Bone Marrow Transplantation (2001) 27, 689–692

www.nature.com/bmt

Peripheral blood stem cells

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

P Anderlini[1], JD Rizzo[2], ML Nugent[2], N Schmitz[3], RE Champlin[1] and MM Horowitz[2]

[1]*University of Texas MD Anderson Cancer Center, Houston, TX;* [2]*IBMTR Statistical Center of the International Bone Marrow Transplant Registry, Health Policy Institute, Medical College of Wisconsin, Milwaukee, WI, USA; and* [3]*EBMT, Kiel, Germany*

Summary:

Donation-related data for 1488 allogeneic peripheral blood stem cell (PBSC) transplants reported to the International Bone Marrow Transplant Registry (IBMTR) or the European Blood and Marrow Transplant Group (EBMT) by 152 teams worldwide between 1994 and 1998 were reviewed. In 1998, 26% of allografts registered with the IBMTR were collected from blood. Median age of PBSC donors was 38 years (range <1–76), and 55% were male. Of 1486 donor–recipient pairs evaluable for HLA compatibility, 1322 (89%) were HLA-identical siblings. Recombinant human granulocyte colony-stimulating factor (G-CSF) was employed to mobilize PBSCs in almost all (99%) cases. One hundred and seventy (20%) of 828 evaluable PBSC donors had a central catheter placed for leukapheresis. Eighty-five percent of 1321 evaluable PBSC grafts were collected with one or two leukaphereses. There were 15 reported donation-related adverse events (1% of evaluable donors). Complications were catheter-related in five. No donation-related fatalities were reported. These data suggest that PBSC donation is becoming more prevalent worldwide. It appears to have a safety profile comparable to marrow harvesting, although experience with the latter is much more extensive. *Bone Marrow Transplantation* (2001) **27,** 689–692.

Keywords: recombinant human granulocyte colony-stimulating factor (G-CSF); leukapheresis; allogeneic peripheral blood stem cell transplantation; normal donor

Cytokine-mobilized peripheral blood stem cells (PBSC) are increasingly used as an alternative to bone marrow for allogeneic transplantation.[1–3] Potential advantages of this approach over bone marrow transplantation include donor-related and recipient-related factors, which are reviewed in detail elsewhere.[1–3]

PBSC collection may allow donors to avoid surgery, anesthesia (general or spinal), hospitalization and potential exposure to allogeneic blood products.[2,3] Data on the safety and efficacy of PBSC apheresis are increasing but remain limited to relatively small published series reported by single institutions.[4–10] Experience with marrow harvesting is much more extensive.[11–13] The risk of serious complications for marrow donors in published series of 3000 to 8000 patients is 0.3%.[12,13] Before PBSC apheresis can be widely endorsed, evaluation of large numbers of donors harvested at multiple institutions is necessary.

In this study we reviewed donor-related data for nearly 1500 PBSC transplants reported to the International Bone Marrow Transplant Registry (IBMTR) or the European Blood and Marrow Transplant Group (EBMT) between 1994 and 1998.

Materials and methods

Donors for allogeneic PBSC transplants between 1994 and 1998, registered with the IBMTR and/or EBMT were eligible for this analysis.

The IBMTR is a voluntary working group of more than 400 transplant teams worldwide that contribute detailed data on their allogeneic transplantations to the Statistical Center at the Medical College of Wisconsin. Participants are required to register all consecutive hematopoietic stem cell transplantations, regardless of graft type. The IBMTR database includes information on 40–45% of all allogeneic transplantations since 1970. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality.

The EBMT is a voluntary group of 436 transplant centers located primarily in Europe. Data quality of participating centers is checked by the EBMT Statistical Office at the

Correspondence: Dr JD Rizzo, IBMTR/ABMTR, Medical College of Wisconsin, PO Box 26509, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.
Received 5 October 2000; accepted 4 January 2001

University College of London Hospitals and regular site visits to centers selected on a random basis. For this analysis, centers registering allogeneic PBSC transplants in 1995 and 1996 were contacted and asked to provide detailed reports for all consecutive cases of unmanipulated allogeneic PBSC transplants from HLA-identical sibling donors performed between January 1995 and June 1996. Detailed data on bone marrow transplants during this time period were not specifically requested. Data were reviewed to eliminate duplicate transplantations between the two registries.

