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Donor Experiences of Second Marrow or Peripheral Blood Stem Cell Collection Mirror the First, but CD34+ Yields Are Less

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A B S T R A C T

Little is known about the experiences of individuals donating peripheral blood stem cells (PBSCs) or marrow for a second time. To study this, unrelated donors making a second donation through the National Marrow Donor Program between 2004 and 2013 were evaluated. Experiences of second-time donors giving marrow (n = 118: first donation was PBSC in 76 and marrow in 42) were compared with those making only 1 marrow donation (n = 5829). Experiences of second-time donors giving PBSCs (n = 602) (first donation was PBSCs in 362; marrow in 240) were compared to first-time PBSC donors (n = 16,095). For donors giving a second PBSC or marrow donation there were no significant differences in maximum skeletal pain, maximum symptoms measured by an established modified toxicity criteria, and recovery time compared with those who donated only once. Notably, the yield of marrow nucleated cells and PBSC $CD34^+$ cells with second donations was less. As previously noted with single first-time donations, female (PBSCs and marrow) and obese donors (PBSCs) had higher skeletal pain and/or toxicity with a second donation. PBSC donors who experienced high levels of pain or toxicity with the first donation also experienced high levels of these symptoms with their second donation and slower recovery times. In conclusion, for most donors second donation experiences were similar to first donation experiences, but $CD34^+$ yields were less. Knowledge of the donor's first experience and stem cell yields may help centers decide whether second donations are appropriate and institute measures to improve donor experiences.

INTRODUCTION

Most hematopoietic stem cell transplants involving HLA-compatible related and unrelated donors using marrow or peripheral blood stem cells (PBSCs) result in engraftment and require a single donation procedure. However, some donors are asked to donate a second time to treat graft failure or disease relapse in the same recipient or to treat another recipient [1]. The effects of a single anesthetic exposure and marrow collection or single granulocyte colony-stimulating factor (G-CSF) mobilization and an apheresis procedure for PBSC donation on symptoms, complications, and time to recovery have been well documented [2-5], but less is known about the effects of a second marrow or PBSC donation on the donor experience and collection yield [6-9].

The donation of marrow or G-CSF–mobilized PBSCs by healthy subjects is commonly associated with mild to moderate pain and other symptoms, less commonly with complications, and rarely with severe adverse events [2,10-19]. Marrow donation involves the aspiration of up to 20 mL/kg of marrow from the posterior iliac crests while the donor is under general or regional anesthesia. After donation marrow donors experience pain in the hips and back [10]. Pain related to anesthesia is also common, with approximately one-third reporting throat pain and one-sixth experiencing headaches [10]. Marrow donors also experience fatigue, insomnia, nausea, and dizziness [10].

When healthy subjects are given 5 days of G-CSF to mobilize hematopoietic stem cells before apheresis, they frequently experience headache, bone pain, myalgia, nausea, and insomnia [2,10,11,13]. Generally, these symptoms are mild and disappear within a few days of the collection [11,13], but up to 10% experience severe or intolerable pain [2]. During the collection of PBSCs healthy subjects can experience citrate toxicity, thrombocytopenia, bleeding. or hematoma at i.v. line insertion sites [2,10].

In comparison with first donations, less is known about second marrow and PBSC donations. Studies of healthy subjects who have donated PBSCs twice have noted that when the first and second donations are separated by more than 3 months, the preapheresis concentration of $CD34^+$ cells and mononuclear cells and collections yield for second donations are similar or slightly less than first donations [6-9]. However, donor symptoms and adverse events associated with second PBSC donations have not been investigated. Even less is known about second marrow donations.

This study sought to explore donor symptoms, adverse events, and collection yields of second donations by National Marrow Donor Program (NMDP) donors. It compared second donations with a larger cohort of individuals donating only once and then assessed with multivariate analysis factors that may be associated with different outcomes in those giving second donations.

METHODS

Study Population

NMDP donors between 2004 and 2013 who donated marrow or PBSCs once were compared with those who donated either product twice. Donors who made 3 donations, who donated at international centers, or who received G-CSF and then donated bone marrow were excluded. All donors included in this study provided written informed consent for participation in Center for International Blood and Marrow Transplant Research studies that were approved by the NMDP Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki.

Marrow Donation

Marrow was collected in an operating room from the posterior iliac crests under general or regional anesthesia following NMDP standards. NMDP standards require that no more than 20 mL/kg (donor weight) of marrow to be aspirated, the duration of anesthesia should not exceed 150 minutes, and the duration of the collection should be less than 120 minutes [4].

PBSC Donation

All PBSC collections were performed according to the NMDP-sponsored and Institutional Review Board–approved protocols for the manufacture of PBSC products, operated under an investigational new drug application with the US Food and Drug Administration. Collection of the G-CSF–mobilized PBSCs has been described previously [4]. Briefly, G-CSF was administered subcutaneously for 4 to 5 days at a dose of approximately 10 μg/kg (donor weight) each day. PBSCs were collected by apheresis over 1 or 2 days. The volume of whole blood processed by the apheresis procedure was targeted to be between 12 and 24 L. The total volume of whole blood processed, whether the PBSCs were collected over 1 or 2 days, was limited to 24 L. When PBSCs could not be collected using peripheral veins, a central venous catheter was used.

