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ABSTRACT

Unlike unrelated donor registries, transplant centers lack uniform approaches to related donor assessment and deferral. To test whether related donors are at increased risk for donation-related toxicities, we conducted a prospective observational trial of 11,942 related and unrelated donors aged 18-60 years. Bone marrow (BM) was collected at 37 transplant and 78 National Marrow Donor Program centers, and peripheral blood stem cells (PBSC) were collected at 42 transplant and 87 unrelated donor centers in North America. Possible presence of medical comorbidities was verified prior to donation, and standardized pain and toxicity measures were assessed pre-donation, peri-donation, and one year following. Multivariate analyses showed similar experiences for BM collection in related and unrelated donors; however, related stem cell donors had increased risk of moderate [odds ratios (ORs) 1.42; $P<0.001$] and severe (OR 8.91; $P<0.001$) pain and toxicities (OR 1.84; $P<0.001$) with collection. Related stem cell donors were at increased risk of persistent toxicities (OR 1.56; $P=0.021$) and non-recovery from pain (OR 1.42; $P=0.001$) at one year. Related donors with more significant comorbidities were at especially high risk for grade 2-4 pain (OR 3.43; $P<0.001$) and non-recovery from toxicities (OR 3.71; $P<0.001$) at one year. Related donors with more significant comorbidities were at especially high risk for grade 2-4 pain (OR 3.43; $P<0.001$) and non-recovery from toxicities (OR 3.71; $P<0.001$) at one year. Related donors reporting grade ≥2 pain had significant decreases in Health-Related Quality of Life (HR-QoL) scores at one month and one year post donation ($P=0.004$). In conclusion, related PBSC donors with comorbidities are at increased risk for pain, toxicity, and non-recovery at one year after donation. Risk profiles described in this study should be used for donor education, planning studies to improve the related donor experience, and decisions regarding donor deferral. Registered at *clinicaltrials.gov identifier: 00948636*.

Introduction

Donation of hematopoietic stem cells (HSC) in the form of bone marrow (BM) or peripheral blood stem cells (PBSC) is a commonly performed procedure, with more than 40,000 donations from both volunteer unrelated donors (URD) and related donors (RD) each year.[1,2] Over the past decade, donor registries such as the National Marrow Donor Program (NMDP) have published detailed data describing the URD experience, identifying individuals at increased risk for pain and collection-related symptoms, slower recovery, and severe adverse events.[3-7] Data describing the RD experience, however, are limited, with only one large recent study.[8] This may be because URD are handled by registries that have a mandate to collect and report safety data, whereas RD are cared for by local transplant centers, whose primary focus is care for the recipient and, in most countries, RD safety data are not systematically collected. Inadequate data regarding RD is a cause for concern for many reasons. While URD registries have rigorous standards for donor approval, supported by internal quality initiatives and efforts at international standardization,[9] there are no generally accepted guidelines about deferral of a RD.

With these concerns in mind, North American Investigators teamed with the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR) to conduct a prospective observational trial of RD who donated at 53 transplant centers in the United States between January 2010 and July 2014. This report describes our primary end point comparing pain, toxicities and recovery of RD with URD collected concurrently at 78 BM and 87 PBSC NMDP collection centers.

Methods

Prior to donation, RD underwent a medical evaluation including a detailed history, physical examination, blood tests, and additional work up as necessary according to center standards. RD approved for donation were approached for consent for this Institutional Review Board (IRB)-approved study.

Unrelated donors provided written informed consent for participation as required by the NMDP IRB. URD were evaluated for medical suitability and comorbidities that would require further evaluation or qualify for deferral for BM or PBSC donation as specified by NMDP standards.[10,11]

Data collection

A pre-donation form including history of pre-existing medical conditions (comorbidities) was completed. Detailed collection-related symptoms and pain were collected at five time points: pre-donation, peri-donation [day +5 from start of granulocyte-colony stimulating factor (G-CSF) for PBSCs and 1-2 days after BM collection], and 1, 6 and 12 months post donation. Toxicity was defined by Common Toxicity Criteria measures for symptoms commonly noted during PBSC and BM collection (fever, fatigue, skin rash, local reactions to an injection, nausea, vomiting, anorexia, insomnia, dizziness, and syncope) and is called the Modified Toxicity Criteria (MTC). This approach was validated by the NMDP and has been published previously.[4,5,12,13] Pain was graded from 0-4 as none, mild, moderate, severe, or disabling. Pain and toxicity measures were assessed by the transplant center at pre- and peri-donation time points; the CIBMTR Survey Research Group was responsible for follow-up assessments.

A product-specific collection form detailed information on the collection procedure. A subset of donors underwent assessment of long-term psychological recovery by established Health Related Quality of Life instruments (reported previously[14-16]).

Table 1. Demographics and collection characteristics of first-time bone marrow (BM) donors and first time peripheral blood stem cell (PBSC) donors.

