

Graft Composition

Differences between graft product and donor side effects following bone marrow or stem cell donation

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Summary:

We report graft product stem cell yields and donor safety results of a randomized multicenter study comparing allogeneic peripheral blood stem cell (PBSC) PBSC transplantation with BM transplantation. Matched HLA-identical sibling donors ($n = 329$) were randomized to filgrastim-mobilized PBSC or bone marrow (BM) donation groups. Median yields per kg recipient weight of CD34⁺ cells, T cells, and natural killer (NK) cells, respectively, were approximately two-fold, eight-fold, and greater than eight-fold in the PBSC group than in the BM group (CD34⁺ cells, $5.8 \times 10^6/\text{kg}$ vs $2.7 \times 10^6/\text{kg}$; T cells, $300.1 \times 10^6/\text{kg}$ vs $35.7 \times 10^6/\text{kg}$; NK cells, $28.2 \times 10^6/\text{kg}$ vs $3.6 \times 10^6/\text{kg}$; $P < 0.001$ for each). In connection with the cell collection procedures, PBSC donors spent a shorter median time in hospital than BM donors (0 vs 2 days; median difference -2 days, 95% CI -2 to 2) and had fewer median days of restricted activity (2 vs 6 days; median difference -3 days, 95% CI -4 to 2). Overall, 65% of PBSC donors and 57% of BM donors reported at least one adverse event (AE), most of which were transient, mild–moderate in severity, and without clinical sequelae. PBSC donors experienced predominantly filgrastim-related AEs, while BM donors experienced predominantly harvest-related AEs.

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Peripheral blood has largely replaced bone marrow as a source of stem cells for autologous transplants over the past decade.¹ The ease of collection and the accelerated stem cell engraftment that occurs in peripheral blood stem cell (PBSC) recipients have clearly demonstrated the advantages of the more recent procedure.^{2,3} It was convincing evidence from autologous transplants that initially prompted attempts at peripheral blood transplantation in the allogeneic setting, despite fears of excessive graft-vs-host disease as a result of the high T cell content of peripheral blood grafts. Early trials, however, documented the feasibility of such transplants without excess mortality, and retrospective analyses and one prospective randomized trial⁴ indicate the advantage of allogeneic PBSC transplantation in advanced leukemias. In early leukemia, equivalent recipient outcomes have been observed to date following PBSC and bone marrow (BM) transplants, but longer follow-up is required to demonstrate the equivalence of the procedures or to establish the superiority of one over the other.^{5,6} The availability of large numbers of stem cells in peripheral blood, as a result of granulocyte colony-stimulating factor (G-CSF) administration, has further facilitated the performance of haploidentical transplantation.⁷

The initial focus of published studies comparing PBSC and BM transplantation centered on recipient outcome.^{8,9} There is a need, however, to direct attention to donors also, demand for whom is likely to increase. Low-intensity conditioning regimes that allow transplantation from older donors to be offered to older patients are increasingly used, and more information about donor aspects of PBSC transplantation is warranted to ensure donor safety and the quality of the graft product.

The complications of bone marrow harvesting are well known, and are usually mild and self-limiting.¹⁰ Severe side effects, such as infections, anesthetic complications, and bleeding, have been described but are rare.¹¹ Adverse events (AEs) experienced by healthy PBSC donors following stem cell mobilization with G-CSF include bone pain, headache,

fatigue, and reversible, usually mild, disturbances in such laboratory parameters as increased levels of lactate dehydrogenase (LDH) and alkaline phosphatase, and thrombocytopenia.^{12,13} In addition, there are isolated reports of splenic rupture^{14,15} and cardiovascular complications¹⁶ occurring during the mobilization phase of the procedure. Consideration also needs to be given to the potential problems associated with extracorporeal circulation during harvesting, such as local symptoms or hypocalcemia secondary to citrate infusion. To date, however, there is little information about long-term consequences in healthy donors mobilized with G-CSF over several days. A potential increase in the risk of acute leukemia has been discussed, although the influence of G-CSF on any future hematological event is difficult to determine given that related donors may share a genetic predisposition to leukemia.¹⁷ Further, little is known about factors affecting graft product composition.

We report here findings from a large, prospective randomized study comparing allogeneic filgrastim (recombinant methionyl human G-CSF)-mobilized PBSC transplantation with allogeneic BM transplantation in siblings of patients with acute leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome, focusing particularly on graft product, donor safety, and donor quality of life. The results of this study as they relate to recipient outcomes are published elsewhere.⁶

Patients and methods

Study design

In this randomized, open-label, multicenter, parallel group study, PBSC donation was compared with BM donation in siblings of patients with defined hematological malignancies. Donor/recipient pairs were randomized to give/receive either PBSCs or BM. An interim analysis carried out after procedures had been performed upon 70 pairs confirmed safety and revealed no unexpected AEs;¹⁸ the study was therefore allowed to proceed to enrollment of the originally envisaged 350 pairs. Study end points were graft composition (numbers of CD34⁺ cells, nucleated cells (NC), T cells, and natural killer (NK) (CD56⁺, CD3⁻) cells), the incidence and severity of AEs, donor quality of life (the duration of hospitalization associated with the collection procedure and the number of days on which regular activities were restricted), and the route of leukapheresis access (peripheral vs central). The study was approved by the ethics committee of each participating institution, and written informed consent was obtained from all donors and recipients before any study-related procedures were performed on them.