Data Collection

Data collection began at the time of the donor's medical evaluation to determine suitability to donate hematopoietic stem cells and continued throughout the time of donation and long term as described below. Both marrow and PBSC donors were contacted by the donor center at 2 days after donation, then at 1 week, and weekly thereafter until complete recovery. "Complete recovery" was judged by the donor center coordinator or medical director based on reports of return to baseline and no ongoing symptoms associated with the collection procedure as ascertained by the weekly follow-up call with the donor. Further contact with the donor occurred at 1 month, 6 months, and annually to assess for the presence of any new or residual symptoms. Detailed questions using the toxicity criteria modeled on National Cancer Institute's Common Terminology Criteria for Adverse Events

were used to assess specific symptoms commonly associated with donation (for list of symptoms see Endpoints, below) and to capture any toxicity the donor may have experienced as a result of the hematopoietic stem cell donation process. In addition, a complete blood count and WBC differential were performed at the initial medical evaluation, on the first day of G-CSF, the day(s) of collection, and, for some donors, at annual follow-ups.

Endpoints

The primary objective of this study was to compare symptoms, adverse events, and collection yields related to the first and second PBSC and marrow donation. The following endpoints were analyzed in multivariate models: incidence of grades 2 to 4 skeletal pain, fatigue, and highest toxicity level across selected body symptoms frequently associated with collection (fever in the absence of infection, fatigue, skin rash, local reactions, nausea, vomiting, anorexia, insomnia, dizziness, and syncope). Skeletal pain was defined as pain in at least 1 of the following sites: back, bone, headache, hip, limb, joint, or neck. The severity of skeletal pain was defined as the maximum grade among these pain sites. Endpoints were analyzed at the following time points: the day with the highest level of toxicity (day +6 from start of G-CSF for PBSCs and first assessment after marrow collection, 1 to 2 days after collection) and at 1 week and 1 month after donation. Time to recovery from donation was defined as the time in days from the marrow collection or first day of PBSC collection to report of complete recovery as defined herein.

Statistical Methods

Comparison of second donation experiences with those donating once

The number of apheresis procedures, incidence of adverse events, presence of long-term pain or disability, and occurrence of grades 2 to 4 or 3 to 4 peak toxicity using the modified toxicity criteria (MTC) were compared between first and second donation using chi-square tests. The volume of blood collected and collection yields per liter of blood processed were compared using the Kruskal-Wallis test. The time to complete recovery from donation was compared using the log-rank test. Linear, logistic, or Cox regression analyses depending on the outcome variable was used to adjust for differences in donor characteristics (age, sex, body mass index [BMI], and race).

First donation variables as risk factors for second donation outcome

First donation outcomes were used as covariates in the linear, logistic, or Cox regression models to determine if they are associated with better or worse second donation outcomes. These covariates were only applied to the group where donors donated twice.

RESULTS

Second Donations

Second donation experiences were studied in 720 donors who first donated between 2004 and 2013. Two groups were studied: 1 whose second donation was marrow and 1 whose second donation was PBSCs. Second marrow donation experiences for 118 unrelated donors were compared with the donation experiences of 5829 unrelated donors who donated marrow once. Among those whose second donation was marrow, in 76 the first donation was PBSCs (PBSC-marrow) and in 42 it was marrow (marrow-marrow). The second PBSC donation experience for 602 unrelated donors was compared with the donation experiences of 16,095 unrelated donors who donated PBSCs once. Among the 602 donors for whom the second donation was PBSCs, the first donation was marrow for 240 (marrow-PBSC) and PBSCs for 362 (PBSC-PBSC).

Among those whose second donation was marrow, those whose first donation was marrow more often donated to the same person than those whose first donation was PBSCs (69% versus 46%, $P < .016$). The time between donations was less for PBSC-marrow donors than for marrow-marrow donors (median, 1.3 months [range, .1 to 24.8] versus 7.8 months [range, 1.6 to 39.6]; $P < .001$). For those whose second donation was PBSCs, donors whose first donation was marrow were also more likely to donate for the same person than those whose first donation was PBSCs (85% versus 68%, $P < .001$). The time between donations was less for marrow-PBSC donors than for PBSC-PBSC donors (median, 4.3 months [range, .4 to 78.1] versus 6.1 months [range, .3 to 52.1]; $P < .001$).

Second Donor Demographics

There were no significant differences among characteristics of single and 2-time donation populations except that people whose second donation was PBSCs were significantly older at the time of the first donation than those who donated PBSCs once (Table 1). However, there was no difference in age at the time of the second donation among marrow-PBSC and PBSC-PBSC donors (data not shown).

Second Donation Timing

The year of first donation by those whose second donation was marrow was more likely to occur earlier in the study period than donations by people donating marrow once, but there was no difference in the time of the last donation among marrow-marrow and PBSC-marrow donors (Table 1). There were also significant differences in the year of donation by those whose second donation was PBSCs and the year of donation for people donating PBSCs only once (Table 1). The first donation by those whose second donation was PBSCs was more likely to occur early in the study period than donations by people donating PBSCs once. The year of last donation for PBSC-PBSC donors was more likely to occur later in the study period than for marrow-PBSC donors (Table 1).

Second Marrow Collection Procedures and Yields

The duration of anesthesia for first donations by marrow-marrow donors was less than that of marrow donor who only donated once (Table 2). There was no difference in duration of anesthesia for second marrow donations by marrow-marrow and PBSC-marrow donors compared with those who donated marrow only once (Table 2). For all groups more than 95% of donations involved the use of general anesthesia, and there was no difference in anesthesia type among groups (data not shown).

The quantity of marrow collected was assessed by measuring its volume and total nucleated cell content. The volume of marrow collected, volume collected per kilogram of donor weight, and quantity of total nucleated cells for marrow donors who only donated once were significantly higher than that of the first collections for marrow-marrow donors (Table 2). There was a difference in total volume of marrow collected, volume collected per kilogram donor weight, and quantity of total nucleated cells for those who donated marrow once and the last donation by marrow-marrow and PBSC-marrow donors (Table 2).

