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Matched-pair analysis of peripheral blood stem cells compared to marrow for allogeneic transplantation

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Summary:

We performed a case-control analysis of 42 patients with advanced leukemia or MDS comparing peripheral blood stem cell (PBSC) with marrow grafts (BMT) from HLA-matched sibling donors. PBSC were mobilized with G-CSF (7.5 μg/kg/day) and yielded a median of 6.7×10^6 CD34$^+$ cells/kg (range, 1.6–15.0) and 2.7×10^8 CD3$^+$ cells/kg (range, 1.1–7.1) *vs* marrow grafts with a median of 2.0×10^8 nucleated cells/kg (range, 1.8–2.2). Recovery was significantly faster after PBSCT compared to BMT, with a median of 17 (range, 12–26) *vs* 26 (range, 16–36) days, respectively, to neutrophils $>0.5 \times 10^9$/l ($P < 0.01$), and 22 (range, 12–>60) *vs* 42 (range, 18–>60) days, for platelet recovery ($P < 0.01$). Transplantation of $\geq 7 \times 10^6$ CD34$^+$ cells/kg accelerated recovery to $>20 \times 10^9$ l platelets; median 17 days (range, 12–19) *vs* 23 days (range, 17–36) for those receiving $<7 \times 10^6$/kg ($P = 0.01$). PBSC and marrow recipients had similar risks of grades II–IV or III–IV acute GVHD or extensive chronic GVHD (all $P > 0.3$). At 1 year after PBSCT and BMT, the risk of relapse was 41% and 32%, respectively ($P = 0.47$), and the probability of survival was 46% and 48%, respectively ($P = 0.70$). HLA-matched sibling PBSCT resulted in faster neutrophil and platelet engraftment compared to BMT, with no subsequent differences in acute or chronic GVHD, relapse or survival. A minimum of 7×10^6 CD34$^+$ cells/kg in PBSC grafts may be required for very rapid platelet engraftment. *Bone Marrow Transplantation* (2000) **26,** 723–728.
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Autografting with peripheral blood stem cells (PBSC) has largely replaced autologous bone marrow transplantation (BMT). PBSC may be preferred because of the easier collection and faster hematopoietic recovery associated with autologous PBSC.[1–4] The merits of using PBSC for allografting, however, are still uncertain. Several historically controlled studies and two small randomized trials have recently compared PBSC transplantation (PBSCT) with BMT, using predominantly HLA-matched sibling donors.[5–14] In all of these reports, growth factor mobilization was well tolerated by donors and PBSC engrafted rapidly. Neutrophil recovery was faster after PBSCT than BMT in some,[6,9,11,12,14] but not all[5,7,10,13] studies, whereas platelet recovery was uniformly more rapid in PBSC recipients.[5–7,9–14] The observation that mobilized peripheral blood grafts contain approximately 10-fold more T cells than marrow suggested a potential for increased graft-versus-host disease (GVHD).[15,16] Although no study reported to date has identified a higher incidence or severity of acute GVHD after PBSCT, four studies observed an increased probability of chronic GVHD.[8,12–14] This suggested that the faster engraftment associated with PBSCT may be offset by higher rates of chronic GVHD and a greater requirement for long-term immunosuppression. However, most studies had insufficient follow-up to accurately evaluate the risk of chronic GVHD in PBSC recipients. The optimal stem cell source for allogeneic transplantation therefore remains uncertain. In this study, we describe the outcome of a matched-pair analysis of HLA-matched sibling PBSCT and BMT. Since all PBSC recipients were followed for a minimum of 8 months, a meaningful comparison of chronic GVHD risks was possible. We also examined the effects of CD34$^+$ cell dose on engraftment and CD3$^+$ cell dose on GVHD, to better define the optimal cell content of PBSC grafts.

