Check for updates

# Allogeneic Peripheral Blood Stem Cell Transplantation in Patients With Advanced Hematologic Malignancies: A Retrospective Comparison With Marrow Transplantation

By William I. Bensinger, Reginald Clift, Paul Martin, Frederick R. Appelbaum, Taner Demirer, Ted Gooley, Kathy Lilleby, Scott Rowley, Jean Sanders, Rainer Storb, and C. Dean Buckner

**Allogeneic peripheral blood stem cell (PBSC) transplants from HLA-identical siblings were performed in 37 patients with advanced hematologic malignancies. Outcomes were compared to a historical group of 37 similar patients with advanced hematologic malignancies receiving bone marrow (BM) transplants from HLA-identical donors. The PBSC group and historical BM group were well matched for diagnosis, disease stage, age, and graft-versus-host disease (GVHD) prophylaxis. Patients received PBSC transplants between 1993 to 1995 while BM patients were treated between 1989 to 1994. Engraftment, measured by the time to reach a peripheral neutrophil count >500/L and platelet count >20,000/$\mu$L without transfusions, occurred on days 14 and 11 in the patients transplanted with PBSC compared to days 16 and 15 in the patients receiving BM ($P$ = .00063, .00014). The PBSC group required a median of 8 U of red blood cells and 24 U of platelets compared to 17 U of red blood cells and 118 U of platelets for BM transplant recipients ($P$ = .0005, .0001). The estimated risks of developing grades 2 to 4 acute GVHD were 37% for the PBSC group and 56% for the BM group ($P$ = .18), while the estimated risks of grades 3 to 4 acute GVHD were 14% for the PBSC group and 33% for the BM group, $P$ = .05). Chronic GVHD occurred in 7 of 18 evaluable patients receiving PBSC and 6 of 23 evaluable patients receiving BM, $P$ = .5. The estimated risks of transplant-related mortality at 200 days were 27% versus 45% ($P$ = .33) relapse were 70% versus 53% ($P$ = .27) and of overall survival were 50% and 41% ($P$ = .39) for patients transplanted with PBSC or BM, respectively. This retrospective comparison suggests that compared to marrow transplantation from HLA-identical donors, allogeneic PBSC transplantation from HLA-identical donors is associated with faster engraftment, fewer transfusions, and no greater incidence of acute or chronic GVHD.**

*© 1996 by The American Society of Hematology.*

NUMEROUS STUDIES have shown that peripheral blood stem cells (PBSC) collected after the administration of recombinant human granulocyte-colony stimulating factor (G-CSF) are capable of supporting rapid and complete hematopoietic reconstitution when used for autologous transplantation.[1-5] The relative safety and the low toxicity of G-CSF given to patients for mobilization of autologous PBSC prompted studies of the use of this drug for granulocyte mobilization and collection from normal allogeneic donors and for PBSC mobilization in syngeneic donors.[6,7] Experience to date has suggested that the side effects observed following the administration of G-CSF to normal donors are tolerable, with follow up now extending to 4 years.[7] These observations led to pilot studies of allogeneic transplantation using PBSC collected after the administration of G-CSF to normal family member donors.[8-10] Preliminary results suggest that HLA-identical allogeneic PBSC produce prompt and complete hematopoietic engraftment without an increase in the incidence or severity of acute graft-versus-host disease (GVHD). No formal comparisons, however, have been made of outcomes of patients receiving HLA identical allogeneic PBSC transplants and patients receiving BM transplants. In the present study, we have used a formal, retrospective case-control method to compare the outcomes for 37 patients receiving HLA-identical allogeneic PBSC transplants to a historical group of 37 historical patients transplanted with BM.

## PATIENTS AND METHODS

*Patient accrual and categorization.* Between December 1993 and October 1995, 37 patients with advanced hematologic malignancies received a first allogeneic transplant with PBSC from an HLA-identical sibling at the Fred Hutchinson Cancer Research Center (FHCRC). Patients were eligible for transplant with PBSC if they were between age 18 to 55 and had an advanced malignancy for which marrow transplantation was indicated. Seven of the 37 patients in this study have been previously reported.[8] The 37 patients were among a subset of 42 consecutive patients transplanted with allogeneic PBSC from HLA identical siblings. Five patients were excluded from this analysis because PBSC were used for a second transplant (n = 3) or because of transplant for a nonhematologic malignancy (Wilm's tumor, n = 1) or were transplanted for chronic myeloid leukemia (CML) in chronic phase (n = 1). These patients were excluded to have a more uniform population for analysis. Patient and donor characteristics are shown in Table 1.

*Informed consent.* Patients and donors were asked to participate in a study evaluating transplants with PBSC as an alternative to bone marrow (BM). All patients and donors signed informed consent forms approved by the Institutional Review Board of the FHCRC. This study was conducted under IND exemption #5231 issued by the US Food and Drug Administration.