Patients, donors, and selection criteria

Donors had to be HLA-identical to their respective siblings, and between 16 and 60 years of age. Exclusion criteria were an inability to undergo general anesthesia and BM harvesting or to tolerate PBSC harvesting, the determination at initial examination that peripheral venous

access would be impossible, pregnancy or lactation, positive serology for HIV, hepatitis C and/or hepatitis B surface antigen, concurrent treatment with any other investigational drug, known sensitivity to *Escherichia coli*-derived products, and a history of malignancy.

A total of 350 donor/recipient pairs were enrolled in the study from 42 centers (listed in the Appendix) between January 1995 and December 1999, 176 pairs being randomized to BM transplantation and 174 pairs to PBSC transplantation. In all, 19 donor/recipient pairs (5%) were withdrawn from the study before donor harvesting, because of the relapse (seven patients) or death (two patients) of the intended recipient, withdrawal of consent (four pairs), ineligibility (four pairs), the detection of an unrelated medical condition, Klinefelter syndrome, in one pair, and logistical reasons (one pair). Two donor/recipient pairs were harvested/transplanted off protocol. Harvesting was successfully accomplished from 329 donors (166 in the BM arm, 163 in the PBSC arm) of whom 321 (98%) completed the study, seven donors having been lost to follow-up and one having been withdrawn from the trial as the result of an investigator's decision.

Harvesting procedures

BM was harvested under general anesthesia from both posterior iliac crests according to standard institutional procedures. A minimum NC yield $\geq 2 \times 10^8$ /kg recipient body weight was required. Donors randomized to undergo PBSC harvesting were administered filgrastim (provided by Amgen, Thousand Oaks, CA, USA) at a dose of 10 μ g/kg once daily by subcutaneous bolus injection for 4 or 5 consecutive days. Leukapheresis (101 of whole blood) was performed on the morning of day 5 using an automated continuous-flow cell separator with a peripheral route access or, if this was not practicable, a central venous line. If the target yield of $\geq 4 \times 10^6$ CD34⁺ cells/kg recipient weight was not achieved, an additional dose of filgrastim was administered on day 5 and leukapheresis was repeated on day 6. The minimum yield of CD34⁺ cells regarded as adequate for transplantation was 2×10^6 /kg recipient body weight.

Graft composition was assessed by determination of total NC and CD34⁺, T, and NK cells by local standardized immunophenotyping using the following antibodies: for CD34⁺ cells, HPCA-2-PE antibody (Becton Dickinson, Heidelberg, Germany); for T cells (CD3⁺) and NK cells (CD3⁻, CD56⁺), double-labelling with UCHT-1-FITC (DAKO, Hamburg, Germany) and Leu-19-PE antibodies (Becton Dickinson, Heidelberg, Germany) for CD3 and CD56 antigens, respectively.

Schedule of donor assessments

Donors underwent a physical examination (including weight, height, age, Eastern Cooperative Oncology Group (ECOG) status) within the 2 weeks before cell collection. ECOG performance status was reassessed at the end of the study, which was defined as 30 days post harvesting. Full blood counts, with manual differentials, were performed pre-study (within the 24 h before the first harvest procedure

or the first filgrastim administration), on the morning of each leukapheresis procedure prior to the procedure itself, every 3 days after the last dose of filgrastim until the absolute neutrophil count was within a range of $2 \times 10^9/l$ – $7 \times 10^9/l$, and at the end of the study.

Biochemistry profiles were determined pre-study (within the 24 h before the first harvest procedure or the first filgrastim administration), on the last day of filgrastim administration, and at the end of the study. AEs were assigned preferred terms using an Amgen-modified World Health Organization (WHO) Adverse Reactions Terminology automated dictionary, and the relationship of each to both filgrastim and the harvesting procedure used was recorded as not related, unlikely, possible, probable, or definite, and its severity assigned using the WHO Adverse Events Grading Scale. In particular, following AEs were recorded: problems at injection sites of filgrastim, medical problems during leukapheresis, incidence, duration and severity of pain, complications associated with route of venous access for leukapheresis, and medical interventions directly associated with the mobilization or harvest. AEs requiring medical intervention were considered severe. At the end of the study, the number of nights of hospitalization associated with the respective cell collection procedures and the number of days upon which regular activities could not be maintained were summated. Regular activity was defined as all the activity that could be performed as before collection, at home or at work. Each recipient was asked to report on their respective sibling donor's well-being after 3, 6, 9, 12, 24, and 36 months, at which times each donor was also contacted by telephone.