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Patients and methods

Patients and historical controls

Forty-five patients with advanced or high-risk hematological malignancies received HLA-matched sibling PBSCT between February 1996 and August 1998 in the Blood and Marrow Transplant Program at the University of Minnesota. Patients with chronic phase chronic myelogenous leukemia and standard risk acute leukemia in first complete remission were excluded because of their expected good outcome with conventional allogeneic BMT. Well-matched historical controls treated with HLA-matched sibling BMT at our institution were found for a subgroup of PBSC recipients with advanced leukemia or MDS. Controls for 24 other patients with myeloma, chronic lymphocytic leukemia or non-Hodgkin's lymphoma were not found as BMT for these illnesses had been performed only infrequently; therefore these were excluded. Controls were identified from our

BMT Program database by closely matching the following variables: diagnosis, disease stage, time from diagnosis to transplant, recipient age, GVHD prophylaxis and conditioning regimen. Written informed consent was obtained from all patients and donors, and the study was approved by the Committee on the Use of Human Subjects in Research of the University of Minnesota.

PBSC mobilization and collection

Donor PBSC were mobilized with granulocyte colony-stimulating factor (G-CSF) given subcutaneously at 7.5 μg/kg/day. Collections began on day 5 of mobilization using a Fenwal CS-3000 PLUS cell separator (Baxter, Round Lake, IL, USA) as described elsewhere.[17] $CD34^+$ cell counts in the apheresis products were determined by flow cytometry and, as needed, consecutive daily collections were performed to harvest the target $CD34^+$ cell dose of 5×10^6/kg recipient weight.

Transplant procedure and supportive care

All PBSC and marrow recipients were conditioned with cyclophosphamide (60 mg/kg/day $\times$ 2) and total body irradiation (TBI; 1320 cGy given as 165 cGy fractions twice daily for 4 days). PBSC and marrow were infused on the day of collection without cryopreservation or other manipulation. All patients received GVHD prophylaxis with cyclosporine and short-course methotrexate, as detailed elsewhere.[18] G-CSF was administered at 5 μg/kg/day to PBSC recipients from day +1 until neutrophil recovery ($>2.5 \times 10^9$/l on 2 consecutive days). BMT patients received hematopoietic growth factors only if they failed to engraft by day +21. Details of supportive care were as described previously.[18–20]

Definitions and statistical analysis

Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $>0.5 \times 10^9$/l. Platelet engraftment was defined as the first of 7 days with a platelet count $>20 \times 10^9$/l without transfusion. Grades of acute and chronic GVHD were assigned according to standard criteria.[21,22]

The method of Kaplan and Meier was used to estimate the probabilities of engraftment, GVHD, relapse and survival.[23] Statistical comparisons of these endpoints between the PBSC and marrow groups were completed by the paired Prentice–Wilcoxon test.[24] Statistical comparisons of patient and transplant characteristics between the PBSC and marrow groups were performed using the general Wilcoxon test (age, time from diagnosis to transplant, number of transfusions), Pearson's chi-squared test (sex, CMV serology), and Fisher's exact test (year of transplant).

The correlations between $CD34^+$ cell levels and time to engraftment were measured among patients who received PBSC grafts. The correlations were first measured with Spearman's correlation coefficient, excluding those patients that did not engraft. To account for censored patients, Kaplan–Meier estimation of engraftment was compared between patients receiving less than 7×10^6 $CD34^+$ cells/kg and patients receiving greater than or equal to 7×10^6 $CD34^+$ cells/kg. The division at 7×10^6/kg approximates the median $CD34^+$ cell dose and was chosen to maximize statistical power.

Results

Patient and donor characteristics

The 42 PBSCT and BMT patients were well matched with respect to age, recipient and donor sex, diagnosis, disease stage, time from diagnosis to transplant, and CMV serology (Table 1). Uniform regimens for conditioning (cyclophosphamide and fractionated TBI) and GVHD prophylaxis (cyclosporine and methotrexate) were received by both groups. One difference was the year of transplant, with 81% of BMT patients transplanted during 1992–1995 and all PBSCT patients transplanted from 1996 onwards ($P < 0.01$).