The current prevalence of PBSC transplants was calculated using data available from all centers who registered their consecutive hematopoietic stem cell transplantations with the IBMTR between 1994 and 1998, including EBMT centers who also participate in the IBMTR. More comprehensive research data were available for a subset of these patients submitted on IBMTR Report Forms or EBMT Med-B data collection forms (available on request). These were used for all other descriptive analyses. Donor complications were available only for transplants reported on IBMTR forms or on supplemental data forms completed by EBMT teams and are presented as reported verbatim in response to the question, 'Did a donor complication occur? If yes, please specify.' Data on bone marrow donations done between 1994 and 1998 and reported to the IBMTR were used for comparative purposes. Severity of donor complications, aside from death, is not collected. Decisions regarding whether an event is an anticipated side-effect or a true complication, and whether it is severe enough to warrant reporting are left to the discretion of the team. Chi-square or Wilcoxon rank-sum tests were performed for comparisons of categorical and continuous data, respectively. All statistics were performed using SAS statistical software.

Results

Twenty six thousand seven hundred and eleven allogeneic transplants with either PBSC or bone marrow grafts, for all indications, were registered with the IBMTR between 1994 and 1998. Of these, 4348 (16%) were PBSC grafts, the remainder were bone marrow grafts. In 1994, PBSC was the source of stem cells for only 2% ($n = 92$) of all allogeneic transplants registered with the IBMTR ($n = 4880$). By 1998, 26% ($n = 1341$) of all registered allogeneic transplants ($n = 5153$) were from peripheral blood.

Detailed data were available for 1488 PBSC donors of all ages reported to the IBMTR or EBMT (IBMTR $n = 742$; EBMT $n = 746$) for all indications between 1994 and 1998 by 152 teams worldwide.

Donor characteristics

Characteristics of PBSC donors and collections are shown in Table 1. The median age of PBSC donors was 38 years (range <1–76); 55% were male. Of 1486 evaluable donor–recipient pairs, 1322 (89%) were HLA-identical siblings, with most others being partially HLA-matched relatives. Only 15 (1%) PBSC donors were not related to their recipient. Nearly all evaluable PBSC donors received recombinant human granulocyte colony-stimulating factor (G-CSF) prior to leukapheresis. Approximately 40% of evaluable donors underwent a single leukapheresis procedure. Forty-five percent underwent two, 11% underwent three, and 5% underwent 4 or more leukaphereses. The percent of donors requiring three or more phereses declined from 35% in 1994 to 5% in 1998. Among donors for whom venous access data were available ($n = 828$), 20% had a central vascular catheter placed for leukapheresis. For donors with data on venous access device and number of collections, those using a central vascular device were more likely to require only one collection than donors collected with a peripheral venous catheter (55% *vs* 39%, $p = 0.03$).

Table 1 Characteristics of peripheral blood stem cell and bone marrow donors for patients transplanted for all indications and reported to the IBMTR, and/or EBMT

Variable	*Peripheral blood*		*Bone marrow*[a]	
	n evaluable	*n (%)*	*n evaluable*	*n (%)*
Number of donors	1488		8021	
Donor age, median (range), years	1446	38 (<1–76)	7604	32 (<1–75)
Year of transplant	1488		8021	
1994		40 (3)		2331 (29)
1995		304 (21)		2152 (27)
1996		604 (42)		1856 (23)
1997		367 (25)		1160 (14)
1998		173 (9)		522 (6)
Male gender	1475	819 (55)	7948	4330 (55)
Donor–recipient relationship	1486		8009	
HLA-identical sibling		1322 (89)		5486 (69)
Other relative		149 (10)		491 (6)
Unrelated		15 (1)		2032 (25)
Donor complication occurred	1337	15 (1.1)	6346	30 (0.5)
Type of growth factors given	1306			
G-CSF		1300 (99)		
GM-CSF		6 (<1%)		
Number of leukaphereses	1321			
1		527 (39)		
2		592 (45)		
3		140 (11)		
4		46 (4)		
5		12 (1)		
6		3 (<1)		
Method of vascular access	828			
Peripheral venous catheter		658 (80)		
Central venous catheter		170 (20)		