Statistical analysis

All donors from whom a successful harvest was obtained were included in the analysis of graft products. Graft yields per recipient body weight are summarized using the median and range. In addition, the proportions of donors with target CD34⁺ cell yields of $\geq 2 \times 10^6/kg$ recipient body weight and $\geq 4 \times 10^6/kg$ recipient body weight were calculated. Differences in yields between the BM and PBSC

donors were compared by log-transforming the yields and using the analysis of variance. The PBSC/BM ratios of yields were estimated by back-transforming the differences between the mean log values. The proportions of donors with CD34⁺ cell yields of $\geq 2 \times 10^6/kg$ and $\geq 4 \times 10^6/kg$ (recipient body weights) were compared using the χ^2 test. Other factors influencing yields were assessed using linear regression on the log transformations of the total cell yields (ie, uncorrected for recipient body weight). After adjusting for treatment group, a factor was considered influential if it was significant at the $\alpha=0.05$ level. The proportions of donors in the two groups requiring an overnight hospital stay were compared using the χ^2 test, and the total duration of hospitalization was compared using the Wilcoxon rank-sum test. All the comparisons between donor groups were carried out at the $\alpha=0.05$ level of significance, and all confidence intervals presented are set at 95%.

Results

Donor population

Donor characteristics are summarized in Table 1. The two groups were well balanced with respect to age, sex, height, weight, and body mass index (BMI). The overall median age was 37 years (range 17–60 years), and 54% of the donors were male. In all cases, pre-study physical examination was unremarkable.

Graft product

PBSCs could be harvested using a peripheral venous line from 93% of the donors. A total of 11 donors (7%) required a central venous line. The majority of donors (57%) underwent a single apheresis procedure, while 38% underwent two, and 5% underwent three aphereses. The compositions of the graft products (Table 2) differed in all

Table 1 Donor characteristics

	BM	PBSC	Total
No. of subjects	166	163	329
Sex			
N	166	163	329
Male	89 (54%)	89 (55%)	178 (54%)
Female	77 (46%)	74 (45%)	151 (46%)
Age (years)			
N	166	163	329
Median (range)	37 (16–38)	37 (18–60)	37 (16–60)
Height (cm)			
N	153	155	308
Median (range)	172 (148–192)	169 (150–192)	170 (148–192)
Weight (kg)			
N	165	163	328
Median (range)	75 (44–137)	70 (44–125)	73 (44–137)
BMI (kg/m ²)			
N	153	155	308
Median (range)	24.7 (17.3–48.5)	24.5 (17.8–47.5)	24.7 (17.3–48.5)

Table 2 Graft products

Cell yield ^a	BM	PBSC	PBSC/BM ratio	P
NC ($\times 10^8/kg$)				
N	166	163		
Median	2.7	8.7	3.2	<0.0001
Range	0–38.6	2.4–32.7		
CD34 ⁺ ($\times 10^6/kg$)				
N	160	163		
Median	2.7	5.8	2.1	<0.0001
Range	0–154.5	1.5–68.3		
T ($\times 10^6/kg$)				
N	134	149		
Median	35.7	300.1	8.4	<0.0001
Range	3.6–1699	15.6–2123.4		
NK ($\times 10^6/kg$)				
N	119	139		
Median	3.6	28.2	7.8	<0.0001
Range	0–154.5	0–665.8		
% donors with target CD34 ⁺ yield				
$\geq 4 \times 10^6/kg$	34	81		<0.0001
$\geq 2 \times 10^6/kg$	61	98		<0.0001

^aExpressed per kg recipient body weight.

measured respects between the two groups. In comparison with the BM product, total NC were increased approximately three-fold, CD34⁺ cells approximately two-fold, and T and NK cells each approximately eight-fold in the PBSC product. The proportion of donors yielding a CD34⁺ cell harvest $\geq 4 \times 10^6$ /kg recipient body weight was 81% in the PBSC group as compared with 34% in the BM group. A yield of $\geq 2 \times 10^6$ CD34⁺ cells/kg recipient body weight was achieved by 98% of PBSC donors and 61% of BM donors.

Of the 166 BM donors, three underwent subsequent harvesting of filgrastim-mobilized PBSCs. In the cases of two of these, the BM harvest cell yield had been considered by the respective investigators to be inadequate and, as a result of slow recipient engraftment, they were each subjected to an apheresis procedure. The third had initially produced an adequate BM harvest, but the treating center desired to retransplant the recipient with PBSC 40 days after BM transplantation. Data relating to these second harvests are excluded from the analyses.