*Historical control group.* An historical group of 37 patients who received allogeneic BM from an HLA-identical sibling was identified. Using the FHCRC database each patient who received an allogeneic PBSC transplant was matched with 1 historical patient who received BM. Historical patients were chosen by computer using the patients most recently transplanted with BM from HLA identical sibling donors. As many variables as possible were matched between the control patient and the patient receiving PBSC in the following

*From the Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, WA.*

*Submitted July 12, 1995; accepted May 29, 1996.*

*Supported by National Cancer Institute Grants No. CA 18029, CA 47748, CA 18221, CA 15704, CA 09319, CA 09515, and the Jose Carreras Foundation against Leukemia and the Joseph Steiner Krebsstiftung.*

*Address reprint requests to William I. Bensinger, MD, Fred Hutchinson Cancer Research Center, 1124 Columbia St, M-185, Seattle, WA 98104.*

*The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.*

*© 1996 by The American Society of Hematology.*

*0006-4971/96/8807-0033$3.00/0*



Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024

**Table 1. Patient and Donor Characteristics**

| | PBSC | BM |
|---|---|---|
| No. of patients | 37 | 37 |
| Dates of transplant | 12/21/93-10/11/95 | 1/23/89-12/12/94 |
| Age in yr, median (range) | | |
| Patient | 38 (20-52) | 39 (22-55) |
| Donor | 38 (17-63) | 36 (18-64) |
| Gender* | | |
| Patient female | 14 (38%) | 11 (30%) |
| Donor female | 12 (32%) | 15 (41%) |
| Donor multiparous | 6 (50%) | 13 (87%) |
| Cytomegalovirus serology* | | |
| Patient and donor negative | 15 (41%) | 10 (27%) |
| Diagnosis* | | |
| Acute myeloid leukemia | 15 (41%) | 15 (41%) |
| Non-Hodgkin's lymphoma | 9 (24%) | 9 (24%) |
| Acute lymphoid leukemia | 5 (14%) | 5 (14%) |
| Hodgkin's disease | 4 (11%) | 4 (11%) |
| CML | 2 (5%) | 2 (5%) |
| Multiple myeloma | 2 (5%) | 2 (5%) |
| Phase of disease* | | |
| Relapse | 33 (89%) | 30 (81%) |
| Blast crisis of CML | 2 (5%) | 2 (5%) |
| Remission > = 2 | 2 (5%) | 5 (14%) |

* No. of patients (% of patients).

order of priority: diagnosis, disease phase at transplant, patient age ±5 years, and GVHD prophylaxis. Only patients receiving their first transplant were included in this analysis. Characteristics of the control group are shown in Tables 1 and 2.

*Donors.* All PBSC donors were given G-CSF (Amgen, Inc, Thousand Oaks, CA) 16 μg/kg/d in 2 subcutaneous injections performed once daily for 5 days, beginning 4 days before PBSC collection and once after the first collection. Apheresis was performed for 1 or 2 consecutive days beginning on day 5 of G-CSF administration. Day 5 of G-CSF administration to the donor was timed to coincide with day 0 of the allograft recipient. Donor venous access was obtained through venipuncture of both arms in 34 patients or through a subclavian or femoral catheter in 3 patients. Apheresis was performed with the use of a continuous flow blood cell separator (Cobe Laboratories, Lakewood, CO) as previously described.[8] After each collection, apheresis products were infused into recipients immediately. A goal of this study was to collect and infuse a minimum of $15 \times 10^6$ $CD34^+$ cells/kg with 1 or 2 apheresis procedures. In the historical group, BM was obtained from donors by established methods.[11] Day 0 for the recipient was defined as the day of BM or first day of PBSC infusion.

Treatment regimens are shown in Table 2. Descriptions of chemotherapy regimens, total body irradiation, GVHD prophylaxis and supportive care are included in other publications.[8] Seven patients who received BM were given posttransplant G-CSF (n = 3) or granulocyte-macrophage CSF (GM-CSF) (n = 4), whereas none of the patients who received PBSC were given a hematopoietic growth factor.[12]

*Evaluation and definitions.* PBSC were analyzed for $CD34^+$ cells and T-cell subsets by flow cytometry as previously described.[13] Engraftment was documented by increasing neutrophil and platelet counts unsupported by transfusions, by in situ Y chromosome hybridization or conventional cytogenetics with BM or blood samples in sex mismatched donor-recipient pairs and by analysis of variable number tandem repeat (VNTR) polymorphisms in BM or blood samples in sex-matched pairs.[14,15] Neutrophil engraftment was defined as the first of 2 consecutive days with an absolute neutrophil count (ANC) >500/μL following the posttransplant nadir. Platelet engraftment was defined as the first of 7 consecutive days with a platelet count >20,000/μL without platelet transfusions. Acute GVHD was graded as previously described.[16] Chronic GVHD was assessed using data derived from the day 80 evaluation or from subsequent follow-up studies.[17]