Second PBSC Collection Procedures and Yields

The collection procedures for second donations that were PBSCs were similar to procedures by those who donated PBSCs once, except the $CD34^+$ cell yields of the second PBSC donations was less than the yields from those who donated only once (Table 3). There was no difference in G-CSF dose, need for a 2-day collection procedure, and the use of a central venous collection catheter between the first donation values of PBSC-PBSC donors and those who donated PBSCs once and among second PBSC donations for PBSC-PBSC and marrow-PBSC donors (Table 3).

There was no difference in the volume of whole blood processed during the collection for the first donation by PBSC-PBSC donors and those who donated PBSCs once (Table 3). However, the volume of whole blood processed during the PBSC collection was less for the last donation by PBSC-PBSC

Table 1
Characteristics of Donors Who Donated PBSCs and Marrow Between 2004 and 2013 by Products Donated

	PBSC	Marrow-PBSC	PBSC-PBSC		Marrow	PBSC-Marrow	Marrow-Marrow	
Variable	N (%)	N (%)	N (%)	P*	N (%)	N (%)	N (%)	P*
Number of donors	16,095	240	362		5829	76	42	
Sex				.434				.588
Female	5942 (37)	84 (35)	123 (34)		2291 (39)	27 (36)	14 (33)	
Male	10,151 (63)	156 (65)	239 (66)		3538 (61)	49 (64)	28 (67)	
Unknown	2 (N/A)	0 (N/A)	0 (N/A)					
Race				.403				.947
White	11,932 (74)	170 (71)	273 (75)		3916 (67)	55 (72)	31 (74)	
Hispanic	1383 (9)	27 (11)	35 (10)		697 (12)	9 (12)	3 (7)	
African/African American	680 (4)	12 (5)	18 (5)		395 (5)	3 (4)	3 (7)	
Asian/Pacific Islander	824 (5)	13 (5)	11 (3)		318 (5)	5 (7)	2 (5)	
Native American	146 (1)	4 (2)	5 (1)		67 (1)	0	1 (2)	
Multiple races/other	1012 (6)	11 (5)	19 (5)		391 (7)	4 (5)	2 (5)	
Unknown/declined	118 (1)	3 (1)	1 (<1)		45 (1)	0	0	
Age at donation, first donation				.009				.063
18-29 yr	6599 (41)	77 (32)	139 (38)		2371 (41)	28 (37)	12 (29)	
30-39 yr	4602 (29)	75 (31)	94 (26)		1760 (30)	23 (30)	19 (45)	
40-49 yr	3425 (21)	69 (29)	86 (24)		1269 (22)	15 (20)	11 (26)	
≥50 yr	1466 (9)	19 (8)	43 (12)		428 (7)	10 (13)	0	
Unknown	3 (N/A)	0 (N/A)	0 (N/A)		1 (N/A)	0 (N/A)	0 (N/A)	
Median (range)	33 (18-61)	35 (20-60)	34 (19-61)	.012	33 (19-61)	34 (20-58)	34 (20-49)	.603
BMI, kg/m^2, first donation				.887				.791
Underweight, <18.5	110 (1)	1 (<1)	2 (1)		30 (1)	0	0	
Normal, 18.5-24.9	5147 (32)	74 (32)	104 (29)		1837 (32)	29 (38)	12 (31)	
Overweight, 25-29.9	6148 (38)	87 (38)	148 (41)		2162 (38)	30 (39)	16 (41)	
Obese, 30 +	4684 (29)	70 (30)	108 (30)		1715 (30)	17 (22)	11 (28)	
Unknown	6 (N/A)	8 (N/A)	0 (N/A)		85 (N/A)	0 (N/A)	3 (N/A)	
BMI, kg/m^2, second donation				.370				.489
Underweight, <18.5	(N/A)	2 (1)	0		(N/A)	0	0	
Normal, 18.5-24.9	(N/A)	71 (30)	106 (30)		(N/A)	27 (36)	12 (29)	
Overweight, 25-29.9	(N/A)	90 (38)	141 (39)		(N/A)	24 (32)	18 (43)	
Obese, 30	(N/A)	77 (32)	112 (31)		(N/A)	24 (32)	12 (29)	
Unknown	(N/A)	0 (N/A)	3 (N/A)		(N/A)	1 (N/A)	0 (N/A)	
Year of donation, first donation				<.001				<.001
2004-2007	4309 (27)	123 (51)	163 (45)		1910 (33)	35 (46)	24 (57)	
2008-2010	4920 (31)	61 (25)	127 (35)		1682 (29)	21 (28)	14 (33)	
2011-2013	6866 (43)	56 (23)	72 (20)		2237 (38)	20 (26)	4 (10)	
Year of donation, last donation				<.001				.132
2004-2007	4309 (27)	88 (37)	80 (22)		1910 (33)	18 (24)	13 (31)	
2008-2010	4920 (31)	72 (30)	141 (39)		1682 (29)	21 (28)	17 (40)	
2011-2013	6866 (43)	80 (33)	141 (39)		2237 (38)	37 (49)	12 (29)	

* The Pearson chi-square test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables.

and marrow-PBSC donors than for those who donated PBSCs once.