As shown in Table 3, BMI ($P=0.0022$) and weight ($P=0.0009$) appeared to influence absolute CD34⁺ cell yield irrespective of the treatment group, increased numbers of CD34⁺ cells being obtained from donors with greater values for each of these parameters. None of the other covariates (sex, age, height) had any significant effect on CD34⁺ cell yield in the multivariate analysis. In contrast, fewer T cells were collected from older donors ($P=0.0017$), in both PBSC and BM graft products.

Donor safety

The proportions of donors experiencing at least one AE did not differ significantly between the PBSC and BM groups

(65 vs 57%, odds ratio (OR) 1.4, 95% CI 0.9–2.19), although the natures of the AEs were different (Table 4). Among PBSC donors, 59% reported characteristic filgrastim-related AEs such as musculoskeletal pain, headache, and increased levels of LDH and alkaline phosphatase. The subject incidence of harvesting procedure-related AEs was greater among BM donors than among PBSC donors (55 vs 37%, OR 0.49, 95% CI 0.31–0.76). In 96% of all donors, AEs were mild to moderate in severity and transient in nature; severe AEs were reported in 4% of donors. The subject incidence of severe AEs was greater in the PBSC group (7%) than in the BM group (1%) (OR 6.47, 95% CI 1.42–29.4), and the nature of the severe AEs also differed between the two. One of the BM donors complained of severe nausea and vomiting after general anesthesia, while another required two red blood cell transfusions because of a hemoglobin level below 10 g/dl post harvest. Among the PBSC group, 12 donors reported severe AEs, with incidences as follows: chest pain (one), hypertension (one), headache (three), somnolence (one), tetany (one), thrombocytopenia (two), hypoglycemia (one), hypocalcemia (one), and musculoskeletal pain (seven). One serious AE was reported in a PBSC donor who developed severe hypocalcemia with tetany during leukapheresis as a result of not taking prescribed calcium supplements. No death occurred among the donors in either group, nor did any patient prematurely terminate filgrastim dosing or withdraw from the study as result of an adverse event.

Duration of hospitalization and days of restricted activity

The duration of hospitalization associated with the collection procedure and the numbers of days of restricted activity of donors post harvesting are summarized in

Table 3 Factors influencing graft products

	CD34 ⁺ cell yield ($\times 10^8$), median (range)		T cell yield ($\times 10^8$), median (range)	
	BM	PBSC	BM	PBSC
Overall	2.03 (0.15–47.49)	4.19 (0.86–33.14)	24.2 (3.0–386.9)	218.0 (12.3–1783.7)
Sex				
Male	2.27 (0.15–47.49)	4.34 (1.45–10.41)	21.9 (3.0–386.9)	218.0 (17.1–1783.7)
Female	1.78 (0.18–16.72)	3.93 (0.86–33.14)	26.5 (4.2–273.0)	215.4 (12.3–947.9)
BMI (kg/m ²) ^a				
<20	1.51 (0.18–4.92)	3.33 (1.67–33.14)	50.7 (4.2–147.0)	189.1 (64.8–677.6)
20–25	1.80 (0.25–16.72)	3.93 (1.05–13.69)	28.2 (10.2–163.4)	224.6 (12.3–880.0)
>25	2.40 (0.15–47.49)	4.58 (0.86–11.59)	21.8 (3.0–386.9)	209.5 (14.1–1783.7)
Weight (kg) ^b				
<60	2.21 (0.25–47.49)	3.34 (0.86–33.14)	26.3 (10.5–224.4)	198.8 (66.1–947.9)
60–90	1.78 (0.15–16.72)	4.32 (1.05–13.69)	23.1 (3.0–273.0)	211.0 (12.3–1783.7)
>90	3.43 (1.34–11.54)	5.30 (3.12–7.97)	35.8 (11.7–386.9)	254.7 (65.1–825.0)
Height (m)				
<1.6	1.77 (0.79–8.64)	4.18 (1.65–33.14)	25.2 (9.4–273.0)	192.9 (64.1–638.8)
1.6–1.8	2.13 (0.15–47.49)	4.25 (0.86–10.41)	27.7 (3.0–386.9)	227.5 (12.3–1783.7)
>1.8	2.00 (0.19–10.45)	3.96 (2.07–6.07)	21.5 (11.5–172.0)	148.8 (79.1–677.6)
Age (years) ^c				
<25	1.92 (0.54–12.57)	4.32 (1.05–33.14)	44.2 (13.2–263.4)	332.5 (18.0–880.0)
25–40	1.82 (0.15–47.49)	4.32 (1.34–13.69)	22.7 (3.0–273.0)	203.4 (12.3–1783.7)
>40	2.13 (0.25–11.75)	3.96 (0.86–11.29)	21.4 (6.2–386.9)	215.4 (17.1–947.9)

None of the variables examined had any effect on NK cell yields.

