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The Concentration of Total Nucleated Cells in Harvested Bone Marrow for Transplantation Has Decreased over Time

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A B S T R A C T

Bone marrow (BM) is an essential source of hematopoietic stem cell grafts for many allogeneic hematopoietic cell transplant (HCT) recipients, including adult patients (for specific diseases and transplantation strategies) and the majority of pediatric recipient. However, since the advent of granulocyte colony-stimulating factor-mobilized peripheral blood stem cell (PBSC) grafts, there has been a significant decrease in the use of BM in HCT, thought to be due mainly to the increased logistical challenges in harvesting BM compared with PBSCs, as well as generally no significant survival advantage of BM over PBSCs. The decreased frequency of collection has the potential to impact the quality of BM harvests. In this study, we examined >15,000 BM donations collected at National Marrow Donor Program centers between 1994 and 2016 and found a significant decline in the quality of BM products, as defined by the concentration of total nucleated cells (TNCs). The mean TNC concentration in BM donations dropped from 21.8×10^6 cells/mL in the earliest era (1994 to 1996) to 18.7×10^6 cells/mL in the most recent era (2012 to 2016) (means ratio, .83; $P < .001$). This decline in BM quality was seen despite the selection of more donors perceived to be optimal (eg, younger and male). Multivariate regression analysis showed that higher-volume centers (performing >30 collections per era) had better-quality harvests with higher concentrations of TNCs collected. In conclusion, we have identified a significant decrease in the quality of BM collections over time, and lower-volume collection centers had poorer-quality harvests. In this analysis, we could not elucidate the direct cause for this finding, suggesting the need for further studies to investigate the key factors responsible and to explore the impact on transplant recipients.

INTRODUCTION

Bone marrow (BM) is the original, and an essential, hematopoietic stem cell (HSC) source for many allogeneic hematopoietic cell transplantation (HCT) recipients. However, with the advent of granulocyte colony-stimulating factor-mobilized peripheral blood stem cell (PBSC) transplants, and given the logistical advantages of PBSC collection over BM collection, significant decreases in the use of BM have occurred at many transplantation centers. Since the introduction of PBSCs, the use of BM as the HSC source in the unrelated donor setting has declined from 100% in the early 1990s to 19% in 2017 [1]. Nonetheless, BM remains the preferred cell source for specific disease indications in adults (eg, aplastic anemia), for the majority of pediatric transplants, and when the benefits of a decreased risk of chronic graft-versus-host disease (GVHD) outweigh other considerations [2–4]. Indeed, several studies have demonstrated that recipients of BM grafts experience less chronic GVHD than recipients of PBSC grafts [2,5,6]. In addition, other studies have shown that pediatric patients receiving BM have a survival advantage over patients receiving PBSCs [3,7,8]. The recent use of HLA-mismatched and haploidentical transplants at some centers and in current clinical trials has also led to an increased use of BM in these settings, owing to a presumed increased risk of GVHD overall with these transplants [9,10].

The decreased use of BM in allogeneic HCT has several potential consequences, including negatively affecting the overall quality of BM donations owing to a lack of experience with the harvesting procedure at both center and operator levels. Although standard operating procedures are in place and centers provide initial training, ongoing competency assessment is often difficult when few procedures are performed per year in many centers. The Foundation for Accreditation of Cellular Therapies (FACT) standard requires the BM harvest team of an accredited facility to perform at least 1 BM harvest per year average in the accreditation cycle (ie, a minimum of 3 BM harvests in the accreditation cycle of 3 years), to perform quality assessment of collection procedures, and to implement standardized protocols [11]. However, FACT standards do not address individual collector experience, a minimum number of collections per individual collector per year, specific staff training, and collection techniques. In addition, proper assessment of BM harvest metrics, including total nucleated cell (TNC) dose collected compared with target dose, quality of BM collected, and adverse reactions in donors following collection, is difficult in an individual collection center when limited procedures are performed, and comparable evaluations from other centers are not easily obtained.

In a single-center study, quality measurements found decreasing TNC doses over time in BM products collected externally and received for individual patients (personal communication, N. Prokopishyn, Jan 2008). We sought to confirm and explore potential reasons for this observation in a validation cohort. Thus, the aim of this study was to examine the trends in BM harvest quality in a large cohort of National Marrow Donor Program (NMDP) donors over several decades to establish whether this single-center observation could be generalized. To this end, we assessed the BM quality (defined as concentration of TNC per BM volume collected) in harvests performed by NMDP centers between 1994 and 2016. In addition to the number of harvests per center per era, other donor and procedure factors were examined to evaluate their impact on BM quality.

