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Original Article

Second donation from volunteer hematopoietic stem cell donors in Taiwan

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ABSTRACT

Objectives: Unrelated hematopoietic stem cell donors may donate twice. We studied donors' preference for peripheral blood stem cell (PBSC) collection or bone marrow (BM) harvest and compared the yields of and side effects associated with two BM harvests.
Materials and Methods: The psychosocial and physical experience of 13 donors who underwent two different stem cell collection procedures and their preferences were collected via a self-reported questionnaire. Among four donors who underwent two BM harvests, we compared the yields of and the side effects associated with the first and second harvest via chart review and self-reported questionnaire, respectively.
Results: The median recovery time associated with PBSC (1 day) was significantly shorter than that associated with BM harvest (7 days) ($p < 0.01$). Although most of the donors who underwent both procedures felt that BM harvest was more physically demanding, caused more preprocedural anxiety, was more time consuming, and was more inconvenient than PBSC collection, 63.6% of them preferred BM donation. This preference for BM harvest over PBSC collection is different from previous studies. There was no significant difference in the yields of marrow nucleated cells ($p = 0.25$) and no significant differences in the incidence of side effects and recovery time between the first and second BM donations.
Conclusion: Further understanding of donors' preferences and reducing side effects associated with stem cell harvesting procedures will help the registry improve its work.

1. Introduction

The source of hematopoietic stem cells (HSCs) used for allogeneic transplantation has diversified over time. There are now three choices, bone marrow (BM) HSC, peripheral blood stem cells (PBSCs), and cord blood. They seem to have similar transplant outcomes although the usage varies according to recipient's age, weight, and disease and donor's preference. Recently, PBSC has been increasingly used as the source of HSCs because of convenience of collection, higher stem cell doses with faster engraftment, and a potentially better graft versus leukemia effect. The National Marrow Donor Program of the United States reported that PBSC comprised 72% of all stem cell donations in 2007 [1]. Although PBSC collection is generally considered safer than BM harvest for adult donors, there are still many complications of granulocyte-colony stimulating factor (G-CSF)-mobilized PBSC harvest, including G-CSF-related side effects, vessel access-related disorders, and apheresis-related illness. However, it is difficult to compare these two stem cell collection procedures according to different donors' experience. There is little discussion comparing BM and PBSC donations from the donors' psychosocial experiences.

A second donation from the same donor is requested in cases of graft failure, a decrease in donor chimerism, or disease relapse. The impact of a second HSC donation on the harvest yields and side effects has not been well addressed. In this study, we evaluated the impact of stem cell donations on a cohort of donors who donated HSCs at least twice either by BM harvest, PBSC collection, or both. Data on the psychosocial implications and side effects were gathered via a self-reported questionnaire. We also evaluated the yields of and side effects associated with two BM harvests.

Conflict of interest: none.

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2. Materials and methods

2.1. Institutional policy

According to our regulations for HSC donation, a single donor can make no more than three donations, including BM stem cells, PBSC, and lymphocytes. Donors are limited to one G-CSF-mobilized PBSC donation because of safety concerns with G-CSF. The method by which the HSC were harvested for the second donation was based both on the donor's preference and our regulations on donation.

2.2. Donors and procedures

Consecutive unrelated donors who had made more than one donation of stem cells at Buddhist Tzu-Chi Stem Cell Center (BTCSCC) from May 1994 to May 2009 were enrolled in this study. A total of 17 of the 1738 volunteer donors underwent second HSC donations. The harvests were performed by a standard operating procedure at two hospitals affiliated with the Buddhist Compassion Relief Tzu-Chi foundation. Informed consent was obtained from every donor before the procedure. This study was approved by the Institutional Review Board of our hospital.

2.3. BM harvest

The BM harvest procedure was performed as in our previous report [2]. Under general anesthesia, marrow was collected from the bilateral posterior iliac crests using a single-hole needle technique before March 2002 and a multiple-hole aspiration needle after March 2002. The targeted volume of BM collection was 20 mL/kg of the recipient's body weight. All BM donors were hospitalized for 2 days.

2.4. PBSC harvest

G-CSF (filgrastim, Kirin Brewery Co, Tokyo, Japan) 10 μg/kg/d was administered subcutaneously on a daily basis for 5 days at local clinics to mobilize circulating stem cells [3]. Vascular access was obtained via either two antecubital veins with 16–18 gauge catheters or one antecubital vein with a 16–18 gauge catheter plus one radial artery with a 20 gauge catheter. Generally, venous catheterization was the first choice. If two venous accesses were difficult to obtain (according to the evaluation of a physician or after more than three attempts), an arterial access was then performed. If peripheral vessel access was very difficult, a central venous catheter was placed via the femoral vein. The processed blood volume was based on the recipient's body weight as follows: 12 L for recipients weighing less than 35 kg, 15 L for those weighing from 35 kg to 45 kg, and 18 L for recipients weighing more than 45 kg. Large volume leukapheresis was used using a continuous-flow cell separator (Cobe Spectra, Cobe Laboratories, Denver, CO) at a flow rate of 40–60/min. If the $CD34^+$ cell dose was less than 5×10^6/kg of the recipient weight, a second collection with 6 L of blood was performed the morning of the following day. All PBSC donors spent 1 day in the hospital.