^aThere was an independent effect of BMI on CD34⁺ cell yield ($P=0.0022$).

^bThere was an independent effect of donor weight on CD34⁺ cell yield ($P=0.0009$).

^cThere was an independent effect of donor age on T cell yield ($P=0.0017$).

Table 4 Subject incidence of adverse events occurring in >5% of BM or PBSC donors

	BM donors (n = 166)	PBSC donors (n = 164 ^a)
Any AE	95 (57%)	107 (65%)
Harvesting procedure-related AEs		
Any harvest-related	91 (55%)	61 (37%)
Access pain	39 (23%)	2 (1%)
Anemia	17 (10%)	0 (0%)
Pain back	16 (10%)	4 (2%)
Nausea	10 (6%)	1 (1%)
Arthralgia	8 (5%)	1 (1%)
Vomiting	8 (5%)	0 (0%)
Pain skeletal	3 (2%)	10 (6%)
Filgrastim-related AEs		
Any filgrastim-related		96 (59%)
Musculoskeletal		71 (43%)
Headache		19 (12%)
LDH increased		14 (9%)
Alkaline phosphatase increased		8 (5%)

^aThe safety analysis set includes one PBSC donor excluded from the efficacy analyses by virtue of failing to generate a stem cell yield sufficient to justify transplantation, but who, nevertheless, had been mobilized with filgrastim and undergone apheresis.

Table 5 Duration of collection procedure-associated hospitalization and subsequent days of restricted activity

	BM donors	PBSC donors
Nights in hospital		
N ^a	153	149
0	5 (3%)	111 (74%)
1	21 (14%)	9 (6%)
2–7	127 (83%)	28 (19%)
>7 ^b	0 (0%)	1 (1%)
Mean	2.0	0.7
Median	2.0	0.0
Range	0.0–7.0	0.0–8.0
Median difference		–2.0
95% CI		–2–2
Days of restricted activity		
N ^a	149	142
0	3 (2%)	22 (15%)
1	10 (7%)	33 (23%)
2–7	76 (51%)	66 (46%)
8–14	29 (19%)	18 (13%)
>14	31 (21%)	3 (2%)
Mean	10.3	3.6
Median	6.0	2.0
Range	0.0–192	0.0–23.0
Median difference		–3.0
95% CI		–4.0–2.0
1 or <1 day restricted activity	13/149 (0.087)	55/142 (0.387)
Difference in proportions (95% CI)		0.300 (0.208–0.392)

^aThe numbers of patients included in these analyses represent all those in each category for whom information was available.

^bThe single PBSC donor who remained in hospital for >7 nights lived some distance away, and remained in hospital for 8 nights for logistical reasons.

Table 5 and Figure 1. In general, PBSC donors spent a shorter time in hospital than BM donors, with a clear reduction in the proportion of them requiring an overnight stay (26 vs 97%; $P = 0.0001$). For BM donors, the median

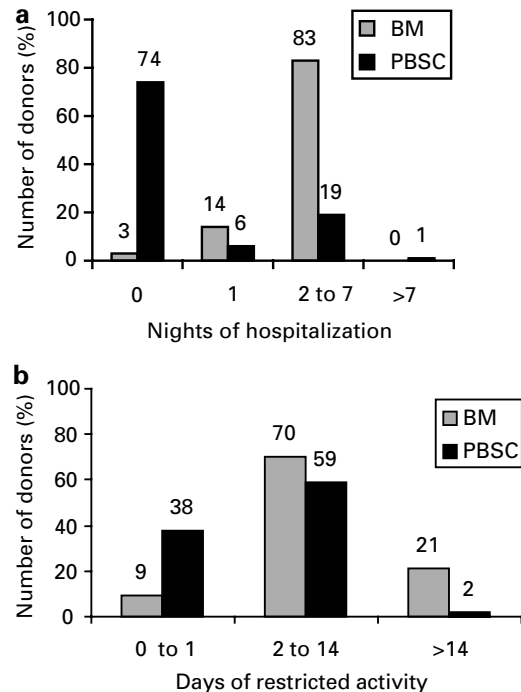


Figure 1 Donor quality of life. Duration of collection procedure-associated hospitalization and subsequent periods of restricted activity among BM and PBSC donors.

number of days of hospitalization was 2 days, while 74% of PBSC donors required no hospitalization, 6% required one night in hospital, and 20% required a stay of longer than one night. The longest hospitalized PBSC donor remained for 8 nights purely for logistical reasons, because she lived far away from the study center. The median number of days on which activity was restricted was also clearly less for PBSC donors (2 days) than for BM donors (6 days), the median difference being 3 days less in the former. Among PBSC donors, 61% reported >1 day of restricted activity, as against 91% of BM donors. PBSC donors were also less likely to experience a prolonged duration of restricted activity, only 2% reporting such a period of 2 weeks, as against 21% of BM donors.