METHODS

Study Population

The study population comprised domestic unrelated first-time BM donors of products collected at NMDP centers between 1994 and 2016. Data on donor and donation characteristics were recorded on standard data forms by the NMDP. All donors included in this study provided written informed consent for participation in Center for International Blood and Marrow Transplant Research (CIBMTR) studies that were approved by the NMDP's Institutional Review Board.

BM Donation

BM was collected in an operating room from the posterior iliac crests under general or regional anesthesia in accordance with NMDP standards. NMDP standards mandate aspiration of no more than 20 mL/kg (donor weight) of marrow, a duration of anesthesia not to exceed 150 minutes, and a duration of collection <120 minutes [12].

Data Collection

All data used in our analysis were reported by collection centers to the NMDP/CIBMTR at the time of collection/transplantation. The number of collections per center per era was calculated using the number of collections reported to the NMDP in this population.

Endpoints

The primary study outcome was the measurement of TNCs collected per milliliter of BM as an estimate of HSC product quality. For each harvest, this was calculated based on TNCs in the product and the volume of the final product, including additives. The calculation was performed before any processing at the transplantation center. The number of collections performed per harvest center and era was also determined.

Statistical Methods

The study population was analyzed over 5 eras: 1994 to 1996, 1997 to 2001, 2002 to 2006, 2007 to 2011, and 2012 to 2016. Eras were selected to represent 5 years per period, except for the first era, which covers only 3 years, 1994 to 1996, because before 1994, insufficient data were available for analysis. A variety of donor characteristics, including sex, age, and body mass index (BMI), as well as collection volume with and without additives per donor weight, were compared between eras using the chi-square test. Donor weight, duration of anesthesia, duration of the collection procedure, product volume with additive, and TNC concentration in the BM product were compared using the Kruskal-Wallis test. Collection centers were subdivided based on collection center volume per harvest center per era. High-volume centers were defined as centers collecting ≥30 BM products per center per era; low-volume centers, as those collecting <30 BM products per center per era.

For multivariate analysis, log transformation was applied to TNC concentrations to induce normality. Multiple linear regression was used to model log TNC concentrations as a function of the primary variable of interest (era of donation), as well as donor characteristics (ie, sex, race, age, and weight) and the number of donations per harvest center per era. Stepwise variable selection was used to select variables in addition to the primary variable of interest. Interactions between the primary variable of interest and the other covariates were assessed. Effects are summarized as ratios of means of the TNC concentrations, owing to the use of log transformation for modeling. We also investigated accounting for potential harvest center effects through the use of linear mixed models, including a random effect for harvest center; however, we found no significant center effect, and the results were not meaningfully impacted by adjusting for random center effects, and so those results were omitted from our analysis.

RESULTS

More than 15,000 BM donations collected between 1994 and 2016 were examined in this study. Donor, collection, and product data are provided in Table 1. We found a significant decline in the mean concentration of TNCs in the BM products over time, from 21.8×10^6 TNCs/mL in the earliest era (1994 to 1996) to 18.7×10^6 TNCs/mL in the most recent era (2012 to 2016) (means ratio, .83; $P < .001$) (Table 2 and Figure 1).

In recent eras, BM donors were significantly more likely to be young ($P < .001$) and male ($P < .001$) (Table 1). In the 2012 to 2016 era, 54% of the donors were age <30, compared with only 25% in 1994 to 1996 and 1997 to 2001. Similarly, 65% of the donors were male in the 2012 to 2016 era, compared with 53% in 1994 to 1996 era. Moreover, there was a significant difference in donor weight over time, with donors in the 2012 to 2016 era weighing more than donors in earlier eras (Figure 2). Univariate analysis of recipient weight found significant differences over time as well (Figure 3).

The number of centers performing collections varied from a high of 106 centers in the 1997 to 2001 era to a low of 73 centers in the most recent era examined, 2012 to 2016 (Table 1). Similarly, the highest number of total BM collections was recorded in the 1997 to 2001 era. However, the mean number of collections per center was highest in the 2012 to 2016 era. The average number of collections per era increased over the last 3 eras (Table 1) even though the number of collection centers performing BM harvests declined.