[a]Includes patients receiving allogeneic transplants for all indications reported to the IBMTR by teams worldwide, including EBMT teams who customarily also report to the IBMTR.

Compared to PBSC donors, bone marrow donors were significantly younger (median age 32 *vs* 38 years, $P = 0.0001$) (Table 1). The gender distributions of bone marrow and PBSC donors were similar. Among bone marrow donor–recipient pairs, 69% were HLA-identical siblings, whereas 25% were unrelated.

Complications

Donation-related complications were reported in 1.1% ($n = 15$) of 1337 evaluable PBSC donors. These are listed, as taken from Report forms, in Table 2.

Table 2 Peripheral blood donor complications as reported verbatim in Report forms

Bleeding around catheter site during apheresis
Capillary leak syndrome
Episode of pericarditis 1 month after collection
Hematoma from catheter placement
Hemothorax (related to) catheter placement
Hypercalcemia, anxiety requiring hospitalization
Hypertension
Hypotension, hypoxia, dyspnea
Nausea, diarrhea
Platelet count drop
Thrombocytopenia
Subclavian vein thrombosis
Back pain, hypertension
Catheter replacement twice (kinks)
Decreased platelet count

One third of the reported complications appear to be central venous catheter-related. Patients having central vascular catheters were more likely than those having peripheral vascular catheters to have a complication reported (3.6% *vs* 1.1%, $P = 0.02$). There was a linear association between increasing complication rates and increasing number of collections. This trend remained significant after adjusting for type of catheter used (central *vs* peripheral). PBSC donors requiring two or fewer collections also had lower complication rates than donors requiring three or more (0.9% *vs* 2.5%, $P = 0.04$). No donor fatalities were reported.

The overall donor complication rate was higher for PBSC donors than for bone marrow donors reported to the IBMTR during the same time period (1.1% *vs* 0.5%). There were two fatalities reported among 7857 reported bone marrow donations during the same time period.

Discussion

Marrow harvesting is well established as a procurement method for hematopoietic stem cells. Its record of safety has been confirmed in several studies of related and unrelated donors.[11–13] The safety of PBSC donation was recently reviewed.[14] It may be equally safe and less intensive than bone marrow harvesting, but experience remains limited. The purpose of this analysis was to expand on the limited information currently available by evaluating donors reported to the IBMTR and EBMT. Although neither organization collects extensive donor-related data, each has information on reported adverse events in a very large cohort of allograft donors.

Two interesting findings emerged from this study. The first was that only 40% of donors underwent a single apheresis and that a sizable (15%) proportion underwent three or more collections. Recently reported data from US and European centers suggest 50–70% of normal donors can be successfully harvested with one collection, and about 85% in two or fewer collections.[6,15,16] Differences in target hematopoietic stem cell dose, leukapheresis procedures and duration and type of vascular access may explain the variation in the number of aphereses performed. Greater use of large volume apharesis may reduce the need for multiple collections. A somewhat surprising finding was that 20% of donors had a central vascular catheter placed for apheresis. Several recent reports suggest central catheterization is necessary for venous access in as few as 5% of donors,[4–6,15] while other centers may use them routinely.[17]

G-CSF was almost universally employed as the mobilizing cytokine. This is consistent with cytokine use in normal PBSC donors reported in the literature.[14,18,19]