PBSC collection

G-CSF was well tolerated by donors. Apheresis procedures lasted a median of 5 hours (range 3–6) and processed a median of 15 liters of blood (range 9.8–21.2). To obtain the target dose of 5×10^6 $CD34^+$ cells/kg, 11 donors (52%) required one collection, eight donors (38%) required

Table 1 Patient and donor characteristics

	PBSC	*Marrow*	*P value*[a]
Number of patients	21	21	
Median age in years (range)[b]	43 (29–54)	43 (31–59)	NS
Sex (recipient:donor)			
Female:Female	4 (19)	6 (29)	NS
Female:Male	6 (29)	3 (14)	
Male:Female	4 (19)	5 (24)	
Male:Male	7 (33)	7 (33)	
Disease and stage[b]			
AML			
CR1	2 (10)	2 (10)	
CR2	2 (10)	2 (10)	
Relapse	5 (24)	5 (24)	
MDS	8 (38)	8 (38)	
CML			
Accelerated phase	3 (14)	3 (14)	
Second chronic phase	1 (5)	1 (5)	
Months from diagnosis to transplant, median (range)[b]	5 (1–34)	7 (1–23)	NS
Year of transplant			
1992–1995	–	17 (81)	<0.01
1996–1998	21 (100)	4 (19)	
CMV serology			
Recipient negative, donor negative	5 (24)	6 (29)	NS
Recipient negative, donor positive	2 (10)	2 (10)	
Recipient positive	14 (67)	13 (62)	

Data are expressed as the number (%) of patients with the specified characteristic, unless otherwise noted. Percentages may not sum to 100 because of rounding.
[a]NS denotes $P > 0.20$.
[b]Matching variable. Only CR1 patients with high risk features (post MDS, secondary leukemia or delay to CR1) were eligible.

Table 2 Cell collections

	PBSC	*Marrow*
Nucleated cells ($\times 10^8$/kg)	8.6 (4.5–16.1)	2.0 (1.8–2.2)
$CD34^+$ cells ($\times 10^6$/kg)	6.7 (1.6–15.0)	NA
$CD3^+$ cells ($\times 10^8$/kg)	2.7 (1.1–7.1)	NA

Data are median values with the range in brackets.
NA = not available.

two collections, and one donor (5%) each required three and four collections. Centrally placed venous access was necessary in five cases (24%). At the completion of apheresis, platelet counts dropped to a median of 127×10^9/l (range 28–269) and were $<50 \times 10^9$/l only in the two donors who needed ⩾3 collections. The cell doses harvested for PBSCT and BMT are shown in Table 2.

Engraftment

The recovery of neutrophils and platelets is shown in Figure 1. With the exception of one PBSC and four marrow recipients who died before day 30, all patients achieved neutrophil engraftment. Neutrophils recovered to $>0.5 \times 10^9$/l at a median of 17 days (range, 12–26) in PBSC recipients, significantly faster than the marrow recipient's median of 26 days (range, 16–36) ($P < 0.01$). Platelet recovery to $>20 \times 10^9$/l was also more rapid, occurring at a median of 22 days (range, 12–>60) and 42 days (range, 18–>60) in the PBSC and marrow groups, respectively ($P < 0.01$). PBSC recipients had lower platelet transfusion requirements in the early post-transplant period. During the first 60 days after PBSCT and BMT, platelets were transfused on a median of 14 days (range, 3–45) and 21 days (range, 4–55), respectively ($P = 0.03$). No correlation was observed between the number of $CD34^+$ cells in PBSC grafts and time to neutrophil recovery ($r = 0$, $P > 0.80$). However, larger $CD34^+$ cell doses were associated with shorter platelet recovery times ($r = 0.67$, $P < 0.01$), and although numbers in each group were small, platelet engraftment was significantly faster in patients receiving $\geqslant 7 \times 10^6$ $CD34^+$ cells/kg compared with those receiving lower doses ($P = 0.01$) (Figure 2).

Graft-versus-host disease

The incidence of grades II–IV acute GVHD after PBSCT and BMT was 10/21 (48%) and 8/21 (38%), respectively. Severe (grades III–IV) acute GVHD occurred in five PBSC and two marrow recipients. Figure 3 shows the Kaplan–Meier analysis of the probability of grades II–IV acute GVHD. This was not significantly different after PBSCT and BMT, with risks of 52% (95% confidence interval (CI): 29–75%) and 47% (95% CI: 23–71%), respectively $P > 0.80$). The probability of grades III–IV acute GVHD was also similar in PBSC and marrow recipients, estimated at 27% (95% CI: 7–47%) and 12% (95% CI: 0–28%), respectively ($P = 0.32$).