Patients who died posttransplant after relapse were categorized as dying of relapse irrespective of the proximate cause. Infection was listed as the cause of death when a bacterial, viral, or fungal infection was the approximate cause of death in the absence of relapse. Death due to interstitial pneumonitis caused by cytomegalovirus (CMV) infection was categorized separately. Interstitial pneumonia syndrome (IPS) was defined as diffuse pulmonary infiltrates without identifiable cause. GVHD was listed as the cause of death in patients who died of infection with grade 3 or 4 acute GVHD.[16]

*Statistical evaluations.* Outcome data, including time to engraftment of neutrophils and platelets, transfusion requirements, development of acute and chronic GVHD, relapse and death were analyzed and compared between the 2 groups. The proportions of patients within each subgroup of characteristics and outcomes for patients receiving PBSC or BM were compared by using Fisher's test (two-tailed). Data with a non-normal distribution (eg, numbers of transfusions or length of follow-up) were analyzed with a nonparametric test (Wilcoxon). The probabilities of neutrophil and platelet recovery, mortality within 100 days, acute GVHD, relapse and survival were compared by performed using the method of Kaplan and Meier[18] with log-rank analysis (SAS, Inc, Cary, NC).

## RESULTS

*Comparability of PBSC and control groups.* As shown in Table 1, the PBSC and BM groups were well matched for diagnosis, age, and phase of disease and treatment.

The recipients of allogeneic PBSC received a median of $15.1 \times 10^8$ (range 7.1 to 36.3) nucleated cells/kg and $12.3 \times 10^6$ (range 3.84 to 21.64) $CD34^+$ cells/kg. Ten patients received only a single apheresis product whereas the remaining 27 were given apheresis products from 2 consecutive days. The PBSC product contained a median of 407.6 (range 81.3 to 974.7) CD3 cells, 246.4 (range 44.7 to 578.4) CD4 cells, and 126.4 (range 33.0 to 354.6) CD8 cells $\times 10^6$/kg. Those in the historical BM group received a median of $2.07 \times 10^8$ (range 0.22 to 4.18) nucleated cells/kg. The median followup for patients receiving PBSC is 285 days (110 to 720) and 817 (295 to 2,224) for patients receiving BM ($P = .001$).

*Engraftment and transfusion requirements.* Engraftment

**Table 2. Treatment Characteristics**

| | PBSC | BM |
|---|---|---|
| No. of patients | 37 | 37 |
| Myelo-ablative regimens* | | |
| Cy/$TBI^+$-Bu | 32 (86%) | 33 (89%) |
| Bu/Cy, Bu/TT | 5 (14%) | 2 (5%) |
| Carmustine/Cy/Etoposide | 0 | 2 (5%) |
| GVHD prophylaxis* | | |
| Cyclosporine and methotrexate | 19 (51%) | 20 (54%) |
| Cyclosporine and prednisone | 18 (49%) | 17 (46%) |

Abbreviations: cy, cyclophosphamide; TBI, total body irradiation; Bu, busulfan; TT, thiotepa.

* No. of patients (% of patients).

Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024

**Table 3. Engraftment and Transfusions**

| | PBSC | BM | P |
|---|---|---|---|
| Total no. of patients | 37 | 37 | |
| No. of patients not achieving ANC > 500/μL* | 1 (3%) | 2 (5%) | 1.0‡ |
| Day ANC > 500/μL | | | |
| Median (range) | 14 (9-33) | 16 (8-33) | 0.0063† |
| No. of patients not achieving platelets > 20,000/μL* | 5 (14%) | 12 (32%) | 0.097‡ |
| Day platelets > 20,000/μL | | | |
| Median (range) | 11 (1-46) | 15 (3-190) | 0.0014† |
| No. of platelet units transfused | | | |
| Median (range) | 24 (6-246) | 118 (7-988) | 0.0001‡ |
| No. of RBC units transfused | | | |
| Median (range) | 8 (0-116) | 17 (2-105) | 0.0005‡ |

* No. of patients (% of patients).
† Log-rank.
‡ Wilcoxon.

parameters and transfusion requirements are shown in Table 3. One patient transplanted with PBSC and one patient transplanted with BM died on days 15 and 29, respectively, before reaching 500 neutrophils/μL. Among those who did reach an ANC of 500, the median day to achieve a such a count was 14 for recipients of PBSC and 16 for recipients of BM. The time to a count of >500 neutrophils/μL, shown in Fig 1, was significantly shorter for patients receiving PBSC ($P$ = .0063). The median number of days to achieve neutrophil counts of 500/μL for patients in the PBSC group who received prednisone (n = 18) or methotrexate (MTX) (n = 18) were 12 and 15, respectively. The median number of days to achieve neutrophil counts of 500/μL for patients in the BM group receiving prednisone (n = 17) or MTX (n = 19) were 12 and 20, respectively.