Variable	First-time BM donors RD N (%)	First-time BM donors URD N (%)	First-time BM donors P^a	First-time PBSC donors RD N (%)	First-time PBSC donors URD N (%)	First-time PBSC donors P^a
Number of donors	126	2553		956	8307	
Number of centers	37	78		42	87	
Age at donation (years)			<0.001			<0.001
18 to 29	54 (43)	1231 (48)		102 (11)	4011 (48)	
30 to 39	22 (17)	702 (27)		135 (14)	2091 (25)	
40 to 49	21 (17)	455 (18)		254 (27)	1520 (18)	
50 to 60	29 (23)	165 (06)		465 (49)	685 (08)	
Median (range)	33 (18-61)	30 (19-60)	0.070	49 (18-61)	30 (18-61)	<0.001
Gender			0.078			<0.001
Male	67 (53)	1558 (61)		537 (56)	5341 (64)	
Female	59 (47)	995 (39)		419 (44)	2966 (36)	
Weight (kg)						
N Eval	126	2553		952	8307	
Median (range)	83 (50-150)	81 (40-154)	0.330	86 (43-198)	82 (37-176)	<0.001
BMI (kg/m^2)			0.069			<0.001
Underweight, <18.5	0	14 (01)		3 (<1)	66 (01)	
Normal, 18.5-24.9	40 (33)	867 (34)		209 (23)	2884 (35)	
Overweight, 25-29.9	34 (28)	938 (37)		325 (36)	3064 (37)	
Obese, 30+	47 (39)	734 (29)		368 (41)	2288 (28)	
Unknown	5 (N/A)	0 (N/A)		51 (N/A)	5 (N/A)	
Race			0.003			<0.001
Caucasian	89 (71)	1637 (64)		788 (82)	6132 (74)	
Hispanic	15 (12)	332 (13)		63 (07)	698 (08)	
African / African American	15 (12)	188 (07)		58 (06)	314 (04)	
Asian / Pacific Islander	4 (03)	146 (06)		29 (03)	444 (05)	
Native American	3 (02)	21 (01)		6 (01)	62 (01)	
Multiple races / other	0	208 (08)		7 (01)	592 (07)	
Unknown / declined	0	21 (01)		5 (01)	65 (01)	
Comorbidity group[b]						
Comorbidities absent	64 (51)			403 (42)		
Comorbidities present, acceptable	22 (17)			171 (18)		
Comorbidities present, indeterminate	29 (23)			297 (31)		
Comorbidities present, defer	11 (09)			85 (09)		
Unknown	0 (N/A)			0 (N/A)		
Year of donation			0.001			<0.001
2010	21 (17)	496 (19)		113 (12)	1604 (19)	
2011	38 (30)	622 (24)		301 (31)	1977 (24)	
2012	51 (40)	757 (30)		375 (39)	2370 (29)	
2013	16 (13)	678 (27)		167 (17)	2356 (28)	
PBSC collection-related						
Number of days of collection						<0.001
1				646 (68)	7478 (90)	
2				283 (30)	829 (10)	
3				16 (02)	0	
4				10 (01)	0	
5				1 (<1)	0	
Average daily G-CSF dose (g)						
N Eval				918	8183	
Median (range)				948 (300-2040)	900 (420-1260)	<0.001

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Average daily G-CSF dose per donor weight (g/kg/day)			
N Eval	914	8183	
Median (range)	10.3 (4.7-22.1)	10.6 (5.5-18.7)	<0.001
Absolute CD34+ at pre-collection			
N Eval	539	8283	
Median (range)	87.0 (7.1-1342)	80.0 (0.3-2123)	<0.001
Total blood volume processed			<0.001
Small, <12 L	54 (06)	233 (03)	
Standard, 12-18 L	325 (34)	1882 (23)	
Large, ≥ 18 L	576 (60)	6182 (75)	
Unknown	1 (N/A)	10 (N/A)	
Median (range)	20.0 (0.3-112.6)	21.2 (0.7-45.4)	0.040
Central line placement-Male			<0.001
No	470 (88)	5219 (98)	
Yes	67 (12)	121 (2)	
Unknown	0 (N/A)	1 (N/A)	
Central line placement-Female			<0.001
No	259 (62)	2460 (83)	
Yes	160 (38)	506 (17)	
Central line site-All donors			
Femoral	8 (4)	209 (33)	<0.001
Internal jugular	208 (92)	389 (62)	
Subclavian	11 (5)	26 (4)	
Other site	0	3 (<1)	

RD: related donor; URD: unrelated donor; N: number; N Eval: number evaluated; BMI: Body Mass Index; G-CSF: granulocyte-colony stimulating factor. [a]Pearson χ^2 test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables. [b]Applicable to RD only.

End points

Pain was assessed for the following sites: back, bones, head, hip, intravenous injection (IV) site, joints, limbs, muscles, neck, throat, or other. Severity of pain was defined as the maximum grade among these pain sites. Body symptoms were assessed using the MTC outlined above and the peak toxicity level across symptoms was analyzed. Recovery to pre-donation levels by one year was defined as a pain or symptom score less than or equal to the score at pre-donation.

Pre-donation comorbidity ascertainment included: assessment of bleeding, gastrointestinal, genitourinary, hematologic, hepatic, pulmonary, cardiovascular, psychiatric, central nervous system (CNS), endocrine, autoimmune disorders, or other significant coexisting diseases (*Online Supplementary Table S1*). We divided comorbidities into three categories: 1) comorbidities that would not result in deferral from URD donation according to NMDP standards;[10,11] 2) comorbidities that would have resulted in deferral; and 3) comorbidities that could possibly have led to a deferral, but more detailed donor clinical data would be needed to make that judgment.

Statistical analysis

Analyses were conducted separately for BM and PB donations. Pre-donation baseline variables were compared between RD and URD groups using the Pearson χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables.

χ^2 tests or Fisher's Exact tests as appropriate were used to compare the incidences of skeletal pain and MTC symptoms as well as recovery to pre-donation levels between RD and URD groups. Multivariate analyses using logistic regression models were conducted to compare the RD and URD groups accounting for differences in donor characteristics. The following donor characteristics were examined for inclusion in the multivariate model: donor type, race, gender, age, Body Mass Index (BMI), collection year, comorbidity status among related donors, pre-donation counts [white blood cell (WBC) count, platelets, neutrophils, mononuclear cells, hemoglobin], and pre-donation symptoms (skeletal pain or maximum MTC grade). Additional PB donation-specific variables considered were: placement of a central venous line, total blood volume, absolute CD34+ cells and WBC pre-collection, and daily GCSF dose (absolute and per kg).