PBSC collection yields expressed as total CD34$^+$ cells collected, CD34$^+$ cells/L of blood processed during apheresis, and CD34$^+$ cells/kg of donor weight were significantly higher for PBSC donors who only donated once compared with those whose second donation was PBSCs and first donations by PBSC-PBSC donors (Table 3). A pairwise comparison of first and second PBSC collection yields for PBSC-PBSC donors revealed that individual donors' second collections generally had lower numbers of CD34$^+$ cells as measured by total CD34$^+$ cells collected (mean, -49.091×10^6; $P = .011$, n = 307), CD34$^+$ cells/L of whole blood processed (mean, -2.473×10^6/L; $P = .007$), and CD34$^+$ cells/kg donor weight (mean, $-.676 \times 10^6$/kg; $P = .004$).

Donor Pain, Symptoms, and Time to Recovery

Second marrow donations

For those whose second donation was marrow, there was no difference in maximum skeletal pain at day 2 (Figure 1A), maximum MTC (Figure 1B), and time to recovery to baseline (Figure 2) compared with those who donated marrow once. Multivariate analysis found that maximum skeletal pain (grades 2 to 4) at day 2 was dependent on sex and race, whereas time to recovery to baseline was dependent on sex and age (Table 4). Male donors experienced less skeletal pain than female donors, and time for recovery was shorter for males than for females.

Second PBSC donations

For donors whose second donation was PBSCs, there were no significant differences in maximum skeletal pain (grades 2 to 4) (Figure 3A), maximum MTC (grades 2 to 4) (Figure 3B), and time to complete recovery (Figure 4) compared with donors who donated PBSCs once. For those whose second procedure was PBSCs, multivariate analysis found that maximum MTC (grades 2 to 4) at collection was dependent on donor group, sex, race, age, collection year, and BMI but not on whether the collection was the second procedure (Table 5). When the second donation was PBSCs, female donors experienced lower maximum MTC grades 2 to 4 symptoms than females who made 1 PBSC donation, whereas male donors experienced more maximum MTC grades 2 to 4 symptoms than males donating PBSC only once.

Maximum skeletal pain (grades 2-4) at collection was dependent on sex, age, and BMI (Table 5). Males experienced less skeletal pain than females during second PBSC donations (odds ratio [OR], .59; $P < .001$).

Table 2
Marrow Collection Procedures and Yields

Variable	Marrow N (%)	PBSC-Marrow N (%)	Marrow-Marrow N (%)	P*
Number of donors	5829	76	42	
Duration of anesthesia, min, first collection				
No. evaluated	5706	0	39	
<60 min	626 (11)	(N/A)	12 (31)	<.001
<120 min	4548 (80)	(N/A)	35 (90)	.120
<150 min, NMDP recommendation	5295 (93)	(N/A)	38 (97)	.263
<200 min	5646 (99)	(N/A)	39 (100)	.520
Median (range)	90 (25-355)	(N/A)	71 (50-198)	<.001
Duration of anesthesia, min, last collection				
No. evaluated	5706	76	42	
<60 min	626 (11)	12 (16)	7 (17)	.211
<120 min	4548 (80)	59 (78)	36 (86)	.566
<150 min, NMDP recommendation	5295 (93)	71 (93)	39 (93)	.978
<200 min	5646 (99)	75 (99)	41 (98)	.689
Median (range)	90 (25-355)	86 (36-210)	87 (42-246)	.341
Collection volume, first donation				.041
<1 L	2516 (44)	(N/A)	25 (64)	
1-1.5 L	2447 (43)	(N/A)	10 (26)	
≥1.5 L	733 (13)	(N/A)	4 (10)	
Unknown	133 (N/A)	(N/A)	3 (N/A)	
Median (range), in mL	1063.2 (103.0-2323.0)	(N/A)	668.0 (193.0-1921.0)	<.001
Collection volume, last donation				.014
<1 L	2516 (44)	27 (36)	27 (68)	
1-1.5 L	2447 (43)	41 (54)	10 (25)	
≥1.5 L	733 (13)	8 (11)	3 (8)	
Unknown	133 (N/A)	0 (N/A)	2 (N/A)	
Median (range), in mL	1063.2 (103.0-2323.0)	1116.0 (364.0-1780.0)	813.0 (276.0-1648.0)	.010
Collection volume per kg of donor weight, first donation				.005
<10 ml/kg	1700 (30)	(N/A)	22 (56)	
10 to <15 ml/kg	1834 (32)	(N/A)	8 (21)	
15 to <20 ml/kg	1769 (31)	(N/A)	7 (18)	
≥20/kg	375 (7)	(N/A)	2 (5)	
Unknown	151 (N/A)	(N/A)	3 (N/A)	
Median (range)	13.2 (1.2-29.0)	(N/A)	8.5 (2.2-20.5)	<.001
Collection volume per kg of donor weight, last donation				.089
<10 ml/kg	1700 (30)	20 (26)	21 (53)	
10 to <15 ml/kg	1834 (32)	25 (33)	10 (25)	
15 to <20 ml/kg	1769 (31)	27 (36)	7 (18)	
≥20/kg	375 (7)	4 (5)	2 (5)	
Unknown	151 (N/A)	0 (N/A)	2 (N/A)	
Median (range)	13.2 (1.2-29.0)	13.9 (4.2-21.6)	9.7 (3.2-22.6)	.007
Total nucleated cell, $\times 10^8$, first donation				
No. evaluated	2887	0	19	
Median (range)	242 (26-631)	(N/A)	197 (57-408)	.024
Total nucleated cell, $\times 10^8$, last donation				
No. evaluated	2887	40	17	
Median (range)	242 (26-631)	268 (81-545)	133 (62-237)	<.001

* The Pearson chi-square test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables.