Five patients (14%) receiving PBSC and 12 patients (32%) receiving BM died without reaching platelet transfusion independence ($P$ = .097). All other PBSC patients were transfusion independent by day 46. Three recipients of BM survived beyond day 100 but did not achieve platelet independence before death. There were no such patients in the group receiving PBSC. The median time to achieving platelet independence was day 11 for the PBSC group and day 15 for the BM group. The latest day to platelet transfusion independence was 46 for the PBSC group and 190 for the BM group. The incidence of achieving platelet independence, also shown in Fig 1, was significantly shorter for patients receiving PBSC compared to BM ($P$ = .0014). The median day to achieve a platelet count of 20,000/μL for patients in the PBSC group who received prednisone (n = 17) or MTX (n = 15) were 9 and 12, respectively ($P$ = .05). The median days to achieve a platelet count of 20,000/μL for patients in the BM group receiving prednisone (n = 13) or MTX (n = 12) were 15 and 19, respectively ($P$ = .03).

The median number of units of platelets transfused was 24 in the group receiving PBSC compared to 118 for the BM group ($P$ = .0001). The median number of units of red blood cells transfused was 8 units in the PBSC group compared to 17 in the BM group ($P$ = .0005).

*Chimerism studies.* Informative chimerism studies were available in 29 recipients of PBSC and 21 recipients of BM. In patients transplanted with allogeneic PBSC 100% donor cells were documented in PB or BM by testing VNTR in 12 patients and by testing Y chromosome in situ hybridization (ISH) in 12 patients between 30 to 95 days after transplant. Host cells were detected in 3 patients by VNTR analysis and 2 patients by ISH just before or during documented clinical relapse. In BM recipients, 100% donor chimerism was documented by ISH or cytogenetic analysis in 18 patients between 21 to 98 days after transplant, and host cells associated with relapse were detected by ISH in 3 patients.

*Acute and chronic GVHD.* As shown in Table 4, the incidence of grades 2 to 4 acute GVHD was 37% in patients transplanted with PBSC compared to 56% in patients who were transplanted with BM ($P$ = .18 ). Grades 3 to 4 acute GVHD occurred in 14% and 33% of patients receiving PBSC or BM, respectively ($P$ = .10). The actuarial probabilities

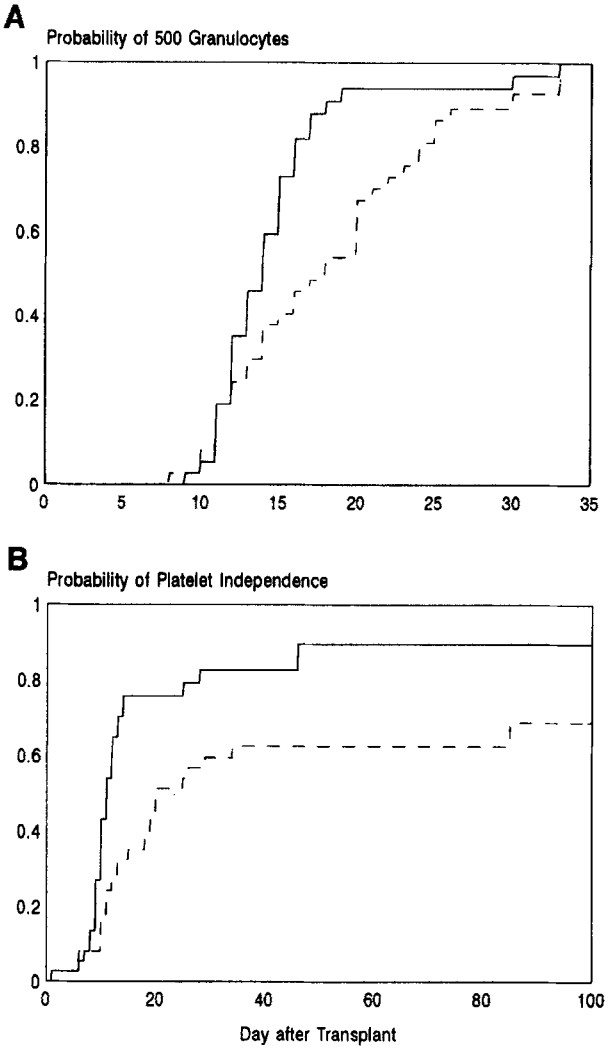



**Fig 1. Probability of achieving 500 granulocytes/μL (A) or platelet independence (20,000/μL untransfused, B) after transplantation of allogeneic PBSCs (solid line) BM (broken line).**

Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024

**Table 4. GVHD**

| | PBSC | BM | P |
|---|---|---|---|
| Acute GVHD-no. evaluable* | 35 (95%) | 36 (97%) | 0.18† |
| Grade 2-4* | 13 (37%) | 20 (56%) | 0.10† |
| Grade 3-4* | 5 (14%) | 12 (33%) | |
| Chronic GVHD-affected/evaluable* | 10/17 (59%) | 14/23 (61%) | |
| Clinical-extensive* | 4 (24%) | 3 (13%) | |
| Clinical-limited* | 3 (18%) | 3 (13%) | 0.5† |
| Subclinical* | 3 (18%) | 8 (35%) | |

* No. of patients (% of patients).
† Fisher's Test.