No PBSC donor reported restricted activity beyond day 23. In the BM group, all donors resumed regular activity before day 100, except for one woman who suffered from severe back pain especially in cold weather, until day 192 after donation.

Discussion

The results of this prospective, randomized study comparing PBSC donation with BM donation show that the two differ significantly in terms of graft product and donor quality of life. The PBSC product contained approximately two-fold more CD34⁺ cells and approximately eight-fold more of both T and NK cells than BM harvests, confirming and extending previous results.^{18,19} PBSC collection resulted in a greater number of stem cells independently of all other factors. Greater numbers of CD34⁺ cells were

obtained from heavier donors and those with a greater BMI, but age and sex seemed to exert no significant impact on stem cell yield. The PBSC collection procedure was successful, and the target yield of stem cells was achieved by >80% of donors, for less than 10% of whom a central venous line was required for leukapheresis, and for almost two-thirds of whom only one apheresis procedure was required for the target stem cell yield to be achieved. These findings are consistent with those of other reports.^{20,21}

Regardless of the procedure, stem cell donation is invasive for donors, being associated with possible complications and impairment of quality of life and the need for hospitalization and time off work. Nevertheless, PBSC donation is generally less traumatic for donors in terms of post harvest discomfort, and does not require general anesthesia. Overnight hospitalization was not necessary for the majority (74%) of PBSC donors in the present study, whereas the great majority (97%) of BM donors did require hospitalization for at least one night. The overall duration of hospitalization associated with the collection procedure was shorter for PBSC donors than for BM donors, and recovery post harvesting, as assessed by the number of days of restricted activity, was also more rapid for the former.

At least one AE, the great majority of which were mild–moderate in severity, transient and self-limiting, was experienced by 57% of BM donors and 65% of PBSC donors. Severe AEs were reported in 1% of BM donors and 7% of PBSC donors. PBSC donors principally reported AEs connected with filgrastim administration, while AEs reported by BM donors principally represented donation procedure and anesthesia-related complications. A single serious AE occurred in one PBSC donor who accidentally neglected to take prescribed calcium supplement and developed tetany during leukapheresis. Prophylactic calcium administration during PBSC donation should now be considered standard.²²

Yields of CD34⁺ cells and T cells obtained through PBSC donation have previously been reported to be greater than may be achieved through BM donation,^{4–6,8,18,19} but few studies have analyzed factors potentially capable of influencing the efficacy of stem cell mobilization. Mifflin *et al*²³ noted that PBSCs could be mobilized in significantly greater quantities in male donors than in female, and a trend in this direction was noted in the present study although it was not statistically significant. There was no apparent effect of donor age on CD34⁺ cell yield. More than half of all PBSC donors generated the target CD34⁺ cell yield of $\geq 4 \times 10^6$ cells/kg recipient body weight in one leukapheresis procedure, which may be a consequence of the protocol requirement for 10l of whole blood to be subjected to apheresis. Current trends toward the apheresis of large blood volumes result in a reduced need for multiple collections and may decrease the incidence of AEs experienced by donors.

One of the primary study end points was the incidence and severity of AEs consequent upon PBSC donation. The great majority of AEs experienced by both BM and PBSC donors were mild and self-limiting, and no such rare life-threatening events as severe complications due to anesthesia or splenic rupture and cardiovascular

events^{11,14–16,24} were observed. This may simply have been chance, or it may be related to the strict inclusion criteria that existed for donors and the standardized pre-donation evaluation. Although it is not possible at this stage to draw any conclusions about the long-term safety of PBSC mobilization by filgrastim, the donors enrolled in the present study are being followed for a total period of 3 years, and subsequent findings in this population will be the subject of a later report.

The incidence and severity of acute side effects might be greater with less stringent inclusion criteria that allow the participation of older donors or those with significant comorbidity. This is important in relation to the increasing use of hematopoietic stem cell transplantation in older recipients.

The possibility of an increased risk of acute leukemia arising as a result of mobilization with filgrastim has been discussed,^{17,25,26} but it may very well never be possible to assess accurately this risk since it has been calculated that to detect a 10-fold increase in leukemia among healthy PBSC donors would require more than 2000 of them to be followed for 10 years or more.²⁷

The relative merits of allogeneic PBSC or BM transplantation also encompass economic, psychosocial, and ethical concerns that were not investigated in the present study. Economic analyses have shown the overall costs associated with the two procedures, from the start of donor mobilization or bone marrow harvest to 100 days post transplantation, to be approximately equivalent in Canada²⁸ and for PBSC transplantation to be cheaper than BM transplantation by approximately 20% in the US²⁹ and approximately 30% in Spain³⁰. In a recent US National Marrow Donor Program survey,³¹ donors with experience of both procedures reported that they had found BM donation physically more difficult and more time consuming, and expressed a preference for PBSC donation. In another study, the levels of physical discomfort reported by stem cell donors undergoing one or other harvesting procedure were similar, but symptoms in PBSC donors resolved more rapidly.³² Munzenberger *et al*³³ measured quality of life in terms of pain and anxiety before, during, and after PBSC donation in a small group of subjects and found that not all donors reacted in the same way to their own personal experience or in terms of their attitudes toward donation, relationships with other family members, and awareness of the risk involved. No randomized prospective comparison of psychosocial aspects of PBSC and BM donation in a larger population has yet been published.