Multivariate analysis confirmed the impact of era on reduced BM quality over time, with a ratio of means TNC concentration of .83 in 2012 to 2016 compared with 1994 to 1996 (95% confidence interval [CI], .81 to .84; $P < .001$) (Table 3). Donor race was also found to be associated with a reduction in BM quality over time, with significantly lower TNC doses in Hispanic, African/African American, and Asian Pacific Islander donors compared with Caucasian donors (mean ratio, .98 [95% CI, .96 to .99], .85 [95% CI, .84 to .87], and .90 [95% CI, .88 to .92], respectively). Older donors had lower BM quality with compared to the youngest donors (age 18 to 29 years). Donor factors associated with increased BM quality included female sex (mean ratio compared with male donors, 1.04; 95% CI, 1.03 to 1.06), and donor weight, with better quality in heavier donors. The heaviest donor group, weighing >83 kg, had a mean ratio of 1.14 compared with the lightest donors weighing ≤69 kg (95% CI, 1.12 to 1.16). The number of BM collections at a center per era was also associated with BM quality, with centers performing ≥30 collections per era having a significantly better correlation with BM quality compared with centers performing <30 collections per era (mean ratio, 1.02; 95% CI, 1.01 to 1.04) (Table 3, Figure 4).

DISCUSSION

In this large study of unrelated BM donor harvests, we found a significant decrease in the quality of BM products over time, as demonstrated by a drop in the TNC dose collected in recent years. Interestingly, these results were found despite the increased use of what are considered optimal donors (eg, younger males) in more recent eras [13–16]. The use of younger male donors has been linked to higher TNC doses in BM products in some studies [14,16]; however, this was not found in our study, in which lower BM quality was associated with male sex. Older age and all other races except Caucasian and Native American were associated with lower TNC doses collected. Although there was a change in racial diversity of the donor population over time, with a reduction from 81% Caucasian in the earliest era to 61% Caucasian in the most recent era, racial diversity is not likely responsible for the decreasing TNC doses over time, given that even with adjustments for race in the multivariate model, the effect remained significant. Donor weight >69 kg was associated with higher BM quality. Interestingly, we noted an increase in donor weight in the recent era. However, this increase in donor weight and its purported positive effects on BM quality did not prevent the significant decline in BM quality in the current era. As such, shifts in donor types used in BM collection today do not explain the observed decline in TNC concentration. Unfortunately, approximately 34% of donors did not have an associated recipient weight reported, and thus no conclusions could be drawn regarding the impact of time on the TNC dose collected per kilogram of recipient weight. The reduction in recipient weight seen in the later eras may be a result of an increased proportion of the BM products used in pediatric recipients.

Multivariate analysis showed that volume of collection center BM harvests may play a crucial role in BM quality, as we found that higher-volume collection centers collected higher-quality BM products. Specifically, collection centers that collect ≥30 BM products per era collect higher-quality products than those centers collecting <30 BM products per era (Figure 4). Therefore, factors such as collector experience, collection center policies and procedures, collection team training/continuing competency, and collection technique may play significant roles. Indeed, Fagioli et al [17] spoke to the importance of collector training and standardized procedures in the quality of BM harvested. In low-volume centers, the number of harvests performed per collector may be insufficient to maintain the appropriate level of expertise in BM procedures.

In addition, specific technical aspects of the BM collection, which differ from center to center, may have a profound influence on the TNC concentrations collected. For example, the speed of the collection and harvest draws can impact the concentration collected, with faster collections yielding lower TNC concentrations [14,18]. The speed of collection can be influenced both by harvester technique and the type of needle used in the collection [18,19]. In addition, some studies have suggested that large-volume collections and longer collection times can decrease the likelihood of obtaining the desired TNC dose [20,21]. Furthermore, larger aspirate volumes have been shown to produce decreased TNC and $CD34^+$ cell counts compared with smaller aspirate volumes [20,22,23]. Indeed,