**Table 5. Causes of Death**

| | PBSC | BM |
|---|---|---|
| Total | 15 | 26 |
| Progressive disease | 7 (47%) | 11 (42%) |
| GVHD | 1 (7%) | 4 (15%) |
| Infection | 2 (13%) | 9 (35%) |
| Bacterial | 1 | 4 |
| Fungal | 1 | 4 |
| CMV pneumonitis | 0 | 1 |
| Multi-organ failure | 1 (7%) | 1 (3%) |
| Interstitial pneumonia syndrome | 2 (5%) | 0 |
| Hemorrhage | 0 | 1 (4%) |
| Hepatic failure | 2 (5%) | 0 |

No. of patients (% of patients).

of developing grades 2 to 4 acute GVHD were 41% for patients transplanted with PBSC and 58% for patients transplanted with BM ($P$ = .1) (data not shown). The actuarial probabilities of developing grades 3 to 4 acute GVHD were 15% in the group receiving PBSC versus 34% in the group receiving BM ($P$ = .05) (Fig 2).

In the PBSC group, grade 3 to 4 acute GVHD occurred in 3 out of 17 evaluable patients receiving prednisone and in 2 out of 18 evaluable patients receiving MTX. In the BM group, grade 3 to 4 acute GVHD occurred in 6 out of 17 evaluable patients receiving prednisone and in 6 out of 20 evaluable patients receiving MTX.

Clinical or subclinical chronic GVHD of all grades developed in 10 out of 17 (59%) evaluable PBSC recipients and in 14 out of 23 (61%) BM recipients (Table 4). Clinical extensive or limited chronic GVHD developed in 7 out of 17 (41%) evaluable patients who were transplanted with PBSC compared to 6 out of 23 (26%) patients transplanted with BM ($P$ = .5). Among the patients receiving PBSC and prophylaxis that included MTX, clinical chronic GVHD developed in 1 out of 7 evaluable patients compared to 6 out of 10 in patients receiving prednisone. In the BM group receiving MTX clinical chronic GVHD developed in 2 out of 12 patients compared to 4 out of 11 given prednisone for GVHD prophylaxis.

*Causes of death.* As shown in Table 5, 8 of 37 (22%) patients who received PBSC died of transplant-related complications as compared to 15 out of 37 (41%) patients who received BM ($P$ = .13). There were 8 deaths from bacterial or fungal infection in the BM group and 2 in the PBSC group. Fatal fungal infections in the patients receiving BM were caused by aspergillus (n = 2) or candida albicans (n = 2). There were no deaths caused by hemorrhage in the PBSC group and one in the BM group. There were 2 deaths caused by IPS in patients receiving PBSC as compared to none in patients who received BM. One patient died of CMV pneumonitis in the BM group. Seven patients have died of relapse or progressive disease in the group receiving PBSC compared to 11 patients in the BM group.

*Nonrelapse mortality.* The estimates of transplant-related mortality within 200 days of transplant were 27% for recipients of PBSC and 45% for recipients of BM ($P$ = .33) (Fig 3).

*Relapse.* Among patients transplanted with PBSC, 14/37 (38%) patients relapsed and 7 of them have died. In patients transplanted with BM, 13 out of 37 (35%) have relapsed and 11 of them have died. The estimates of relapse at 570 days after transplant for patients receiving PBSC or BM are 70% and 53%, respectively ($P$ = .27).

*Survival.* Twenty-two of 37 (59%) patients who received PBSC are surviving between 110 and 720 days after transplant, 7 of whom have relapsed. In the BM group 11 patients

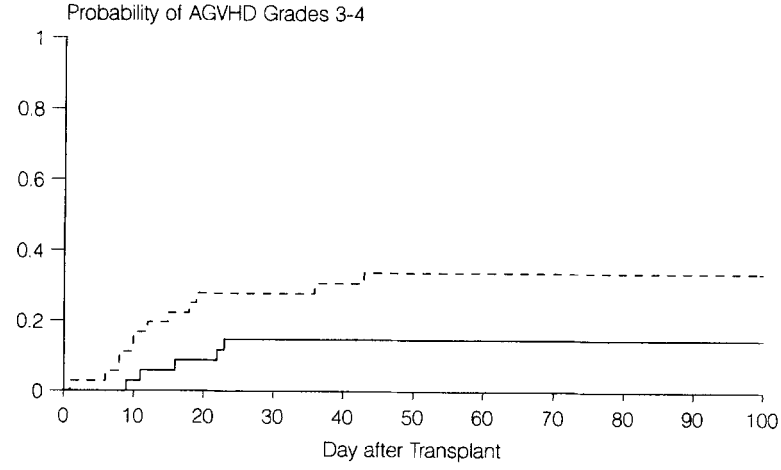



**Fig 2. Probability of developing grade 3 to 4 acute GVHD after transplantation of allogeneic PCSBs (solid line) or BM (broken line).**

Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024

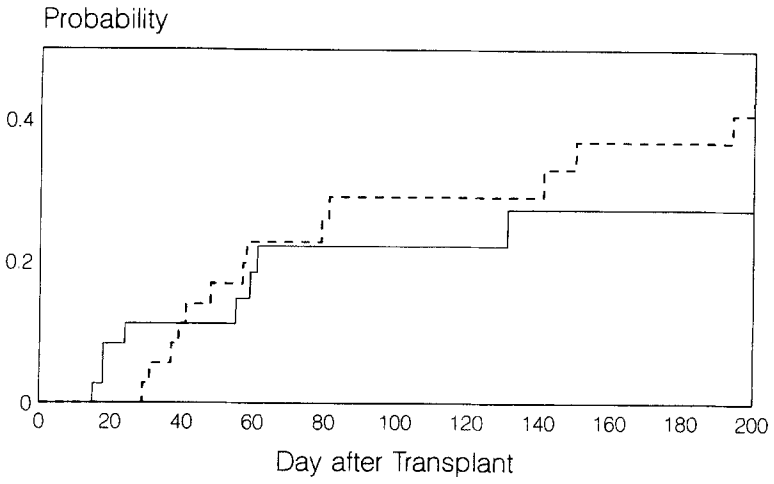



**Fig 3. Probability of nonrelapse death within 200 days after transplantation of allogeneic PBSCs (solid line) or BM (broken line).**

are surviving between 295 and 2,224 days from transplant, 2 of whom have relapsed. The estimates of survival for the PBSC and BM groups at 285 days are 50% and 41%, respectively ($P$ = .39).

## DISCUSSION

This retrospective study compared the results of allogeneic transplantation with G-CSF mobilized PBSC or BM from HLA-matched siblings. The first important observation was that the use of allogeneic PBSC resulted in significantly faster recovery of PB counts than with BM, despite the use of methotrexate in 50% of patients. Both neutrophils and platelets recovered a median of 4 days earlier. In addition, the PBSC group required significantly fewer platelet and red blood cell transfusions. Chimerism studies by in situ Y chromosome or cytogenetic analysis or VNTR showed only donor cells in both the BM and PBSC recipients except in cases of relapse. Although a higher proportion of patients who received BM died of transplant-related complications, the actuarial probabilities of transplant-related mortality within the first 200 days after transplant were not statistically different.

The actuarial probabilities of developing acute GVHD grades 2 to 4 were similar between the 2 groups, but the probability of developing grade 3 to 4 acute GVHD was statistically less in the PBSC group. This may have been influenced by the higher proportion of multiparous female donors in the group. Although follow-up is more limited in the group receiving PBSC there does not appear to be a higher incidence of chronic GVHD. Finally, no significant differences were found in the probabilities of relapse or overall survival.

In this analysis an attempt was made to define outcome differences between recipients of allogeneic PBSC and BM by comparing recent transplants using PBSC to a historical control group who received BM transplants. Although there are inherent problems and limitations to this methodology, the differences in rate of engraftment and lack of an increase in acute GVHD seem convincing and consistent with previously published pilot studies.[8-10]

Patients who received BM died more frequently of bacterial or fungal infections than recipients of PBSC. Patients in the PBSC group had their transplants more recently than most of those in the BM group. During the past 6 years supportive care has improved with the use of ganciclovir for CMV prophylaxis and fluconazole for fungal prophylaxis. None of the patients in the PBSC group died of CMV and only 1 in the BM group died of CMV pneumonitis. Only 2 patients in the PBSC group died of bacterial or fungal infections compared to 8 in the BM group. Although this difference could be attributed to earlier neutrophil recovery in the case of bacterial infections, it is possible that the prophylactic use of fluconazole contributed to the low incidence of death caused by fungal infections in the PBSC group.[19]

Based on our current results and on data from other pilot studies, it can be concluded with some assurance that the risk of acute GVHD is not increased after PBSC transplantation, despite the infusion of 1 to 2 logs more of T cells as compared to BM.[9,10] There are at least 2 possible explanations for this observation. First, it is possible that the number of T cells in a marrow graft is sufficient to produce the maximum possible severity of GVHD for the degree of genetic disparity between donor and recipient and that further increases in T cell dose have no additive effect. Most of the support for this hypothesis comes from clinical studies of T-depleted allogeneic BM. In those studies, a threshold dose of approximately $10^5$ residual CD3 cells/kg was identified, below which acute GVHD was significantly reduced.[20,21] The second, and more likely explanation, is that the T cells in G-CSF–mobilized PBSC are functionally different than those in BM. G-CSF could alter the function of the lymphocytes infused or could alter cytokine production by infused accessory cells. Support for this hypothesis comes from studies in mice, where G-CSF pretreatment was found to polarize CD4 cells toward a T helper type-2 (Th2) response with a decrease in interleukin-2 and interferon production and a corresponding reduction in acute GVHD and improved survival.[22] In addition, in vitro studies have identified increased suppressor cell activity in GM-CSF–mobilized PBSC from patients undergoing autologous transplants and an increase in $CD4^-$, $CD8^-$, TCR, and $\alpha/\beta^+$ cells posttransplant.[23]

Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024

Early attempts have been made to remove T cells from G-CSF–mobilized PBSC by CD34 selection. Preliminary data suggest that the incidence of grade 3 to 4 acute GVHD is not reduced following the transplantation of $CD34^+$ selected G-CSF mobilized PBSC despite the removal of 3 to 4 logs of T cells and the infusion of approximately $1.0 \times 10^6$ CD3 cells/kg.[24,25] Because the dose of CD3 cells infused in these studies exceeded $10^5$/kg, it is not yet clear whether GVHD was caused by the infusion of $10^6$ T cells or by the loss of T cells that were altered by G-CSF exposure.