In conclusion, the findings of the present study demonstrate that greater stem cell yields may be achieved through PBSC donation than through BM donation, and that the procedure is safe and somewhat less of a burden than BM donation in terms of donor quality of life, as reflected by the duration of hospitalization associated with the collection procedure and the number of days of restricted activity post harvesting. Nevertheless, PBSC donation remains an invasive procedure and detailed donor counselling in relation to both physical and psychological aspects of the procedure is essential, as is the close follow-up of donors to assess the long-term effects of donation.

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References

- 1 Gratwohl A, Baldomero H, Horisberger B *et al*. Current trends in hematopoietic stem cell transplantation in Europe. *Blood* 2002; **100**: 2374–2386.
- 2 To LB, Roberts MM, Haylock DN *et al*. Comparison of haematological recovery times and supportive care requirements of autologous recovery phase peripheral blood stem cell transplants, autologous bone marrow transplants and allogeneic bone marrow transplants. *Bone Marrow Transplant* 1992; **9**: 277–284.
- 3 Schmitz N, Linch DC, Dreger P *et al*. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation vs autologous bone-marrow transplantation in lymphoma patients. *Lancet* 1996; **347**: 353–357.
- 4 Bensinger WI, Martin PJ, Storer B *et al*. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N Engl J Med* 2001; **344**: 175–181.
- 5 Powles R, Mehta J, Kulkarni S *et al*. Allogeneic blood and bone-marrow stem cell transplantation in haematological malignant diseases: a randomised trial. *Lancet* 2000; **355**: 1231–1237.
- 6 Schmitz N, Beksaç M, Hasenclever D *et al*. Transplantation of mobilized peripheral blood cells to HLA-identical siblings with standard-risk leukemia. *Blood* 2002; **100**: 761–767.
- 7 Aversa F, Terenzi A, Felicini R *et al*. Haploidentical stem cell transplantation for acute leukemia. *Int J Hematol* 2002; **76** (Suppl. 1): 165–168.
- 8 Blaise D, Kuentz M, Fortanier C *et al*. Randomized trial of bone marrow vs lenograstim-primed blood cell allogeneic transplantation in patients with early stage leukemia: a report from the Société Française de Greffe de Moelle. *J Clin Oncol* 2000; **18**: 537–546.
- 9 Heldal D, Tjønnfjord G, Brinch L *et al*. A randomised study of allogeneic transplantation with stem cells from blood or bone marrow. *Bone Marrow Transplant* 2000; **25**: 1129–1136.
- 10 Stroncek DF, Holland PV, Bartch G *et al*. Experiences of the first 493 unrelated marrow donors in the National Marrow Donor Program. *Blood* 1993; **81**: 1940–1946.
- 11 Hosoya N, Miyagawa K, Mimura T *et al*. Malignant hyperthermia induced by general anesthesia for bone marrow harvesting. *Bone Marrow Transplant* 1997; **19**: 509–511.
- 12 Murata M, Harada M, Kato S *et al*. Peripheral blood stem cell mobilization and apheresis: analysis of adverse events in 94 normal donors. *Bone Marrow Transplant* 1999; **24**: 1065–1071.
- 13 Anderlini P, Rizzo JD, Nugent ML *et al*. Peripheral blood stem cell donation: an analysis from the International Bone Marrow Transplant Registry (IBMTR) and European Group for Blood and Marrow Transplant (EBMT) databases. *Bone Marrow Transplant* 2001; **27**: 689–692.
- 14 Becker PS, Wagle M, Matous S *et al*. Spontaneous splenic rupture following administration of granulocyte colony-stimulating factor (G-CSF): occurrence in an allogeneic donor of peripheral blood stem cells. *Biol Blood Marrow Transplant* 1997; **3**: 45–49.
- 15 Falzetti F, Aversa F, Minelli O, Tabilio A. Spontaneous rupture of spleen during peripheral blood stem-cell mobilisation in a healthy donor. *Lancet* 1999; **353**: 555.
- 16 Vij R, Adkins DR, Brown RA *et al*. Unstable angina in a peripheral blood stem and progenitor cell donor given granulocyte-colony-stimulating factor. *Transfusion* 1999; **39**: 542–543.
- 17 Anderlini P, Przepiorka D, Körbling M, Champlin R. Blood stem cell procurement: donor safety issues. *Bone Marrow Transplant* 1998; **21** (Suppl. 3): S35–S39.
- 18 Schmitz N, Bacigalupo A, Hasenclever D *et al*. Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 1998; **21**: 995–1003.
- 19 Couban S, Simpson DR, Barnett MJ *et al*. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. *Blood* 2002; **100**: 1525–1531.
- 20 Majolino I, Cavallaro AM, Bacigalupo A *et al*. Mobilization and collection of PBSC in healthy donors: a retrospective analysis of the Italian Bone Marrow Transplantation Group (GITMO). *Haematologica* 1997; **82**: 47–52.
- 21 Anderlini P, Donato M, Chan K-W *et al*. Allogeneic blood progenitor cell collection in normal donors after mobilization with filgrastim: The M.D. Anderson Cancer Center experience. *Transfusion* 1999; **39**: 555–560.
- 22 Bolan CD, Cecco SA, Wesley RA *et al*. Controlled study of citrate effects and response to IV calcium administration during allogeneic peripheral blood progenitor cell donation. *Transfusion* 2002; **42**: 935–946.
- 23 Mifflin G, Charley C, Stainer C *et al*. Stem cell mobilization in normal donors for allogeneic transplantation: analysis of safety and factors affecting efficacy. *Br J Haematol* 1996; **95**: 345–348.
- 24 Buckner CD, Clift RA, Sanders JE *et al*. Marrow harvesting from normal donors. *Blood* 1984; **64**: 630–634.
- 25 Anderlini P, Körbling M, Dale D *et al*. Allogeneic blood stem cell transplantation: considerations for donors. *Blood* 1997; **90**: 903–908.
- 26 Cavallaro AM, Lilleby K, Majolino I *et al*. Three to six year follow-up of normal donors who received recombinant human granulocyte colony-stimulating factor. *Bone Marrow Transplant* 2000; **25**: 85–89.
- 27 Hasenclever D, Sextro M. Safety of alloPBSC donors: Biometrical considerations on monitoring long term risks. *Bone Marrow Transplant* 1996; **17** (Suppl. 2): S26–S30.
- 28 Couban S, Dranitsaris G, Andreou P *et al*. Clinical and economic analysis of allogeneic peripheral blood progenitor cell transplants: a Canadian perspective. *Bone Marrow Transplant* 1998; **22**: 1199–1205.
- 29 Bennett CL, Waters TM, Stinson TJ *et al*. Valuing clinical strategies early in development: a cost analysis of allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; **24**: 555–560.
- 30 Madero L, Vicent MG, Ramirez M *et al*. Clinical and economic comparison of allogeneic peripheral blood progenitor cell and bone marrow transplantation for acute lymphoblastic leukemia in children. *Bone Marrow Transplant* 2000; **26**: 269–273.
- 31 Switzer GE, Goycoolea JM, Dew MA *et al*. Donating stimulated peripheral blood stem cells vs bone marrow: do donors experience the procedures differently? *Bone Marrow Transplant* 2001; **27**: 917–923.
- 32 Rowley SD, Donaldson G, Lilleby K *et al*. Experiences of donors enrolled in a randomized study of allogeneic bone