During second PBSC donations, obese donors experienced greater maximum skeletal pain (OR, 1.57; $P < .001$) and maximum MTC (grades 2 to 4; OR, 1.56; $P < .001$) than donors who were underweight or had a lean BMI. Older second PBSC donors aged 50 to 59 years experienced less grades 2 to 4 skeletal pain (OR, .61; $P < .001$) and grades 2 to 4 MTC (OR, .85; $P = .021$) than the youngest donors, aged 18 to 29 years.

Time to recovery to baseline was dependent on donor sex, race, age, and collection year (Table 5). For females the time to recovery to baseline after a second PBSC donation was longer than males.

Prognostic factor analysis of PBSC-PBSC and marrow-PBSC donations revealed several important points concerning second PBSC donations (Table 6). There was an increased risk of maximum MTC (grades 2 to 4) or maximum skeletal pain (grades 2 to 4) for the second donation if the first donation was marrow and second was PBSCs. Among second-time PBSC donors high maximum MTC with the first donation predicted high maximum MTC (OR, 3.29; $P < .001$) and skeletal pain (OR, 1.93; $P = .011$) with second donation and longer recovery time (hazard ratio, .76; $P = .009$). High first donation skeletal pain predicted high second donation pain (OR, 2.74; $P < .001$), and slower first PBSC donation recovery predicted slower second donation recovery. An obese BMI predicted high maximum MTC with the second donation (OR, 2.99; $P < .001$). More than 12 months between donations also predicted slower recovery after the second PBSC donation (hazard ratio, .79; $P = .006$).

DISCUSSION

Although rare, approximately 3% of unrelated hematopoietic stem cell donors are asked to donate a second time to the same or a different person. This analysis of NMDP data found that the levels of pain and donation-related symptoms of those donating a second time were similar to first

Table 3
PBSC Collection Procedures and Yields

Variable	PBSC N (%)	Marrow-PBSC N (%)	PBSC-PBSC N (%)	P*
Number of donors	16,095	240	362	
Total G-CSF dose per donor weight, μg/kg, first donation				
No. evaluated	15,892	0	359	
Median (range)	52.9 (26.8-112.1)	(N/A)	52.5 (36.8-63.9)	.174
Total G-CSF dose per donor weight, μg/kg, last donation				
No. evaluated	15,892	233	354	
Median (range)	52.9 (26.8-112.1)	52.7 (34.3-67.6)	52.7 (40.5-68.7)	.435
Two-day collection, first donation				.321
No	13,347 (83)	(N/A)	293 (81)	
Yes	2748 (17)	(N/A)	69 (19)	
Two-day collection, last donation				.134
No	13,347 (83)	207 (86)	311 (86)	
Yes	2748 (17)	33 (14)	51 (14)	
Central line insertion, first donation				.442
No	14,637 (91)	(N/A)	325 (90)	
Yes	1456 (9)	(N/A)	37 (10)	
Unknown	2 (N/A)	(N/A)	0 (N/A)	
Central line insertion, last donation				.204
No	14,637 (91)	211 (88)	325 (90)	
Yes	1456 (9)	29 (12)	37 (10)	
Unknown	2 (N/A)	0 (N/A)	0 (N/A)	
Volume of whole blood processed, first donation				.748
Small, <12 L	407 (3)	(N/A)	11 (3)	
Standard, 12-18 L	3065 (19)	(N/A)	65 (18)	
Large, ≥18 L	12,603 (78)	(N/A)	284 (79)	
Unknown	20 (N/A)	(N/A)	2 (N/A)	
Volume of whole blood processed, last donation				<.001
Small, <12 L	407 (3)	10 (4)	8 (2)	
Standard, 12-18 L	3065 (19)	71 (30)	75 (21)	
Large, ≥18 L	12,603 (78)	158 (66)	279 (77)	
Unknown	20 (N/A)	1 (N/A)	0 (N/A)	
Duration of apheresis in hours (day 5), first donation				
No. evaluated	16,080	0	361	
Median (range)	4.5 (0.3-23.8)	(N/A)	4.6 (2.0-9.8)	.219
Duration of apheresis in hours (day 5), last donation				
No. evaluated	16,080	239	362	
Median (range)	4.5 (.3-23.8)	4.4 (1.7-8.8)	4.6 (2.0-10.3)	.266
$CD34^+$ at collection, $\times 10^6$, first donation				
No. evaluated	14,860	0	313	
Median (range)	657.4 (2.8-6000.0)	(N/A)	577.7 (41.8-2480.0)	.001
$CD34^+$ at collection, $\times 10^6$, last donation				
No. evaluated	14,860	222	342	
Median (range)	657.4 (2.8-6000.0)	526.5 (63.1-4525.4)	543.1 (17.5-2822.7)	<.001
$CD34^+$ at collection per liter of whole blood processed, first donation				
No. evaluated	14,853	0	313	
Median (range)	34.0 (.2-333.3)	(N/A)	30.2 (1.7-114.2)	.002
$CD34^+$ at collection per liter of whole blood processed, last donation				
No. evaluated	14,853	221	342	
Median (range)	34.0 (.2-333.3)	28.9 (2.5-188.6)	27.8 (.7-122.1)	<.001
$CD34^+$ at collection per kg of donor weight, first donation				
No. evaluated	14,860	0	313	
Median (range)	8.0 (.0-89.6)	(N/A)	7.1 (.7-27.2)	<.001
$CD34^+$ at collection per kg of donor weight, last donation				
No. evaluated	14,860	222	342	
Median (range)	8.0 (.0-89.6)	6.7 (1.0-37.2)	6.5 (.2-31.0)	<.001

* The Pearson chi-square test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables.

donation experiences. For second donations that were either marrow or PBSCs, pain, peak MTC, and time to recovery were no different from that of those who donated once. These results provide reassurance that second donations of either marrow or PBSCs do not present an increase in donation-associated risk to unrelated donors.