Although follow-up is more limited in the PBSC group than in the BM group, we found no evidence that the use of PBSC was associated with an increased risk of chronic GVHD compared to results with BM. Further follow-up and the results of ongoing randomized trials will be of interest in this regard. Previous studies from this institution have shown an increased incidence of chronic GVHD when unstimulated buffy coat cells were given in addition to BM.[26] One hypothesis that G-CSF–mobilized cells are functionally different from T cells aspirated from BM would be supported if results from future randomized studies confirm that G-CSF–mobilized PBSC do not increase the risk of chronic GVHD.

Follow-up of the PBSC group is too limited to permit definite conclusions about relapse. However, the actuarial probability of relapse in the PBSC group, even with limited follow-up, is 70% at 570 days. Because a 10-fold increase in the number of T cells given with PBSC did not result in a measurable increase in acute or chronic GVHD as compared to BM, it is possible that unmodified PBSC will not have an improved antileukemic effect compared to marrow. The current ongoing randomized multicenter trials of BM versus PBSC, which include good risk patients, should help clarify this issue.

This analysis did not suggest a survival or event-free survival advantage for PBSC as compared to BM. However, there were significant differences in speed of engraftment and morbidity. In general, there is excellent donor tolerance for donating PBSC as compared to BM. In addition, the ability to collect large quantities of PBSC offers greater leeway in manipulating the stem cell product than is possible with BM.

## REFERENCES


1. Sheridan WP, Morstyn G, Wolf M, Dodds A, Lusk J, Maher D, Layton JE, Green MD, Souza L, Fox RM: Granulocyte colony-stimulating factor and neutrophil recovery after high-dose chemotherapy and autologous bone marrow transplantation. Lancet 2:891, 1989

2. Bensinger W, Singer J, Appelbaum F, Lilleby K, Longin K, Rowley S, Clarke E, Clift R, Hansen J, Shields T, Storb R, Weaver C, Weiden P, Buckner CD: Autologous transplantation with peripheral blood mononuclear cells collected after administration of recombinant granulocyte stimulating factor. Blood 81:3158, 1993

3. Bensinger WI, Longin K, Appelbaum F, Rowley S, Weaver C, Lilleby K, Gooley T, Lynch M, Higano T, Klarnet J, Chauncey T, Storb R, Buckner CD: Peripheral blood stem cells (PBSCs) collected after recombinant granulocyte colony stimulating factor (rhG-CSF): An analysis of factors correlating with the tempo of engraftment after transplantation. Br J Haematol 87:825, 1994

4. Namdemanee A, Sniecinzki IJ, Schmidt CA, Dagis AC, O'Donnell M, Snyder DS, Parker PM, Stein AS, Smith EP, Arturo M, Stepan DE, Somlo G, Margolin KA, Woo SD, Niland JC, Forman SJ: High-Dose therapy followed by autologous peripheral-blood stem-cell transplantation for patients with hodgkin's disease and non-hodgkin's lymphoma using unprimed and granulocyte colony-stimulating factor-mobilzed peripheral-blood stem cells. J Clin Oncol 12:2176, 1995

5. Bolwell BJ, Fishman EK, Andresen S, Lichtin A, Yanssens T, Burwell R, Baucco P, Green R: G-CSF primed peripheral blood progenitor cells in autologous bone marrow transplantation: Parameters afecting bone marrow engraftment. Bone Marrow Transplant 12:609, 1993

6. Weaver CH, Buckner CD, Longin K, Appelbaum FR, Rowley S, Lilleby K, Miser J, Storb R, Hansen JA, Bensinger W: Syngeneic transplantation with peripheral blood mononuclear cells collected after the administration of recombinant human granulocyte colony-stimulating factor. Blood 82:1981, 1993

7. Bensinger WI, Price TH, Dale DC, Appelbaum FR, Clift R, Lilleby K, Williams B, Storb R, Thomas ED, Buckner CD: The effects of daily recombinant human granulocyte colony stimulating factor administration on normal granulocyte donors undergoing leukapheresis. Blood 81:1883, 1993

8. Bensinger WI, Weaver CH, Appelbaum FR, Rowley S, Demirer T, Sanders J, Storb R, Buckner CD: Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. Blood 85:1655, 1995

9. Schmitz N, Dreger P, Suttorp M, Rohwedder EB, Haferlach T, Löffler H, Hunter A, Russell NH: Primary transplantation of allogeneic peripheral blood progenitor cells mobilized by Filgrastim (G-CSF). Blood 85:1666, 1995