The effects were estimated *via* odds ratios (OR). In all multivariate models, donor type was forced into the model and stepwise model selection was used to determine additional donor characteristics to be included. Interactions between donor type and each donor characteristic were tested for in all multivariate models.

Results

Demographics

Table 1 details RD and URD donating BM or PBSC. RD tended to be older than URD, with 23% *versus* 6% of BM donors and 49% *versus* 8% of PBSC donors collected aged between 50-60 years. Although males donated more often in both RD and URD groups, a higher percentage of females donated in the RD group. There was a trend toward higher BMI in RD *versus* URD giving BM (BMI 30+, 39% *versus* 29%; P=0.07), and a significant difference in obesity in RD *versus* URD giving PBSC with 41% *versus* 28% (BMI 30+; P<0.001).

There are several notable differences between RD and

URD involving collection procedures (Table 1). While 90% of URD PBSC donations occurred in a single day, and no collection took more than two days, 30% of RD required two days, and 2% and 1% took three and four days, respectively, with collection for one donor taking place over five days (P<0.001). Notably, more RD were collected with lower volume procedures (<18L, 40% *vs.* 26%; P<0.001). A major difference in RD *versus* URD practice was noted in the increase in central venous line placement in RD for both female and male donors (female RD 38%, female URD 17%, P<0.001; male RD 12%, male URD 2%, P=0.001). Of note, the differences were not impacted by age, although obesity had an impact in female donors, and number of collection procedures performed impacted both male and female donors (*Online Supplementary Table S2*).

Univariate analyses of bone marrow collection, pain and donation-related symptoms

Figure 1A and B show rates of grades 1-4 skeletal pain and collection-related symptoms in RD and URD before, peri-donation, and one year after the BM collection procedure. *Online Supplementary Figure S1A-D* detail locations of pain and types of symptoms experienced. It is notable that 5-10% of healthy URDs and 10-20% of RDs reported mild pain or symptoms pre-donation. Almost all donors reported some level of pain or symptoms during the procedure; however, because grade 1 pain and symptoms rarely require intervention, we focused our analyses on higher grades. Univariate analyses showed RD to have higher rates of grade 2-4 pain pre-donation (2.4% *vs.* 0.6%; P=0.043) (*Online Supplementary Table S3*). Grade 2-4 pain levels at collection were similar, but grades 3-4 pain were substantially higher in RD (10% *vs.* 0.6%; P<0.001). At one year, 10% and 5% of RD *versus* URD reported grade 2-4 pain (P=0.060). Pre-donation, MTC symptoms were similar in RD and URD. At collection, grade 2-4 and 3-4 symptoms were higher in RD *versus* URD (24% *vs.* 17% grade 2-4, 3.3% *vs.* 0.4% grade 3-4; P=0.049 and 0.002, respectively), with higher rates of dizziness, site reactions, nausea, and syncope in RD (P=0.005, 0.008, 0.021, and 0.028, respectively) (*Online Supplementary Figure S1C*).