Donor characteristics, reasons for and type of second HSC donation, and the yields from BM harvest were abstracted from the medical records. Donors who underwent two different HSC collection procedures (BM and PBSC) were given a 10-item questionnaire comparing differences in the side effects and recovery time between the two procedures, the level of inconvenience associated with the two procedures, and their preference for one procedure over the other. The questionnaire is illustrated in Table 1. Donors who underwent two BM harvests were given a questionnaire comparing the side effects and recovery time between the first and the second procedure. The side effects, including bone pain, fatigue, headache, dizziness, vomiting, and difficulty walking, were graded as none, mild, moderate, or severe. Both questionnaires also contained two psychosocial questions; "Was it difficult for you to make the decision to donate a second time?" and "Did any of your family members or friends disapprove of your decision to donate a second time?" Cover letters explaining the study, consent forms, and questionnaires were delivered to donors via volunteers of the BTCSCC Donor Care Group. All donors agreed to participate in the study and returned the questionnaire.

Table 1
Questionnaire for donors experiencing both BM and PBSC harvest

Questionnaire
First, which type of donation was physically more difficult?
Second, which type of donation made you more nervous prior procedure?
Third, which type of donation spent more of your time?
Fourth, which type of donation was more convenient?
Fifth, if you are ask to donate again, which type of donation would be your first choice and why?
Sixth, if your family member was requested to donate hematopoietic stem cell, which method would you recommend?
Seventh, was there any headache, lower back pain, hip pain, pain at puncture sites, pain in other site, difficult walking, fatigue, or other side effect related to the donation?
Eighth, how long did them take to recovery?
Ninth, was it hard for you to make the decision of doing second donation?
Tenth, were there any family member or friend against you doing second donation?

BM = bone marrow; PBSC = peripheral blood stem cell.

2.5. Statistics

The side effects associated with BM and PBSC harvest were compared by the χ^2 test. The yields of the two BM harvests were compared using the Wilcoxon test. A p value less than 0.05% was considered significant.

3. Results

3.1. Donor characteristics

A total of 17 of the 1738 unrelated donors (0.98%) underwent second stem cell donations. The first procedures included BM harvest in 12 donors and PBSC collection in 5 donors. Among these 17 donors, 4 underwent two BM harvests and 13 underwent one BM harvest and one PBSC collection. In addition, 5 of the 17 donors donated the second collection of HSC to different recipients and the other 12 donors donated to the same patient on both occasions. The indications for the second donation from these 12 donors were graft failure (5 of 12; 41.7 %) and disease relapse (7 of 12; 58.3%). Among the five patients with graft failure, two had severe aplastic anemia, one had chronic myeloid leukemia, one had acute myeloid leukemia, and one had non-Hodgkin's lymphoma. Disease relapse occurred in four patients with acute lymphoblastic leukemia, two patients with acute myeloid leukemia, and one with non-Hodgkin's lymphoma. The 13 donors who experienced one BM harvest and one PBSC collection were followed up annually with hemograms, biochemistry, and assessment of relevant health condition after PBSC donation and all were physically well. The four donors who experienced two BM harvests were followed up annually with hemograms, biochemistry, and assessment of relevant health condition for 3 years and they were all well.

3.2. Psychosocial and physical experience of donors who underwent two stem cell donations

The side effects and recovery time among the 13 donors who underwent a BM harvest procedure and a PBSC collection are

Table 2
Side effects of BM versus PBSC donation from the experience of donors who had donated both ($n = 13$)

Side effects	Percentage	p
Headache		
BM	0	0.42
PB	23.1	
Fatigue		
BM	46.2	0.18
PB	84.6	
Bone pain		
BM	69.2	0.12
PB	46.2	
Dizziness		
BM	23.1	0.5
PB	30.8	
Insomnia		
BM	N/A	N/A
PB	7.7	
Vomiting		
BM	0	N/A
PB	0	
Difficulty in walking		
BM	38.5	N/A
PB	N/A	
Median recovery time (d)		
BM	7	<0.01
PB	1	

BM = bone marrow; N/A = not available; PBSC = peripheral blood stem cell.