10. Körbling M, Przepiorka D, Huh YO, Engel H, van Besien K, Giralt S, Andersson B, Kleine HD, Seong D, Deisseroth AB, Andreeff M, Champlin R: Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: Potential advantage of blood over marrow allografts. Blood 85:1659, 1995

11. Thomas ED: Allogeneic marrow transplantation using matched sibling donors. Transplant Proc 6:115, 1974

12. Nemunaitis J, Buckner CD, Appelbaum FR, Higano CS, Mori M, Bianco J, Epstein C, Lipani J, Hansen J, Storb R, Thomas ED, Singer JW: Phase I/II trial of recombinant human granulocyte-macrophage colony-stimulating factor following allogeneic bone marrow transplantation. Blood 77:2065, 1991

13. Bensinger W, Appelbaum F, Rowley S, Storb R, Sanders J, Lilleby K, Gooley T, Demirer T, Schiffman K, Weaver C, Clift R, Chauncey T, Klarnet J, Montgomery P, Petersdorf S, Weiden P, Witherspoon R, Buckner CD: Factors that influence collection and engraftment of autologous peripheral-blood stem cells. J Clin Oncol 13:2547, 1995

14. Kirk JA, VanDavantar DR, Biberman J, Bryant EM: Y chromosome loss in chronic myeloid leukemia detected in both normal and malignant cells by interphase fluorescence in situ hybridization. Genes Chromosomes Cancer 11:141, 1994

15. Budowle B, Chakraborty R, Giusti AM, Eisenberg AJ, Allen RC: Analysis of the VNTR locus DIS80 by the PCR followed by high-resolution PAGE. Am J Hum Genet 48:137, 1991

16. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED: Consensus conference on acute GVHD grading. Bone Marrow Transplant 15:825, 1995

17. Sullivan KM, Witherspoon RP, Storb R, Anasetti C, Appelbaum FR, Bigelow C, Clark J, Doney K, Hill R, Loughran T, Matthews DD, Nims J, Petersen F, Sanders J, Schüning F, Shields A, Strom S, Thomas ED: Chronic graft-versus-host disease: Recent advances in diagnosis and treatment, in Gale RP, Champlin R (eds): Bone Marrow Transplantation: Current Controversies. UCLA Sym-


Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024

posia on Molecular and Cellular Biology, New Series, vol 91. New York, NY, Liss, 1989, p 511

18. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958

19. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, Meyers JD, Bowden RA: Efficacy and safety of fluconazole for fungal infections after marrow transplant - A prospective, randomized, double-blind study. J Infect Dis 171:1545, 1995

20. Kernan NA, Collins NM, Juliano L, Cartagenia T, Dupont B, O'Reilly RJ: Clonable T lymphocytes in T cell-depleted bone marrow transplants correlate with development of graft-versus-host disease. Blood 68:770, 1986

21. Verdonck LF, Dekker AW, de Gast GC, van Kempen ML, Lokhorst HM, Nieuwenhuis HK: Allogeneic bone marrow transplantation with a fixed low number of T cells in the marrow graft. Blood 83:3090, 1994

22. Pan L, Delmonte J Jr, Jalonen CK, Ferrara JLM: Pretreatment of donor mice with granulocyte colony-stimulating factor polarizes donor T lymphocytes toward type-2 cytokine production and reduces severity of experimental graft versus host disease. Blood 86:4422, 1995

23. Talmadge JE, Reed EC, Kessinger A, Kuszynski CA, Perry GA, Gordy CL, Mills KC, Thomas ML, Pirruccello SJ, Letheby BA, Arneson MA, Jackson JD: Immunologic attributes of cytokine mobilized peripheral blood stem cells and recovery following transplantation. Bone Marrow Transplant 17:101, 1996

24. Yeager AM, Holland HK, Mogul MJ, Forte K, Lauer M, Boyer MW, Turner C, Vega RA, Beatty PG, Jacobs CA, Benyunes MC, Wingard JR: Transplantation of positively selected $CD34^+$ cell from haploidentical parental donors for relapsed acute leukemia in children. Blood 86:1149, 1995 (abstr, suppl 1)

25. Schiller G, Rowley S, Buckner CD, Berenson R, Benyunes M, Appelbaum FR, Bensinger WI: Transplantation of Allogenic $CD34^+$ Peripheral Blood Stem Cells (PBSC) in older patients with advanced hematologic malignancy. Blood 86:1545, 1995 (abstr, suppl 1)

26. Sullivan KM, Storb R, Buckner CD, Fefer A, Fisher L, Weiden PL, Witherspoon RP, Appelbaum FR, Banaji M, Hansen J, Martin P, Sanders JE, Singer J, Thomas ED: Graft-versus-host disease as adoptive immunotherapy in patients with advanced hematologic neoplasms. N Engl J Med 320:828, 1989

Downloaded from http://ashpublications.org/blood/article-pdf/88/7/2794/1641814/2794.pdf by guest on 12 February 2024