The donor complication rate reported in this study was 1.1%, with one third of PBSC donor complications catheter-related. All reported catheter-related complications occurred in the central vascular catheter group. This overall rate is comparable to the complication rates for marrow harvesting published in the literature (on much larger numbers of donors), which have ranged from 0.27% to 5.9%.[11–13] It is higher than the complication rate for marrow donors found in the IBMTR database (0.5%). No fatalities were reported among PBSC donors. Serious adverse events have been reported elsewhere, including splenic rupture.[20,21]

One limitation of this study is the potential for reporting bias. PBSC collections and peri-procedural medical management of donors is often exclusively performed by the bone marrow transplantation service. Conversely, anesthesiologists and operating room staff are more involved in bone marrow harvest procedures, and may not be included in the usual complication reporting mechanisms to the IBMTR. These two factors, along with the relatively novel nature of PBSC collection, may favor reporting of complications in the PBSC donor group. While this bias may affect the comparison of complication rates between the bone marrow and PBSC donor groups, it should not affect comparisons within the PBSC donor group.

Another limitation is the open-ended nature of the inquiry regarding complications. Complications considered 'unimportant' might not have been reported in either group. Thrombocytopenia, reported as a complication in three donors in the PBSC group, may be reasonably considered an anticipated side-effect, although severity in each case is not known.

In conclusion, these data suggest that PBSC donation for allogeneic PBSC transplantation is becoming more prevalent worldwide. Although experience with bone marrow harvesting is much more extensive, PBSC donation appears to be reasonably safe. Data from this study would suggest caution in use of central vascular catheters for cell collection. The issue of possible long-term effects must be addressed as additional follow-up data for PBSC donors become available.

Acknowledgements

Supported by Public Health Service Grants P01-CA-40053 and U24-CA76518 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute, of the US Department of Health and Human Services; and grants from Amgen, Inc.; Anonymous; Baxter Fenwal; Berlex Laboratories; Blue Cross and Blue Shield Association; Lynde and Harry Bradley Foundation; Bristol-Myers Squibb Oncology; Cell Therapeutics; Center for Advanced Studies in Leukemia; Chimeric Therapies; Chiron Therapeutics; COBE BCT Inc.; Eleanor Naylor Dana Charitable Trust; Deborah

J Dearholt Memorial Fund; Empire Blue Cross Blue Shield; Eppley Foundation for Research; Fromstein Foundation; Fujisawa Healthcare, Inc.; Genentech, Inc.; Hoechst Marion Roussel; Horizon Medical Products; Human Genome Sciences; IDEC Pharmaceuticals; Immunex Corporation; IMPATH/BIS; IntraBiotics Pharmaceuticals; Kaiser Permanente; Kettering Family Foundation; Kirin Brewery Company; Robert J Kleberg, Jr and Helen C Kleberg Foundation; Herbert H Kohl Charities; Life Trac/Allianz; The Liposome Company; Nada and Herbert P Mahler Charities; Market Certitude; Mayer Ventures; MDS Nordian; MedImmune, Inc.; Milliman & Robertson, Inc.; Milstein Family Foundation; Miltenyi Biotech; Milwaukee Foundation/ Elsa Schoeneich Research Fund; Mutual of Omaha; Nexell Therapeutics; NeXstar Pharmaceuticals, Inc; Samuel Roberts Noble Foundation; Novartis Pharmaceuticals; Orphan Medical; Ortho Biotech, Inc.; John Oster Family Foundation; Jane and Lloyd Pettit Foundation; Pfizer, Inc.; Pharmacia and Upjohn; Principal Life Insurance Company; Protide Pharmaceuticals; RGK Foundation; Rhône-Poulenc Rorer Pharmaceuticals, Inc.; Roche Laboratories; SangStat Medical Corporation; Schering AG; Schering-Plough Oncology; Searle; SmithKline Beecham Pharmaceutical; Stackner Family Foundation; The Starr Foundation; StemCell Technologies; SyStemix; Therakos; TheraTechnologies; United Resource Networks; US Oncology; and Wyeth-Ayerst Laboratories.