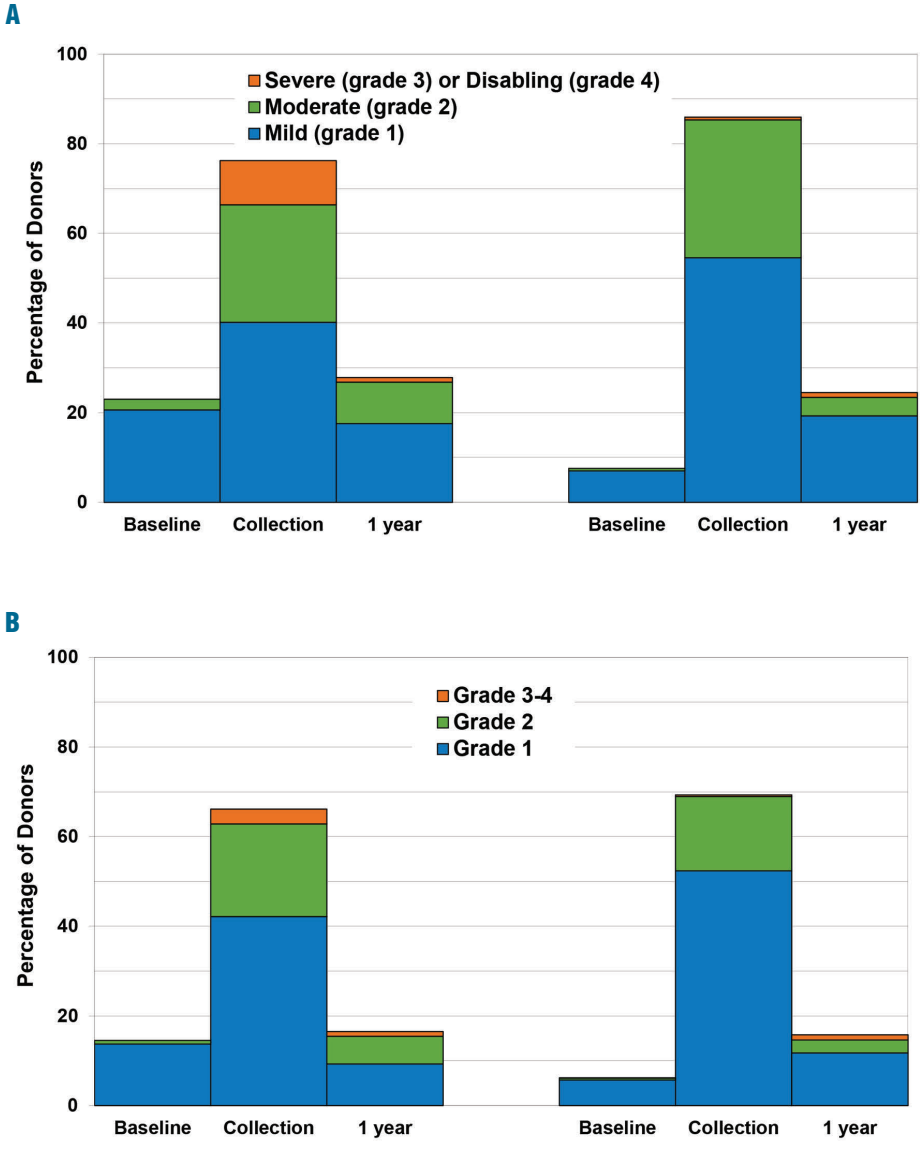

Figure 1. Severity of skeletal pain and highest toxicity level across key body symptoms experienced by first time related *versus* unrelated bone marrow donors at baseline, two days post donation, and one year post donation. (A) Skeletal pain. (B) Highest toxicity level across key body symptoms.

Univariate analyses of peripheral blood stem cell collection, pain and donation-related symptoms

Figure 2A and B show rates of grades 1-4 skeletal pain and MTC symptoms in RD and URD before, on day +5 of G-CSF administration (day of peak symptoms), and one year after the PBSC collection procedure. *Online Supplementary Figure S2A-D* detail locations of pain and types of symptoms experienced by RD and URD undergoing PBSC collection. *Online Supplementary Table S4* shows that at pre-donation baseline, day +5 of G-CSF, and one year, all measures of grade 2-4 and 3-4 pain are higher in RD compared to URD (all $P<0.001$). In addition, 10% fewer RD return to pre-donation levels of pain at one year ($P<0.001$). Collection-related MTC symptoms are also experienced significantly more and to a higher degree at all time points, and non-recovery to pre-donation levels of these symptoms at one year occurs more often after RD procedures (17% *vs.* 12%; $P<0.001$).

Multivariate analyses of bone marrow and peripheral blood donor experiences: related *versus* unrelated donor

Multivariate analysis showed that Grade 2-4 pain after BM collection was similar between RD and URD (Table 2). Grade 2-4 symptoms after BM collection were 1.5 times more likely for RD, but this did not reach significance ($P=0.075$). Related PBSC donors were at higher risk for grade 2-4 and 3-4 pain (OR 1.42, 8.91, respectively; both $P<0.001$) and grade 2-4 symptoms (OR 1.84; $P<0.001$) with collection, as well as the presence of grade 2-4 symptoms at one year (OR 1.56; $P=0.021$). A notable finding was that RD reporting no comorbidities had a risk of grade 2-4 pain at one year similar to URD. But if RD reported any comorbidities, their risk of grade 2-4 pain was significantly increased, with the highest risk noted in RD with comorbidities that would have led to deferral by NMDP standards (OR 3.43; $P<0.001$).

Table 2 also describes analyses of failure to recover to pre-donation levels of pain and donation-related symptoms at one year. RD of PBSC had an OR of 1.42 for non-recovery to pre-donation levels of pain at one year ($P=0.001$). Recovery to pre-donation levels of symptoms was associated with comorbidity: RD who had no comorbidities were similar to URD, but RD who had comorbidities had a higher risk of non-recovery at one year. Notably, RD identified as having comorbidities that would have led to NMDP deferral had a more than 3-fold increase in risk of non-recovery to pre-donation levels compared to URD (OR 3.71; $P<0.001$).

Multivariate analysis: other factors affecting risk of pain, symptoms, or non-recovery at one year

For BM donation, women were 67% more likely to experience grade 2-4 pain and nearly 3 times more likely to experience grade 2-4 symptoms ($P<0.001$) (Table 3). Age was an important risk factor for failure to recover to pre-donation levels, as donors aged 50-60 years were more than twice as likely as their younger counterparts to have non-recovery at one year (Table 4). In addition, women's risk of non-recovery at one year to pre-donation levels of symptoms was twice that of men ($P<0.001$).

Risk factors for pain and MTC symptoms after PBSC collection included both new and previously described clinical characteristics (Tables 3 and 4). A new finding is that high $CD34^+$ counts (≥80.5/μL) prior to day 1 of collection was associated with more grade 2-4 collection pain (OR 1.25; $P<0.001$). Another novel finding was that there was a dose level of G-CSF above which pain levels increased significantly. If a donor received an average daily dose exceeding 960 μg/day, reported pain levels were

Table 2. Multivariate analysis of collection toxicities and long-term recovery after bone marrow (BM) and peripheral blood stem cell (PBSC) donations showing the effect of donor type. The odds ratios are for comparing related donor (RD) *versus* unrelated donor (URD).

Event and time point	BM donors OR (95% CI)	*P*	PBSC donors OR (95% CI)	*P*
Skeletal pain				
Grade 2-4 at collection	1.19 (0.81-1.74)	0.375	1.42 (1.17-1.72)	<0.001
Grade 3-4 at collection[a]			8.91 (6.63-12.0)	<0.001
Grade 2-4 at one year[a]				<0.001
RD, comorbidities absent			1.02 (0.63-1.65)	0.944
RD, comorbidities present, acceptable			2.66 (1.60-4.42)	<0.001
RD, comorbidities present, indeterminate			1.62 (1.04-2.52)	0.033
RD, comorbidities present, defer			3.43 (1.86-6.35)	<0.001
Non-recovery to pre-donation level at one year	0.96 (0.56-1.63)	0.871	1.42 (1.15-1.74)	0.001
Max MTC symptoms				
Grade 2-4 at collection	1.50 (0.96-2.36)	0.075	1.84 (1.49-2.28)	<0.001
Grade 2-4 at one year[a]			1.56 (1.07-2.27)	0.021
Non-recovery to pre-donation level at one year	1.08 (0.58-2.01)	0.819		<0.001
RD, comorbidities absent			0.94 (0.64-1.37)	0.743
RD, comorbidities present, acceptable			1.98 (1.26-3.12)	0.003
RD, comorbidities present, indeterminate			1.77 (1.24-2.52)	0.002
RD, comorbidities present, defer			3.71 (2.14-6.45)	<0.001

OR: odds ratio; CI: Confidence Interval; Max: maximum; MTC: Modified Toxicity Criteria. [a]Number of events for BM donors was not sufficient for multivariable analysis.

higher (OR 1.21; *P*=0.006). This increase in pain levels was not noted when analyzed by dose per/kg.