marrow or peripheral blood stem cell transplantation. *Blood* 2001; **97**: 2541–2548.

- 33 Munzenberger N, Fortanier C, Macquart-Moulin G *et al*. Psychosocial aspects of haematopoietic stem cell donation for allogeneic transplantation: how family donors cope with this experience. *Psychooncology* 1999; **8**: 55–63.

Appendix

This study was conducted at the following institutions under the auspices of the named principal investigators: Allgemeines Krankenhaus, Vienna, Austria (H Greinix); University Hospital, Innsbruck, Austria (D Niederwieser, D Nachbauer); University Hospital, Leuven, Belgium (M Boogaerts); Cliniques Universitaires St Luc, Brussels, Belgium (A Ferrant); Charité der Humboldt Universität, Berlin, Germany (R Arnold); Hôpital St Louis, Paris, France (E Gluckman); Hôpital St. Antoine, Paris, France (NC Gorin); Universität Ulm, Ulm, Germany (N Frickhofen); Christian-Albrechts Universität, Kiel, Germany (N Schmitz); Universitätsklinikum Eppendorf, Hamburg, Germany (A Zander); St James Hospital, Dublin, Ireland (S McCann); Hadassah University Hospital, Jerusalem, Israel (A Nagler); Ospedale San Martino, Genova, Italy (A Bacigalupo); Kantonsspital Basel, Basel, Switzerland (A Gratwohl); Hammersmith Hospital, London, UK (J Apperley); Nottingham City Hospital, Nottingham, UK (NH Russell); Huddinge Hospital, Huddinge, Sweden

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