References

1 Goldman J. Peripheral blood stem cells for allografting. *Blood* 1995; **85**: 1413–1415.
2 Russell N, Gratwohl A, Schmitz N. The place of blood stem cells in allogeneic transplantation. *Br J Haematol* 1996; **93**: 747–753.
3 Lane TA. Allogeneic marrow reconstitution using peripheral blood stem cells: the dawn of a new era. *Transfusion* 1996; **36**: 585–589.
4 Bishop MR, Tarantolo SR, Jackson JD *et al*. Allogeneic-blood stem-cell collection following mobilization with low-dose granulocyte colony-stimulating factor. *J Clin Oncol* 1997; **15**: 1601–1607.
5 Bensinger WI, Clift R, Martin P *et al*. Allogeneic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: a retrospective comparison with marrow transplantation. *Blood* 1996; **88**: 2794–2800.
6 Brown RA, Adkins D, Goodnough LT *et al*. Factors that influence the collection and engraftment of allogeneic peripheral-blood stem cells in patients with hematologic malignancies. *J Clin Oncol* 1997; **15**: 3067–3074.
7 Martinez C, Urbano-Ispizua A, Rozman C *et al*. Effects of G-CSF administration and peripheral blood progenitor cell collection in 20 healthy donors. *Ann Hematol* 1996; **72**: 269–272.
8 Dreger P, Haferlach T, Eckstein V *et al*. G-CSF-mobilized peripheral blood progenitor cells for allogeneic transplantation: safety, kinetics of mobilization, and composition of the graft. *Br J Haematol* 1994; **87**: 609–613.
9 Russell JA, Luider J, Weaver M *et al*. Collection of progenitor cells for allogeneic transplantation from peripheral blood of normal donors. *Bone Marrow Transplant* 1995; **15**: 111–115.
10 Stroncek DF, Clay ME, Petzoldt ML *et al*. Treatment of normal individuals with granulocyte-colony-stimulating factor: donor experiences and the effects on peripheral blood CD34+ cell counts and on the collection of peripheral blood stem cells. *Transfusion* 1996; **36**: 601–610.
11 Buckner CD, Clift RA, Sanders JE *et al*. Marrow harvesting from normal donors. *Blood* 1984; **64**: 630–634.
12 Bortin MM, Buckner CD. Major complications of marrow harvesting for transplantation. *Exp Hematol* 1983; **11**: 916–921.
13 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.
14 Anderlini P, Körbling M, Dale D *et al*. Allogeneic blood stem cell transplantation: considerations for donors. *Blood* 1997; **90**: 903–908.
15 Anderlini P, Donato M, Chan KW *et al*. Allogeneic blood progenitor cell collection in normal donors after mobilization with filgrastim: the MD Anderson Cancer Center experience. *Transfusion* 1999; **39**: 555–560.
16 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.
17 Luider J, Brown C, Selinger S *et al*. Factors influencing yields of progenitor cells for allogeneic transplantation: optimization of G-CSF dose, day of collection, and duration of leukapheresis. *J Hematother* 1997; **6**: 575–580.
18 Lane TA, Law P, Maruyama M *et al*. Harvesting and enrichment of hematopoietic progenitor cells mobilized into the peripheral blood of normal donors by granulocyte–macrophage colony-stimulating factor (GM-CSF) or G-CSF: potential role in allogeneic marrow transplantation. *Blood* 1995; **85**: 275–282.
19 Vij R, Brown RA, Adkins D *et al*. Mobilization of normal donors with G-CSF + GM-CSF is associated with improved yield of hematopoietic progenitors and increased numbers of activated dendritic cells (abstract). *Blood* 1998; **92**: 682a.
20 Parkkali T, Volin L, Siren MK *et al*. Acute iritis induced by granulocyte colony-stimulating factor used for mobilization in a volunteer unrelated peripheral blood progenitor cell donor. *Bone Marrow Transplant* 1996; **17**: 433–434.
21 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.