Females undergoing PBSC collection had twice the risk of moderate and severe pain and MTC symptoms (Table 3). They were also more likely to have persistent symptoms and to fail to recover to pre-donation levels at one year after BM collection (Table 4). The age effect varied, with PBSC donors aged 30-39 years having higher risk for grade 3-4 pain with collection (OR 1.50; *P*=0.021) (Table 3) and older donors (aged 50-60 years) having lower risks for grade 2-4 pain with collection (OR 0.61; *P*<0.00) (Table 3) and higher risks of reporting grade 2-4 pain at one year (aged 50-60 years: OR 2.72; *P*<0.001) (Table 4). Importantly, donors who started with grade 1 or 2-4 pain or grade 2-4 MTC symptoms were more likely to report higher grades of pain or symptoms with collection (*P*<0.001) (Table 3). These donors also had higher levels of pain and MTC symptoms at one year, but most of them had returned to pre-donation levels. Obesity was important in pain and MTC symptom risk, as donors with 30+

Table 3. Multivariate analysis showing other key predictors for skeletal pain and Modified Toxicity Criteria (MTC) symptoms associated with bone marrow (BM) and peripheral blood stem cell (PBSC) collections.

	Grade 2-4 skeletal pain at collection		Grade 3-4 skeletal pain at collection		Grade 2-4 max MTC symptoms at collection	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
BM donation						
Gender						
Male	1.00				1.00	
Female	1.67 (1.41-1.97)	<0.001			2.74 (2.23-3.37)	<0.001
PBSC donation						
Gender						
Male	1.00		1.00		1.00	
Female	1.76 (1.60-1.93)	<0.001	2.18 (1.69-2.81)	<0.001	1.91 (1.65-2.20)	<0.001
Age at collection (years)		<0.001		0.005		0.013
18 to 29	1.00		1.00		1.00	
30 to 39	1.00 (0.90-1.12)	0.977	1.50 (1.06-2.12)	0.021	1.18 (0.98-1.41)	0.080
40 to 49	0.85 (0.75-0.96)	0.008	1.19 (0.83-1.72)	0.340	1.26 (1.05-1.53)	0.015
50 to 60	0.61 (0.52-0.71)	<0.001	0.77 (0.51-1.16)	0.216	0.91 (0.72-1.16)	0.452
Donor BMI		<0.001		<0.001		<0.001
Underweight / normal	1.00		1.00		1.00	
Overweight	1.13 (1.02-1.26)	0.021	1.30 (0.92-1.84)	0.137	1.31 (1.10-1.57)	0.003
Obese	1.35 (1.18-1.55)	<0.001	2.03 (1.47-2.82)	<0.001	1.63 (1.36-1.96)	<0.001
Unknown	0.92 (0.52-1.63)	0.776	1.21 (0.48-3.05)	0.686	1.11 (0.50-2.45)	0.806
Number of days of collection						
1 day	1.00					
2+ days	0.74 (0.64-0.85)	<0.001				
G-CSF dose		0.007				
0-960 g/day	1.00					
>960 g/day	1.21 (1.06-1.38)	0.006				
Unknown	1.37 (0.96-1.97)	0.086				
Skeletal pain pre-donation		<0.001		0.004		0.006
Grade 0	1.00		1.00		1.00	
Grade 1	1.57 (1.36-1.82)	<0.001	1.39 (0.95-2.02)	0.087	1.31 (1.05-1.64)	0.016
Grade 2-4	2.47 (1.77-3.46)	<0.001	2.33 (1.37-3.96)	0.002	1.65 (1.08-2.52)	0.020
Max MTC pre-donation				0.030		<0.001
Grade 0			1.00		1.00	
Grade 1			0.85 (0.54-1.34)	0.477	1.37 (1.06-1.77)	0.017
Grade 2-4			2.67 (1.22-5.82)	0.014	3.23 (1.86-5.61)	<0.001
Absolute $CD34^+$ at pre-collection		<0.001				
<80.5	1.00					
≥80.5	1.25 (1.14-1.37)	<0.001				
Unknown	1.14 (0.87-1.48)	0.341				

OR: odds ratio; CI: Confidence Interval; BMI: Body Mass Index; G-CSF: granulocyte-colony stimulating factor; Max: maximum.

BMI had increased risk of peri-collection grade 2-4 and 3-4 pain and grade 2-4 MTC symptoms, along with grade 2-4 pain at one year.

Table 4 shows additional factors other than RD/URD status associated with higher levels of late pain/MTC symptoms and lack of recovery to pre-donation levels at one year. Older BM and PBSC donors, and Black and multiple-race PBSC donors were less likely to recover to their pre-donation level of pain. Hispanic and multiple-race PBSC donors were less likely to recover to pre-donation level of MTC symptoms. As might be expected, donors with pre-donation levels of pain or symptoms at grade 1 or grades 2-4 were more likely to recover to that level at one year.