summarized in Table 2. There were no significant differences in incidence of headache, fatigue, bone pain, dizziness, or vomiting between the two procedures. The median recovery time, however, was significantly shorter for PBSC collection than for BM harvest (1 day *vs.* 7 days, $p < 0.01$). Although most of these donors reported that BM harvest was more physically demanding, caused more pre-procedural anxiety, was more time consuming, and was more inconvenient than PBSC collection, 63.6 % (7/11) donors reported that they would choose the BM harvest if they were asked to donate one more time. The detailed preferences and reasons of these 13 donors are illustrated in Table 3. Three donors (numbers 6, 12, and 13) reported that they preferred BM harvest because it was simple and rapid, and there was less pain during general anesthesia. Four female donors (number 4, 5, 7, and 10) complained of discomfort during placement of vascular access and PBSC apheresis. Three of these four female donors weighed only 53 kg, 48 kg, and 47 kg and peripheral vessel access was attempted 8, 8, and 10 times, respectively.

In contrast to the donor's preference, 53.8% (7/13) donors reported that they would recommend PBSC donation to their relatives or friends when they wanted to donate HSC. Donors 2 and 9 followed the request of the transplant center when they were asked for subsequent donations but they recommended PBSC for their relative or friends' donations. Number 7 donor thought BM harvest was tolerable for her but probably would not be tolerable for others, and therefore she recommended PBSC to others.

One-third (5/15) of the donors had difficulty before they donated HSC for the second time. Ten of the 17 donors who underwent two HSC donations encountered discouragement from relatives or friends.

3.3. Two BM harvests

There were no significant differences in the yields between the first and second BM harvests ($p = 0.25$). There were also no differences in side effects or recovery time between the first and second BM harvests. The donor characteristics and BM yields are summarized in Table 4. The median time interval between the first and second BM donations was 1.6 years (0.4–3.2 years).

4. Discussion

In Taiwan, the BTCSCC opened in 1993 and is now one of the most active HSC registries in Asia. We performed the first unrelated BM harvest in May 1994 and the first G-CSF-mobilized PBSC was collected in August 2003. There are 320,000 potential HSC volunteer donors in the registry of the BTCSCC, and since its establishment, more than 1100 BM harvests and more than 700 PBSC collections have been performed (latest update May 2009). The goal of our stem cell registry is to ensure that stem cells are safely collected with a sufficient number of progenitor cells. So, this study aimed to compare the experiences of donors who underwent both BM and PBSC. The harvest outcomes of two BM donations were also analyzed.

BM harvest is associated with anesthesia- and transfusion-related risks as well as operative complications, such as wound pain and infections. PBSC collections are associated with G-CSF-related side effects and problems with apheresis procedures, such as difficult vascular access and citrate toxicity. The side effects of G-CSF injection include bone pain, fatigue, headache, insomnia, and other flu-like symptoms. However, these symptoms are mostly transient and tolerable. The long-term effects of G-CSF in individuals have not been studied completely; therefore, donors are permitted to undergo a PBSC collection only once in a lifetime according to our present regulations. The maximum number of PBSC donations

Table 3
The preference type of donation in 13 donors experiencing both BM and PBSC donations

Donor	Type of first donation	Time of first donation	Interval between two donations (mo)	Gender/age (yr)	BW (kg)	Personal preference	Reason for personal preference	Recommend type for relatives or friends
1	PBSC	Aug 2006	5	M/29	70	PBSC	N/A	PBSC
2	PBSC	Mar 2007	2	F/44	62	N/A	As request by transplant center	PBSC
3	PBSC	Oct 2006	11	M/28	68	PBSC	PBSC: rapid recovery	PBSC
4	PBSC	Sep 2007	20	F/38	53	BM	Discomfort during PBSC procedure	BM
5	PBSC	Jan 2005	9	F/24	48	BM	Discomfort during PBSC procedure	BM
6	BM	Nov 2003	17	F/48	48	BM	BM: simple, rapid, painless during anesthesia	BM
7	BM	Oct 2004	11	F/31	47	BM	Discomfort during PBSC procedure	PBSC
8	BM	Oct 2003	32	M/29	55	PBSC	PBSC: rapid recovery	PBSC
9	BM	Apr 2003	40	F/28	48	N/A	As request by transplant center	PBSC
10	BM	Nov 2001	60	F/42	60	BM	Discomfort during PBSC procedure	BM
11	BM	Sep 2002	67	F/31	104	PBSC	PBSC: rapid recovery	PBSC
12	BM	Aug 2007	13	M/27	65	BM	BM: simple, rapid, painless during anesthesia	BM
13	BM	Mar 2009	1	M/28	86	BM	BM: simple, rapid, painless during anesthesia	BM

BM = bone marrow; BW = body weight; N/A = not available; PBSC = peripheral blood stem cell.