Second donation factors associated with greater toxicity were similar to those previously identified in donors who only donated marrow or PBSCs once [2,3]. For those whose second donation was PBSCs, grades 2 to 4 maximum skeletal pain and grades 2 to 4 maximum MTC were more likely in younger donors and in those with greater BMIs. For those whose second donation was marrow, grades 2 to 4 maximum skeletal pain was more likely to occur in females. Time to recovery was longer in females and younger donors after second donations for both PBSC and marrow donors.

A previous analysis of 2408 NMDP PBSC donors who donated once found that risk factors for incidence of bone pain on day 4 of G-CSF administration were female sex and obesity [2]. Female donors and very heavy donors experienced higher MTC symptoms during mobilization and donation [2]. A more recent comparison of 2726 NMDP marrow and 6768 PBSC donors who donated once found that for both marrow and PBSC donations, women were more

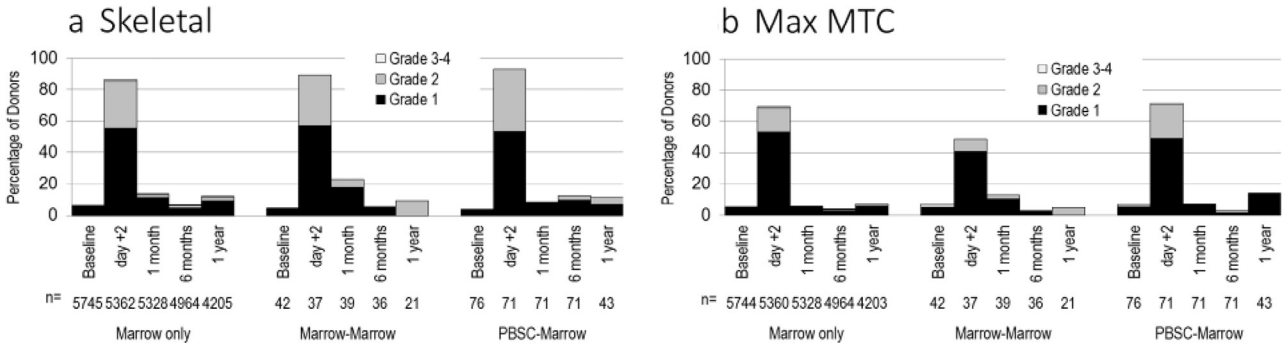

Figure 1. Severity of skeletal pain and maximum MTC for second donations that were marrow. The severity of maximum skeletal pain (A) and maximum MTC (B) scores measured at baseline and at 2 days, 1 month, 6 months, and 1 year postcollection in people who donated marrow once (marrow only), people whose first and second donations were marrow (marrow-marrow), and donors whose first donation was PBSCs and second donation was marrow (PBSC-marrow). Skeletal pain was defined as pain in at least 1 of the following sites: back, bone, headache, hip, limb, joint, and neck. The severity of skeletal pain was defined as the maximum grade among these pain sites. MTC was the highest toxicity level of key symptoms, including fever in the absence of signs of infection, fatigue, skin rash, local reactions, nausea, vomiting, anorexia, insomnia, dizziness, and syncope.

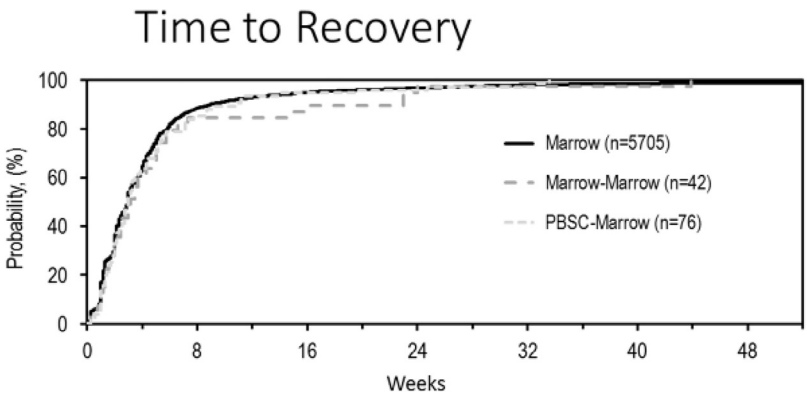

Figure 2. Time to recovery for second donations that were marrow. The proportion of donors who reported recovering to baseline levels at each time postdonation are shown for people who donated marrow once (marrow), people whose first and second donations were marrow (marrow-marrow), and donors whose first donation was PBSCs and second donation was marrow (PBSC-marrow).

Table 4
ORs Comparing Donor Toxicities and Recovery versus Characteristics of Second Donations that Were Marrow with Multivariate Logistic Regression Analysis

	Maximum Skeletal Pain Grades 2-4 at Day 2		Recovery to Baseline	
Variable	OR (95% CI)	*P*	HR (95% CI)	*P*
Group		.315		.573
Marrow	1.00		1.00	
Marrow-marrow	1.07 (.53-2.15)	.851	.87 (.63-1.19)	.378
PBSC-marrow	1.45 (.89-2.36)	.131	.93 (.74-1.17)	.555
Sex		<.001		.005
Female	1.00		1.00	
Male	.59 (.52-.66)		1.08 (1.02-1.14)	
Age at donation, yr				.013
18-29			1.00	
30-39			.90 (.85-.96)	.001
40-49			.95 (.89-1.02)	.172
50-59			.96 (.86-1.06)	.438
Race		<.001		
White	1.00			
Hispanic	.73 (.61-.90)	.001		
African/African American	1.05 (.84-1.32)	.653		
Asian/Pacific Islander	.77 (.59-1.00)	.054		
Native American	.43 (.23-.81)	.009		
Multiple races/other	.81 (.63-1.03)	.086		
Unknown/declined	1.89 (.98-3.64)	.056		

CI indicates confidence interval.