Discussion

Unrelated HSC registries have a responsibility to ensure the safety of volunteer donors performing an altruistic act.[17] They routinely defer donors with minor health problems, erring on the side of safety. Transplant centers, whose primary task is treatment of patients with cancer and other life-threatening illnesses, must also evaluate the medical fitness of donors and advise them about risk, in some cases deferring them. Although recent changes in accreditation requirements for transplant centers emphasize donor education and autonomy, requiring an independent donor advocate,[18-20] RD may or may not listen to advice to forgo donation, being highly motivated and willing to take medical risks for their family member.

Studies have shown that a matched sibling is generally the best HSC donor;[21-23] and recent expansion of haploidentical approaches[24] have put even more family members into a donor role. Over the past decade, however, improvements in URD procedures have led to comparable outcomes using RD and URD in patients with hematologic malignancies,[25-27] offering reasonable HCT alternatives if a RD is unable to donate. With this in mind, when should a transplant center counsel a RD against donation?

Our study shows that the choice to donate by a RD with comorbidities can have consequences. We show by multivariate analysis that RD have more intense early pain and toxicities than URD, and because these symptoms are temporally associated with PBSC collection, there is little doubt that the toxicities are related to the donation procedure. There is a question, however, about whether our observation that RD have more pain and non-recovery to pre-donation levels at one year is due to the procedure itself, or other aspects associated with being a RD.

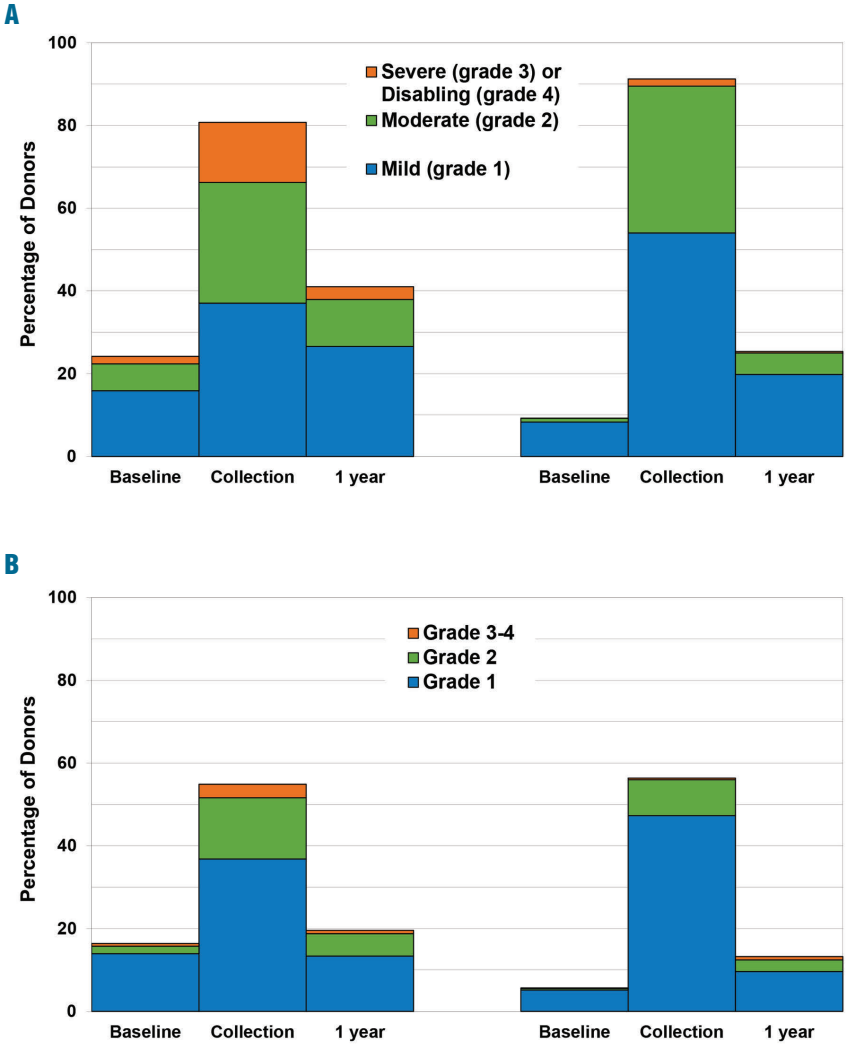

Figure 2. Severity of skeletal pain and highest toxicity level across key body symptoms experienced by first time related *versus* unrelated peripheral blood stem cell (PBSC) donors at baseline, on the first day of collection prior to apheresis, and one year post donation. (A) Skeletal pain. (B) Highest toxicity level across key body symptoms.

Table 4. Multivariate analysis showing other key predictors for long-term skeletal pain and Modified Toxicity Criteria (MTC) symptoms and recovery to pre-donation level after bone marrow (BM) and peripheral blood stem cells (PBSC) donations.