Table 1
Donor, Collection, and Product Data by Era

Variable	1994-1996	1997-2001	2002-2006	2007-2011	2012-2016*	*P* Value†
Number of donors	1720	4439	3135	2999	3583	
Number of centers	90	106	91	80	73	
Sex, n (%)						<.001
Female	806 (47)	2026 (46)	1263 (40)	1164 (39)	1267 (35)	
Male	914 (53)	2413 (54)	1872 (60)	1835 (61)	2316 (65)	
Race, n (%)						<.001
Caucasian	1400 (81)	3235 (73)	2318 (74)	1999 (67)	2174 (61)	
Hispanic	109 (6)	472 (11)	291 (9)	357 (12)	516 (14)	
African/African American	94 (5)	294 (7)	200 (6)	194 (6)	270 (8)	
Asian/Pacific Islander	63 (4)	240 (5)	134 (4)	181 (6)	215 (6)	
Native American	19 (1)	74 (2)	48 (2)	36 (1)	28 (1)	
Multiple/other	19 (1)	94 (2)	121 (4)	210 (7)	352 (10)	
Unknown/declined	16 (1)	30 (1)	23 (1)	22 (1)	28 (1)	
Age at donation, yr						<.001
18-29, n (%)	424 (25)	1089 (25)	927 (30)	1175 (39)	1946 (54)	
30-39, n (%)	640 (37)	1600 (36)	1060 (34)	917 (31)	939 (26)	
40-49, n (%)	514 (30)	1357 (31)	867 (28)	690 (23)	519 (14)	
50+, n (%)	142 (8)	393 (9)	281 (9)	217 (7)	179 (5)	
Median (range)	37 (19-58)	37 (19-61)	36 (19-61)	33 (19-61)	29 (19-60)	<.001
Weight, kg						
Number evaluated	1720	4439	3135	2999	3583	
Median (range)	76 (26-175)	79 (9-200)	82 (14-193)	82 (40-164)	81 (41-150)	<.001
Collection-related variables						
Duration of anesthesia, min						
Number evaluated	0	0	1546	2987	1682	
Median (range)	(.-.)	(.-.)	90 (26-248)	92 (25-355)	88 (34-301)	.042
Duration of collection, min						
Number evaluated	0	0	1559	2989	1686	
Median (range)	(.-.)	(.-.)	55 (7-194)	51 (2-208)	48 (0-221)	<.001
Product-related variables						
Collection volume, without additives, L						<.001
<1, n (%)	0	0	689 (44)	1302 (44)	1490 (42)	
1-1.5, n (%)	0	0	695 (44)	1304 (44)	1424 (40)	
≥1.5, n (%)	0	0	181 (12)	370 (12)	606 (17)	
Unknown, n (%)	1720 (N/A)	4439 (N/A)	1570 (N/A)	23 (N/A)	63 (N/A)	
Median (range)	(.-.)	(.-.)	1064 (68-2360)	1067 (119-2323)	1090 (125-2214)	<.001
Collection volume with additive per donor weight, mL/kg						<.001
<10	0	0	482 (31)	898 (30)	1029 (29)	
10-<15	0	0	490 (31)	984 (33)	1033 (29)	
15-<20	0	0	519 (33)	904 (30)	1087 (31)	
≥20	0	0	74 (5)	190 (6)	371 (11)	
Unknown	1720 (N/A)	4439 (N/A)	1570 (N/A)	23 (N/A)	63 (N/A)	
Median (range)	(.-.)	(.-.)	13.1 (.7-23.6)	13.1 (1.2-29.0)	13.6 (1.3-40.2)	<.001
Product volume, with additive, mL						
Number evaluated	1718	4424	3127	2993	3550	
Median (range)	1200 (91-2782)	1257 (180-3110)	1266 (128-2767)	1246 (139-2557)	1290 (108-2720)	<.001

N/A indicates not applicable.

Helgestad et al [24] reported that small-volume marrow aspirates provide more representative BM results with less blood contamination. Interestingly, our data show that the volume of BM collected increased while the duration of the harvest decreased in the latest era. Previous studies have indicated that larger product volumes are being collected in short time periods, most likely to obtain the requested cell dose for recipients [25]. Although a shorter collection time is beneficial and associated with reduced adverse reactions in donors [26], it may negatively affect the product quality [27], [28]suggesting that a compromise between these extremes may be optimal. Whether the decreased TNC concentrations observed in our study were the result of larger aspirates obtained during harvesting is unknown, given that aspirate volume and speed of draw were not reported. Moreover, the type of needle used for BM collection was not reported, and thus it is impossible to determine the influence of harvesting equipment and supplies on our findings.