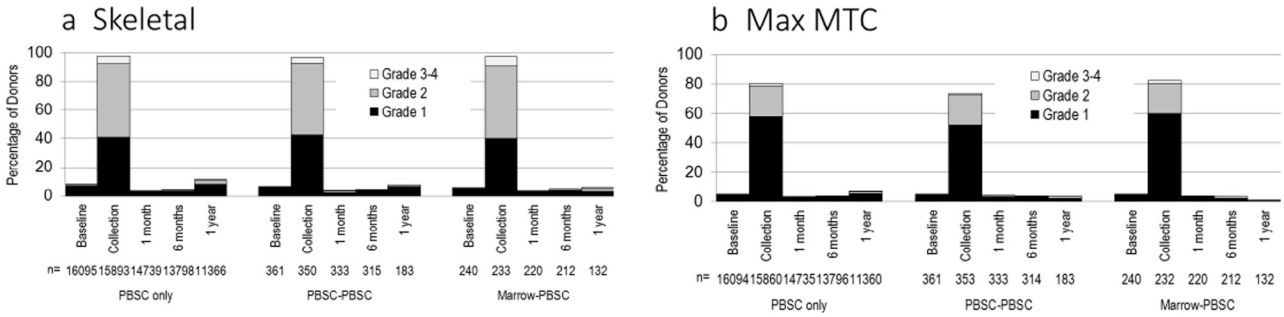

Figure 3. Severity of skeletal pain and MTC for second donations that were PBSCs. The severity of maximum skeletal pain (A) and maximum MTC (B) scores measured at baseline, at the time of collection, and at 1 month, 6 months, and 1 year postcollection in people who donated PBSCs once (PBSC only), people whose first and second donations were PBSCs (PBSC-PBSC), and donors whose first donation was marrow and second donation was PBSCs (marrow-PBSC). Skeletal pain represents pain in at least 1 of the following sites: back, bone, headache, hip, limb, joint, and neck. The severity of skeletal pain was defined as the maximum grade among these pain sites. The severity of MTC was the highest toxicity level of key symptoms, including fever in the absence of signs of infection, fatigue, skin rash, local reactions, nausea, vomiting, anorexia, insomnia, dizziness, and syncope.

likely to experience pain, toxicities, and fatigue in the pericollection period and in the postdonation recovery period [3]. This study also found that older donors were at less risk for grades 2 to 4 pain in the pericollection period. It also found that older donors were at a greater risk for grades 2 to 4 toxicities and fatigue 1 week after the collections. Females were also less likely than males to experience complete recovery from both marrow and PBSC donations.

This study found that several first donation factors were predictive of second donation experiences. Among people whose second donation was PBSCs, longer recovery time from first donations predicted longer recovery time for second donations, greater skeletal pain during the first PBSC donation predicted greater skeletal pain during second donation, and greater MTC during the first donation predicted greater MTC during the second donation.

It is notable that yields of second marrow and PBSC collections were shown to be lower than first collections. For people that donated PBSCs twice, the $CD34^+$ cell yield from both their first and second donations were less than the $CD34^+$ cell yields for PBSC donors who only donated once. In addition, among those who donated PBSCs twice, the $CD34^+$ cell collection yield was less for the second donation than the first. Circulating levels of $CD34^+$ cells were not measured before the apheresis collection, so it is not known if the response to G-CSF differs among PBSC-PBSC donors and those who only donated once. However, because there was no difference in G-CSF dose, duration of apheresis, or volume of blood processed during the first apheresis procedure for PBSC-PBSC donors and those donating PBSCs once, the people donating PBSCs twice appeared to mobilize $CD34^+$ cells less well in response to G-CSF.

Others have found that several donor factors effect G-CSF mobilization of $CD34^+$ cells, including age, sex, and race [20,21]. Previous studies of people donating twice found that the quantity of CD34+ cells collected during the second donation was similar or lower to the quantity collected during first donation [6-9].

With the much larger numbers we have in this study showing that second mobilizations result in lower $CD34^+$ yields, clinicians should carefully consider whether a second PBSC collection will give adequate cells, especially if the yield from the first collection was low. In addition, transplant centers may want to be informed if a donor under consideration for a second donation had poor yields previously. Because this information is relevant to the choice of a given individual for a second donation, donor registries should make this information available to centers for use as part of their approach to choosing a donor. The findings of the variability among first and second collections were unexpected, and we are planning another study to further investigate second donation collection yields.

In conclusion, policies of many registries of unrelated hematopoietic stem cell donors allow people to donate a second

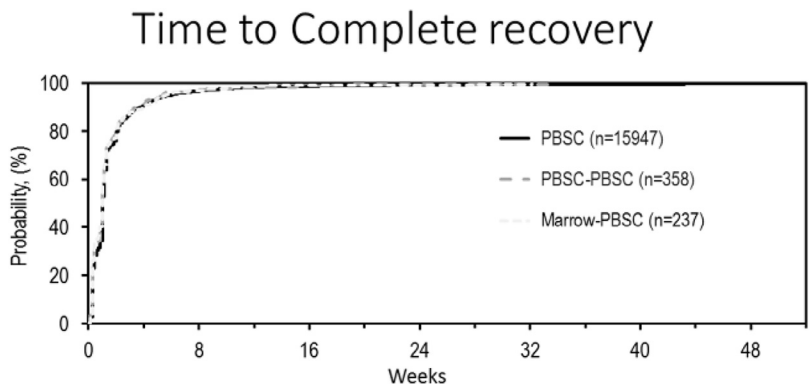

Figure 4. Time to recovery for second donations that were PBSCs. The proportion of donors who reported recovering to baseline measures at each time postdonation are shown for people who donated PBSCs once (PBSC), people whose first and second donations were PBSCs (PBSC-PBSC), and donors whose first donation was marrow and second donation was PBSCs (marrow-PBSC).