	Grade 2-4 skeletal pain at one year		Grade 2-4 max MTC symptoms at one year		Skeletal pain non-recovery to pre-donation level at one year		Max MTC symptoms non-recovery to pre-donation level at one year	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
BM donation								
Gender								
Male							1.00	
Female							1.92 (1.35-2.74)	<0.001
Age at collection						0.012		
18 to 29					1.00			
30 to 39					1.13 (0.78-1.63)	0.521		
40 to 49					1.42 (0.95-2.12)	0.091		
50 to 59					2.21 (1.34-3.64)	0.002		
Skeletal pain pre-donation								
Grade 0					1.00			
Grade 1-4					0.39 (0.20-0.74)	0.004		
Max MTC symptoms pre-donation								
Grade 0							1.00	
Grade 1-4							0.29 (0.11-0.72)	0.008
PBSC donation								
Gender								
Male			1.00					
Female			1.61 (1.15-2.25)	0.005				
Age at collection (years)		<0.001				<0.001		
18 to 29	1.00				1.00			
30 to 39	1.81 (1.19-2.74)	0.005			1.50 (1.21-1.86)	<0.001		
40 to 49	1.85 (1.22-2.82)	0.004			1.78 (1.43-2.22)	<0.001		
50 to 60	2.72 (1.77-4.16)	<0.001			2.18 (1.71-2.78)	<0.001		
Donor BMI		0.013						
Underweight / normal	1.00							
Overweight	1.36 (0.95-1.95)	0.097						
Obese	1.79 (1.25-2.57)	0.002						
Unknown	0.96 (0.31-2.94)	0.943						
Donor race		<0.001				0.001		0.015
Caucasian	1.00				1.00		1.00	
Hispanic	1.45 (0.90-2.33)	0.127			1.14 (0.85-1.54)	0.377	1.54 (1.09-2.18)	0.014
African / African American	2.91 (1.74-4.84)	<0.001			2.05 (1.40-3.00)	<0.001	1.42 (0.87-2.32)	0.166
Asian / Pacific Islander	2.18 (1.26-3.77)	0.006			1.22 (0.87-1.71)	0.243	1.25 (0.81-1.91)	0.310
Multiple races / other	1.88 (1.09-3.22)	0.023			1.52 (1.11-2.08)	0.009	1.62 (1.11-2.38)	0.013
Year of collection								
2010-2011							1.00	
2012-2013							0.74 (0.61-0.91)	0.004
Skeletal pain pre-donation		<0.001		0.044		<0.001		0.004
Grade 0	1.00		1.00		1.00		1.00	
Grade 1	3.17 (2.27-4.43)	<0.001	1.69 (1.04-2.72)	0.033	0.53 (0.40-0.71)	<0.001	1.67 (1.23-2.27)	0.001
Grade 2-4	3.09 (1.71-5.60)	<0.001	1.94 (0.86-4.34)	0.109	0.22 (0.11-0.45)	<0.001	1.35 (0.71-2.59)	0.362
Max MTC symptoms pre-donation		0.040		0.003				<0.001
Grade 0	1.00		1.00				1.00	
Grade 1	0.74 (0.46-1.20)	0.225	1.00 (0.55-1.82)	0.998			0.27 (0.15-0.47)	<0.001
Grade 2-4	3.04 (1.10-8.42)	0.033	5.28 (2.04-13.60)	0.001			0.17 (0.02-1.31)	0.089

OR: odds ratio; CI: Confidence Interval; BMI: Body Mass Index; Max: maximum.

Although attempting to link observed pain at one year directly to PBSC donation was not one of our objectives, an observation that we made may shed light on this question. We performed additional assessments of RD at one and six months; we noted that the donation pain levels do not fully recover at one month, and remain at heightened levels at six and 12 months (P>0.001) (*Online Supplementary Figure S3*), suggesting that persistently elevated pain levels are a consequence of donation.

Given that elevated post-donation pain levels were only grade 1 or 2 (mild/moderate), are these findings clinically significant? This is an important question because self-reported pain from individuals can vary based on characteristics such as gender or cultural differences. To define whether the persistent pain we detected was clinically meaningful, we performed an analysis of the relation of reported pain to donor HR-QoL. In a companion study imbedded in our protocol, 186 RD and URD were randomly chosen for assessment of HR-QoL. We noted that at one month and one year after donation, those reporting grade 2 pain or toxicities had significantly lower physical scores measured by the SF36 multidimensional HR-QoL measure compared to those not reporting pain or toxicities [P=0.002 (1 month) and 0.004 (1 year)] (*Online Supplementary Figure S4*). The findings of our HR-QoL companion study (reported separately) support the outcomes we report (e.g. RD reported the donation to be more painful than URD; at 1 year RD were less likely to feel back to normal and reported a longer period of recovery). These observations allow us to conclude that the persistent pain is clinically meaningful, but the cause of higher levels of persistent pain in RD is unclear. Future studies could explore potential contributing factors, such as the possibility of G-CSF increasing inflammation in donors with comorbid conditions or the relationship of persistent pain to psychological stressors experienced by family donors.

With this in mind, should RD at highest risk of pain or non-recovery consider deferral? Deferring RD who would have been deferred by the NMDP (our highest risk group) is in line with a recent Worldwide Network for Blood and Marrow Transplantation task force recommendation to screen RD using URD registry standards.[9,28] It is likely that unless transplant centers collecting RD accept limits on screening and collection similar to URD registries, RD will remain at higher risk for pain/toxicity and lack of recovery. But should pre-donation standards for deferral of a RD be similar to those for URD? Although there is no clear medical benefit from donation, there is evidence that both URD and RD may experience psychosocial benefits, including feelings of enhanced self-worth. For RD, there are additional benefits of alleviating the suffering or saving the life of a loved one and closer family relationships.[29-31] While some family members may willingly accept increased medical risk in exchange for psychosocial benefits, others may hesitate and feel coerced by family obligations. Striking a balance is a challenge, as transplant centers should support the wishes of RD who are ambivalent about donation and protect those in whom donation could be a serious risk. But at the same time, RD should have the choice as to whether to shoulder some level of increased risk.

This study identified a series of risk factors that could either motivate a transplant center to recommend against use of a given donor, or allow a donor with multiple risk factors to understand their risk and choose to forgo donation (Tables 3 and 4). A desired outcome from this study is to motivate transplant centers to test interventions aimed at minimizing discomfort or preventing persistent pain or symptoms experienced by high-risk RD. The data on risks presented herein should be shared with RD as part of their counseling regarding the donation process.

In summary, this study showed for the first time that adult RD of PBSC are at increased risk for higher levels of pain and symptoms in the short-term after a collection procedure and one year later compared to URD. The presence of comorbidities in a prospective donor heightens this risk, and comorbidities in combination with other factors described in this study should be carefully considered as transplant teams and individuals make decisions regarding BM or PBSC donation.