Extensive chronic GVHD developed in nine patients in both the PBSC and marrow groups. Kaplan–Meier estimates of the risk of extensive chronic GVHD at 1 year following PBSCT and BMT were 58% (95% CI: 33–73%)

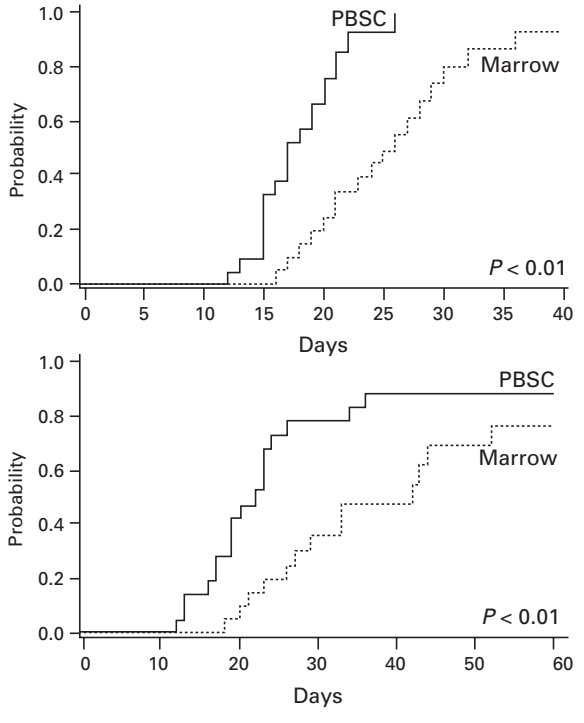


Figure 1 Upper panel: Recovery of neutrophils to $>0.5 \times 10^9$/l after allogeneic PBSCT and BMT. Lower panel: Recovery of platelets to $>20 \times 10^9$/l after allogeneic PBSCT and BMT.

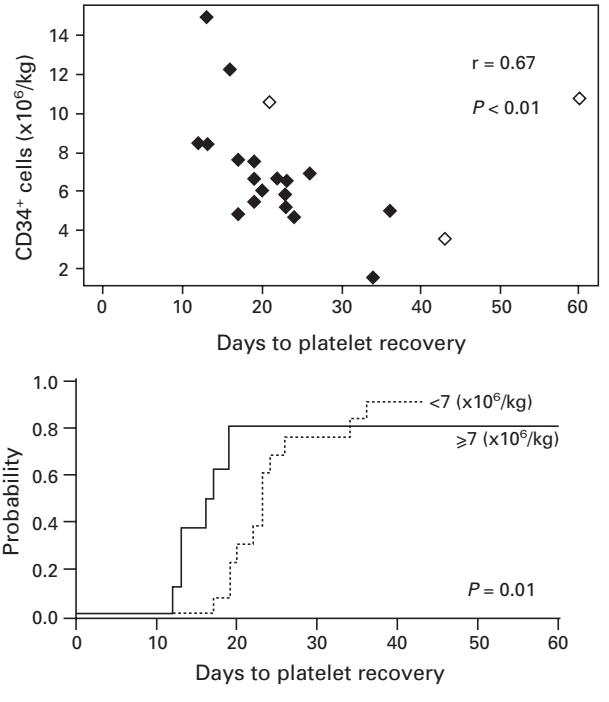


Figure 2 Upper panel: Relationship between the number of $CD34^+$ cells in PBSC grafts and time for platelet recovery to $>20 \times 10^9$/l. Both engrafted patients (solid diamonds) and censored patients (open diamonds) are shown. Lower panel: Platelet recovery to $>20 \times 10^9$/l in PBSC recipients infused with $CD34^+$ cell doses of $\geqslant 7 \times 10^6$/kg or $<7 \times 10^6$/kg.