Table 5
ORs Comparing Donor Skeletal Pain, MTC, and Recovery versus Characteristics of Second Donations that Were PBSCs with Multivariate Logistic Regression Analysis

	Maximum Skeletal Pain Grades 2-4 at Collection		Maximum MTC Grades 2-4 at Collection			Recovery to Baseline	
Variable	OR (95% CI)	*P*	Variable	OR (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Group		.919	Sex × group		<.001		.309
PBSC	1.00		F, PBSC	1.00	.009	1.00	
Marrow-PBSC	1.04 (.80-1.35)	.784	F, marrow-PBSC	.43 (.24-.78)	.006	1.06 (.94-1.21)	.341
PBSC-PBSC	.97 (.78-1.20)	.764	F, PBSC-PBSC	.74 (.48-1.14)	.172	1.07 (.96-1.19)	.220
Sex		<.001	M, PBSC	1.00	.045		<.001
Female	1.00		M, marrow-PBSC	1.53 (1.05-2.21)	.025	1.00	
Male	.59 (.55-.63)		M, PBSC-PBSC	1.20 (.87-1.66)	.264	1.08 (1.04-1.11)	
Race					.003		<.001
White				1.00		1.00	
Hispanic				1.05 (.92-1.20)	.429	.98 (.92-1.03)	.401
African/African American				.77 (.64-.94)	.009	.92 (.86-1.00)	.047
Asian/Pacific Islander				1.22 (1.03-1.44)	.022	.90 (.84-.97)	<.001
Native American				1.27 (.89-1.82)	.189	.89 (.76-1.05)	.171
Multiple races/other				1.17 (1.01-1.36)	.038	.92 (.86-.98)	.009
Unknown/declined				.82 (.50-1.34)	.431	.70 (.58-.84)	<.001
Age at donation, yr		<.001			<.001		.021
18-29	1.00			1.00		1.00	
30-39	1.11 (1.02-1.19)	.011		1.13 (1.03-1.24)	.010	.96 (.93-1.00)	.038
40-49	.79 (.73-.86)	<.001		1.09 (.99-1.21)	.078	.98 (.94-1.02)	.339
50-59	.61 (.54-.68)	<.001		.85 (.73-.98)	.021	1.05 (.99-1.11)	.119
Collection year					<.001		<.001
2004-2007				1.00		1.00	
2008-2010				.86 (.78-.94)	.001	.99 (.95-1.03)	.535
2011-2013				.76 (.69-.83)	<.001	1.06 (1.02-1.10)	.003
BMI, kg/m^2		<.001			<.001		
Underweight/normal, <24.9	1.00			1.00			
Overweight, 25-29.9	1.22 (1.13-1.32)	<.001		1.22 (1.11-1.34)	<.001		
Obese, 30+	1.57 (1.44-1.70)	<.001		1.56 (1.42-1.72)	<.001		

time for either the same person or a different person. This study found no contraindications to this practice. Second donation experiences were similar to first donation experiences, but yields of second grafts were lower. Knowledge of the donor's first experience should help donor centers adjust management of the second donation to improve the donor experience and obtain the needed stem cell dose. To facilitate this donor registries should provide information regarding the first donation experience and stem cell yields. The results of this study can also be used to assist donors in making a more informed decision concerning whether or not to donate marrow or PBSCs after a first donation.

Table 6
Prognostic Factor Analysis for Selected Outcomes of Second PBSC Donations

	MTC Grades 2-4 During Collection		Skeletal Pain Grades 2-4 During Collection		Recovery to Baseline	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Group		.040		.031		
PBSC-PBSC	1.00		1.00			
Marrow-PBSC	1.70 (1.02-2.82)		1.50 (1.04-2.17)			
Group/time to recovery after first donation						<.001
PBSC-PBSC, recovery ≤ 3 days					1.00	
PBSC-PBSC, recovery 4-14 days					.69 (.54-.89)	.004
PBSC-PBSC, recovery > 14 days					.44 (.33-.59)	<.001
Marrow-PBSC					.60 (.48-.77)	<.001
Max MTC grade during collection of first donation		<.001		.040		.031
0-1	1.00		1.00		1.00	
2-4	3.29 (2.06-5.26)	<.001	1.93 (1.16-3.20)	.011	.75 (.61-.93)	.009
Unknown	.69 (.19-2.48)	.574	1.16 (.07-20.05)	.916	.91 (.58-1.43)	.686
Skeletal pain grade during collection of first donation				<.001		
0-1			1.00			
2-4			2.74 (1.86-4.04)	<.001		
Unknown			1.16 (.07-20.05)	.916		
BMI, kg/m^2		<.001				
Underweight / normal, <24.9	1.00					
Overweight, 25-29.9	2.79 (1.58-4.92)	<.001				
Obese, 30+	2.99 (1.67-5.36)	<.001				
Interval between collections						.006
≤12 mo					1.00	
>12 mo					.79 (.66-.93)	

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