic transplantation

The estimated three-year progression-free survival was significantly higher in patients with PET negative scans than in patients with PET positive scans (68% vs. 30%, respectively; $p < 0.003$). The cumulative risk of relapse was also significantly higher in patients with positive PET scans than in patients with negative PET scans (53% vs. 21%, respectively; $p < 0.022$).

Dr. Dodero concluded that PET scans should be included in evaluations of lymphoma patients considering hematopoietic cell transplantation. ■

Best GVHD prophylaxis varies, may depend on donor type

A meta-analysis examining the effectiveness of several types of GVHD prophylaxis has shown that the best GVHD prophylaxis for a patient may depend on whether the patient was transplanted with a related or unrelated donor. The meta-analysis, led by Dr. Ron Ram of Tel Aviv University, Israel, estimated the relative risks (RR) with 95% confidence intervals (CI) of 23 separate randomized controlled trials and pooled the results.[8]

A methotrexate-tacrolimus prophylactic regimen to treat acute GVHD should be the preferred treatment in unrelated donor transplantation

Six clinical trials compared a cyclosporine A (CsA) prophylactic regimen to a regimen of CsA combined with methotrexate (MTX). In the pooled analysis, patients receiving MTX plus CsA prophylaxis experienced a significant reduction of acute GVHD (RR 0.49 [95% CI: 0.38-0.65]). This result applied to all

patients, irrespective of whether a related or unrelated donor graft was used.

However, three clinical trials comparing adding either tacrolimus or CsA to a MTX prophylaxis regimen found that graft source (related or unrelated donor) affected outcomes. In the pooled analysis of these three trials, there was a significant reduction in acute GVHD in both matched-related and matched-unrelated transplantation (RR 0.62 [95% CI: 0.48-0.96]) when using a combination of tacrolimus and MTX. However in matched-related transplantation, there was a significant increase in all types of post-transplant mortality when using tacrolimus and MTX as first-line GVHD prophylaxis compared to CsA and MTX prophylaxis (RR 1.29 [95% CI: 1.04-1.6]).

Dr. Ram therefore concluded that a MTX-tacrolimus prophylactic regimen to treat acute GVHD should be the preferred treatment in matched-unrelated donor transplantation, but that this combination should not be used in matched-related transplants. Dr. Ram notes that because the addition of MTX to a CsA-based regimen reduces acute GVHD, this should remain the first choice in matched-related transplantation. ■