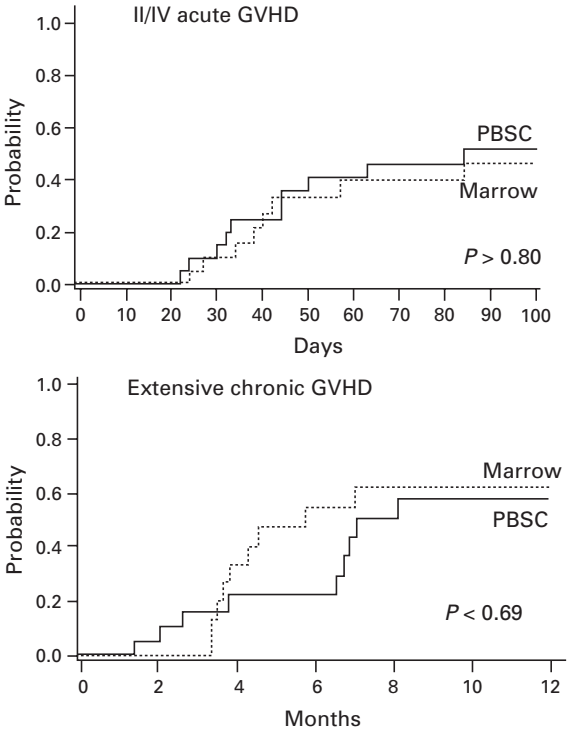


Figure 3 Upper panel: Risk of grades II–IV acute GVHD in recipients of allogeneic PBSC or marrow. Lower panel: Incidence of extensive chronic GVHD after allogeneic PBSCT and BMT.

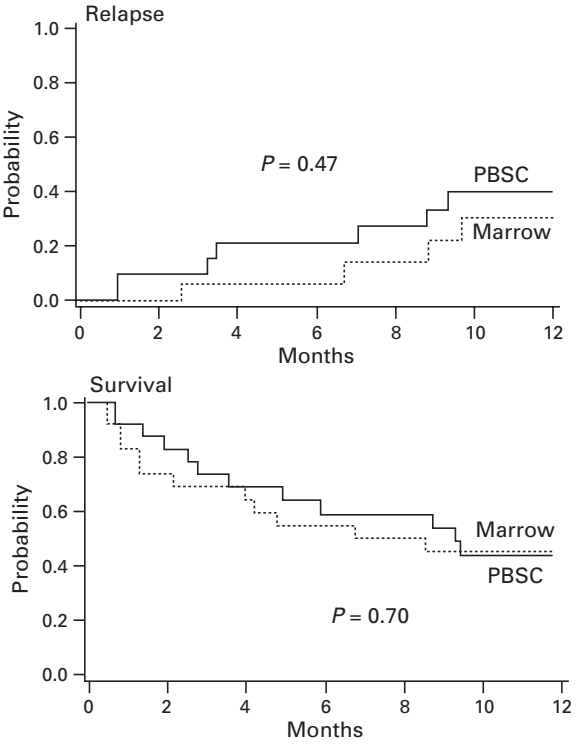


Figure 4 Upper panel: Probability of relapse after allogeneic PBSCT and BMT. Lower panel: Probability of overall survival after allogeneic PBSCT and BMT.

and 62% (95% CI: 37–87%), respectively (Figure 3), which were not significantly different ($P = 0.69$). No correlation was observed between $CD3^+$ cell doses and either acute GVHD or chronic GVHD among PBSC recipients.

Relapse and survival

Median follow-up for PBSC recipients was 12 months (range, 8–22) and for marrow recipients it was 30 months (range, 12–62). The probability of relapse 12 months after PBSCT and BMT was similar (Figure 4), being estimated at 41% (95% CI: 17–65%) and 32% (95% CI: 6–58%), respectively ($P = 0.47$). There was no association between relapse risk and the $CD3^+$ cell dose of PBSC grafts. No statistically significant difference in early transplant-related mortality was seen. One PBSC and three marrow recipients died by day 30 while three PBSC and six marrow recipients died by day 100 ($P = 0.32$). Eleven patients in each group have died and the probability of survival at 12 months post transplant was 46% (95% CI: 24–68%) and 48% (95% CI: 27–69%) for PBSC and marrow recipients, respectively ($P = 0.70$) (Figure 4).