Table 4
Donor characteristics and BM yields of 4 donors with twice BM harvest

Donor	TNC 1 ($\times 10^8$)	TNC 2 ($\times 10^8$)	V 1(mL)	V 2(mL)	Density 1 ($\times 10^8$/mL)	Density 2 ($\times 10^8$/mL)	Age 1	BH 1	BW 1	Interval (mo)
1, male	276	353	1040	1004	0.2654	0.3516	41	165	78	17
2, male	134	157.5	1084	985	0.1236	0.1599	25	172	70	5
3, male	131	151	1043	1035	0.1256	0.1459	20	172	54	22
4, male	207	195	1013	1038	0.2043	0.1879	33	171	76	38
Median	170.5	176.2	1041	1019	0.165	0.174				
p	0.25		0.38		0.25					

1 = first harvest; 2 = second harvest; BH = body height; BW = body weight; density = TNC/volume; TNC = total nucleated cell; V = harvest volume.

allowed by international stem cell registries varies. The British Bone Marrow Registry, Anthony Nolan Trust, and Spanish National Donor Registry allow donors to donate PBSC twice.

In our study, the most common self-reported side effects of BM harvest were bone pain (69.2%), fatigue (46.2%), and difficulty in walking (38.5%). The most common side effects of PBSC were fatigue (84.6%), bone pain (46.2%), dizziness (30.8%), and headache (23.1%). Karlsson et al [4] reported that 85% of BM donors experienced moderate or severe pain compared with 68% of PBSC donors, and 49% of BM donors experienced severe fatigue compared with 16% of PBSC donors. Their findings that bone pain occurred more frequently after BM harvest than after PBSC collection were similar to our study. However, in our study, fatigue occurred more frequently among PBSC donors than among those who underwent BM harvest, which was different from other studies [4,5].

In 2001, Switzer et al [5] studied the psychosocial and physical experiences of donors who underwent PBCS after having undergone a BM harvest. They showed the BM procedure was physically demanding, time-consuming, and inconvenient and that only 20% of donors (5 of 25) preferred BM harvest to PBSC donation. Another study in 1996 demonstrated similar findings. Among 13 family donors who subsequently donated BM and PBSCs, only one donor preferred BM harvest to PBSC collection [6]. In contrast to these studies, 63.6% (7 of 11) of our donors preferred BM harvest. Three donors reported that they liked the rapidity and simplicity of the BM harvest procedure and they experienced less discomfort during harvest with general anesthesia. Four female donors disliked the side effects during PBSC apheresis, which may have been related to the discomfort caused by the establishment of vascular access and problems with large volume apheresis. In our observations, female donors did have higher rates of adverse events with PBSC collection, which is consistent with the findings reported by Pulsipher et al [7]. The preference difference between our study and others might be related to the discomforts of our PBSC collection. To decrease the number of vascular access trials, fixed experienced medical staff have performed the placement of vascular access in the past 2 years. Since November 2007, calcium gluconate supplementation has been administered concomitantly during apheresis to reduce citrate toxicity. In July 2009, we set up maximum processing blood volumes for the first day according to the donor's weight to avoid discomfort associated with large volume apheresis for donors with low body weights. In addition to discomfort from our PBSC procedure, the small case numbers and social or cultural differences between Taiwan and Western countries may also have contributed to this different preference. We need further larger case numbers and comprehensive studies to elucidate the reasons.

Switzer et al [5] reported that 79% of donors did not have difficulty in making the decision to donate again and only 33% of donors had been discouraged by others. Sixty-six percent of our donors had no difficulty in making the decision to donate HSC for a second time, although 59% of donors had been discouraged by relatives or friends from doing so. Further thorough educational activities in the community may decrease misunderstandings and unrealistic medical concerns regarding the risks of BM or PBSC harvest. Through these endeavors, we hope more donors will have a strong intrinsic commitment to donate HSCs with less disagreement from relatives and friends.

The median time interval between the first and second BM donation for the four donors with two BM harvests was 1.6 years (0.4–3.2 years). There were no significant differences in total nucleated cell yield and marrow cell density between the first and second BM harvest (170.5×10^8 *vs.* 176.2×10^8, $p = 0.25$ and 0.165×10^8/mL *vs.* 0.174×10^8/mL, $p = 0.25$, respectively). There were also no differences in side effects or recovery time between the first and second BM harvests. Although Stroncek et al [8] and Akiyama et al [9] both demonstrated no significant difference in complications in the second BM harvest, the nucleated cell yield was lower. This might be related to the younger age of our donors (median age 29 years old) and the small case number in our study.

Although the case number in this study was relatively small, the preference for BM harvest among donors differs from that reported in previous studies despite similar side effects. Discomforts with our PBSC apheresis procedure could be the reason and should be improved first. We think that decreasing the process volume in low-body weight donors, using skilled medical staff to establish vascular access, and more aggressive supplementation with calcium gluconate may further decrease the adverse events associated with the apheresis procedure in the future. Further understanding of donors' preferences and reducing side effects associated with stem cell harvesting procedures will help the registry improve its work.

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