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References

1. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic stem cell transplantation: a global perspective. JAMA. 2010; 303(16):1617-1624.
2. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. Bone Marrow Transplant. 2016; 51(6):786-792.
3. Pulsipher MA, Chitphakdithai P, Logan BR, et al. Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose. Blood. 2009;114(13):2606-2616.
4. Pulsipher MA, Chitphakdithai P, Logan BR, et al. Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. Blood. 2013;121(1):197-206.
5. Pulsipher MA, Chitphakdithai P, Logan BR, et al. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. Blood. 2014;123(23):3655-3663.
6. Lee MH, Jang JH, Min HJ, et al. Predictors of general discomfort, limitations in activities of daily living and intention of a second donation in unrelated hematopoietic stem cell donation. Bone Marrow Transplant. 2017;52(2):258-263.
7. Holig K, Kramer M, Kroschinsky F, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. Blood. 2009;114(18):3757-3763.
8. Kodera Y, Yamamoto K, Harada M, et al. PBSC collection from family donors in Japan: a prospective survey. Bone Marrow Transplant. 2014;49(2):195-200.
9. Lown RN, Philippe J, Navarro W, et al. Unrelated adult stem cell donor medical suitability: recommendations from the World Marrow Donor Association Clinical Working Group Committee. Bone Marrow Transplant. 2014;49(7):880-886.
10. NMDP Standards. Available at: https://bethematch.org/workarea/downloadasset.aspx?id=7711: National Marrow Donor Program; 2015.
11. Miller J. Hematopoietic Progenitor Cell Donation Evaluation. In: Wingard J, Gastineau DA, Leather H, Snyder DL, Szczepiorkowski ZM, eds. Hematopoietic Stem Cell Transplantation: A Handbood For Clinicians. Bethesda, MD: AABB; 2015:93-108.
12. Miller JP, Perry EH, Price TH, et al. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. Biol Blood Marrow Transplant. 2008;14(9 Suppl):29-36.
13. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. Blood. 2009;113(15):3604-3611.
14. Switzer GE, Bruce J, Kiefer DM, et al. Health-Related Quality of Life among Older Related Hematopoietic Stem Cell Donors (>60 Years) Is Equivalent to That of Younger Related Donors (18 to 60 Years): A Related Donor Safety Study. Biol Blood Marrow Transplant. 2017;23(1):165-171.
15. Switzer GE, Bruce J, Kiefer DM, et al. Health-Related Quality of Life among Pediatric Hematopoietic Stem Cell Donors. J Pediatr. 2016;178:164-170.
16. Switzer GE, Bruce J, Pastorek G, et al. Parent versus child donor perceptions of the bone marrow donation experience. Bone Marrow Transplant. 2017;52(9):1338-1341.
17. Shaw BE, Ball L, Beksac M, et al. Donor safety: the role of the WMDA in ensuring the safety of volunteer unrelated donors: clinical and ethical considerations. Bone Marrow Transplant. 2010;45(5):832-838.
18. van Walraven SM, Nicoloso-de Faveri G, Axdorph-Nygell UA, et al. Family donor care management: principles and recommendations. Bone Marrow Transplant. 2010;45(8):1269-1273.
19. O'Donnell PV, Pedersen TL, Confer DL, et al. Practice patterns for evaluation, consent, and care of related donors and recipients at hematopoietic cell transplantation centers in the United States. Blood. 2010;115(24):5097-5101.
20. Anthias C, Shaw BE, Kiefer DM, et al. Significant Improvements in the Practice Patterns of Adult Related Donor Care in US Transplantation Centers. Biol Blood Marrow Transplant. 2016;22(3):520-527.
21. Shaw PJ, Kan F, Woo Ahn K, et al. Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors. Blood. 2010;116(19):4007-4015.
22. Weisdorf DJ, Anasetti C, Antin JH, et al. Allogeneic bone marrow transplantation for chronic myelogenous leukemia: comparative analysis of unrelated versus matched sibling donor transplantation. Blood. 2002;99(6):1971-1977.
23. Hows JM, Passweg JR, Tichelli A, et al. Comparison of long-term outcomes after allogeneic hematopoietic stem cell transplantation from matched sibling and unrelated donors. Bone Marrow Transplant. 2006;38(12):799-805.
24. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641-650.
25. Saber W, Opie S, Rizzo JD, et al. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. Blood. 2012;119(17):3908-3916.
26. Majhail NS, Chitphakdithai P, Logan B, et al. Significant improvement in survival after unrelated donor hematopoietic cell transplantation in the recent era. Biol Blood Marrow Transplant. 2015;21(1):142-150.
27. Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. J Clin Oncol. 2013;31(10):1310-1316.
28. Worel N, Buser A, Greinix HT, et al. Suitability Criteria for Adult Related Donors: A Consensus Statement from the Worldwide Network for Blood and Marrow Transplantation Standing Committee on Donor Issues. Biol Blood Marrow Transplant. 2015;21(12):2052-2060.
29. DiMartini A, Dew MA, Liu Q, et al. Social and Financial Outcomes of Living Liver Donation: A Prospective Investigation Within the Adult-to-Adult Living Donor Liver Transplantation Cohort Study 2 (A2ALL-2). Am J Transplant. 2017; 17(4):1081-1096.
30. Dew M, Boneysteele G, DiMartini A. Unrelated Donors. In: Steel J, ed. Living Donor Advocacy: An Evolving Role Within Transplantation. New York: Springer; 2014:149-167.
31. Simmons RG, Klein SD, Simmons RL. Gift of Life: The Social and Psychological Impact of Organ Transplantation. Am J Sociol. 1979;85(2):179-481.