Discussion

Comparison of HLA-matched sibling PBSCT and BMT revealed significantly faster engraftment in the PBSC recipients. The median time to neutrophil recovery was 9 days earlier in the PBSC group and platelet recovery was 20 days earlier. This is in agreement with the results of other studies of allogeneic PBSCT[5–7,9–14] and may be due to larger numbers of partially differentiated progenitors in mobilized peripheral blood compared to marrow.[11,15] We found no relationship between the $CD34^+$ cell dose of PBSC grafts and neutrophil engraftment. This may indicate that most grafts contained more than the minimum number of progenitor cells necessary for optimal neutrophil recovery. In contrast, a correlation was observed between higher numbers of $CD34^+$ cells and more rapid platelet engraftment. Although numbers are small, our data suggest that a dose of 7×10^6 $CD34^+$ cells/kg may be required for optimal platelet recovery.

Because of the greater number of T cells in PBSC grafts compared with marrow, concern developed that PBSCT might result in more GVHD.[14–16] In the current study, we observed no significant increase in the incidence or severity of acute GVHD after sibling PBSCT compared with BMT. Other groups have reported similar findings.[6,10,11,13] There are two potential explanations for this lack of correlation between T cell number and acute GVHD risk. First, there may be a plateau effect, where the infusion of more T cells above some threshold has no additional biological consequences.[6] Second, T lymphocytes in mobilized peripheral blood may be functionally different from their counterparts in bone marrow. In support of the latter, blood primed with G-CSF showed increased numbers of $CD14^+$ cells which suppressed T cell responses to alloantigens *in vitro*.[25] Furthermore, G-CSF polarized donor T cells towards a type 2 cytokine response in mice.[26] Enhancement of type 2 responses has been associated with reduced severity of experimental GVHD.[26,27]

The risk of extensive chronic GVHD was similar in PBSC and marrow recipients in our study. However, in three other historically controlled studies with sufficient follow-up to evaluate chronic GVHD, PBSCT was associated with an increased incidence of chronic GVHD.[8,12,14] The reasons for these differing outcomes are unclear, but may in part reflect limited patient numbers and the use of historical controls. Early results from two relatively small randomized trials of PBSCT have also been published.[10,13] Both revealed a trend towards a higher incidence of extensive chronic GVHD in PBSC recipients, but the numbers of patients at risk were inadequate for definitive conclusions. The frequency of chronic GVHD is a critical issue in evaluating the role of allogeneic PBSCT. Our observations suggest that it is premature to conclude that PBSC recipients are at higher risk of this complication. Results from large randomized trials of PBSCT and BMT will be required to definitively answer this question.

Since more T cells are infused with PBSC grafts, it seemed plausible that the graft-versus-leukemia (GVL) effect might also be increased. However, we observed similar relapse rates in recipients of sibling PBSC and marrow. In addition, we observed no correlation between the $CD3^+$ cell dose of PBSC grafts and either GVHD or relapse. This might suggest that the number of $CD3^+$ cells infused exceeded a threshold dose needed for biological impact. As discussed above, reasons why GVHD might not increase after PBSCT may also apply to the GVL reaction. Furthermore, with only advanced malignancies included in the current study, effective GVL effects mediated by PBSC grafts may be difficult to demonstrate. Survival was not different in the PBSC and marrow groups in our study. Likewise, other studies have reported that overall survival[6,11,13] or disease-free survival[10] are not affected by stem cell source. Prospective randomized trials currently in progress will more clearly define the place of allogeneic PBSCT in the therapy of hematological malignancies. However, the reported results of phase II trials such as the current study suggest that if a survival advantage over BMT exists, it may only be modest. Additional data are required to demonstrate a large survival difference, if any, compared with BMT. Additional strategies will therefore be required to improve the safety and efficacy of allogeneic hematopoietic cell transplants.

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