Table 2
Concentration of TNCs with Additive over Time

Variable	1994- 1996	1997- 2001	2002- 2006	2007- 2011	2012-2016	*P* Value
Number of donors	1720	4439	3135	2999	3583	
Number of centers	90	106	91	80	73	
Concentration of TNCs with additive, $\times 10^6$/mL						
Number evaluated	1718	4420	3121	2989	3547	
Median (range)	21.8 (4.3-3450.0)	20.3 (4.3-2400.0)	19.8 (.3-1320.0)	19.5 (3.1-16,236.7)	18.7 (1.2-349.8)	<.001

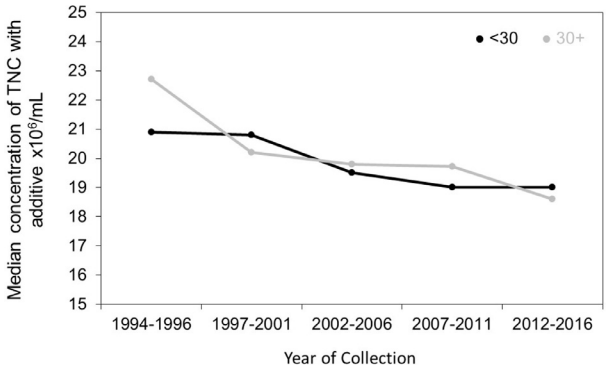

Figure 1. Median concentration of TNCs with additive, $\times 10^6$ cells/mL, by era of collection and collection center size.

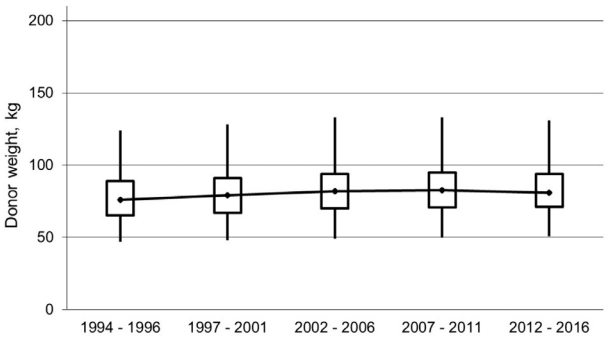

Figure 2. Donor weight increased significantly over time ($P < .001$). Data are for the 1st percentile, lower quartile, median, upper quartile, and 99th percentile by examined eras.

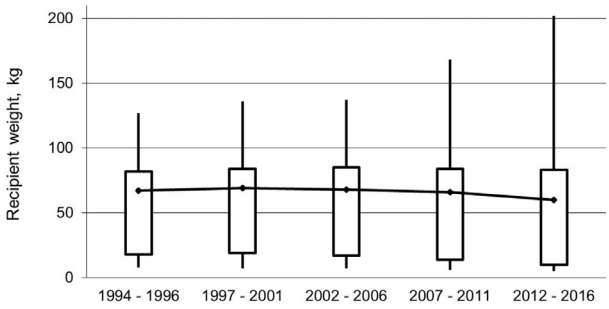

Figure 3. Reduction in weight of BM recipients over time. Data are median, with 1st percentile, lower quartile, upper quartile, and 99th percentile. N = 10,437; associated recipient weight data were available for only 66% of the donors.

Furthermore, details regarding collector experience, technique, training, and staff turnover were not available. Further studies examining the collection process, including training, techniques, equipment, and donor characteristics, will help elucidate the entire process and aid the identification of strategies aimed at improving the quality of BM products collected. For example, examination of the role of educational tools, such as the NMDP's BM collection video, and their impact on technique standardization would be beneficial to determine whether specific variables can help improve BM quality. In addition, the consolidation of BM harvests into centralized "super centers" may affect many of these variables and address several concerns, although such super centers might not be feasible in many settings. Interestingly, the number of centers performing BM harvests has decreased by more than 30% since the peak of 106 centers in 1997 to 2001 (Table 1). However, it is unknown how many of the collections were performed by these centers that no longer perform collections.

In conclusion, we found that the quality of BM harvests has decreased over time, and that collection centers performing smaller numbers of BM harvests per year collect lower-quality

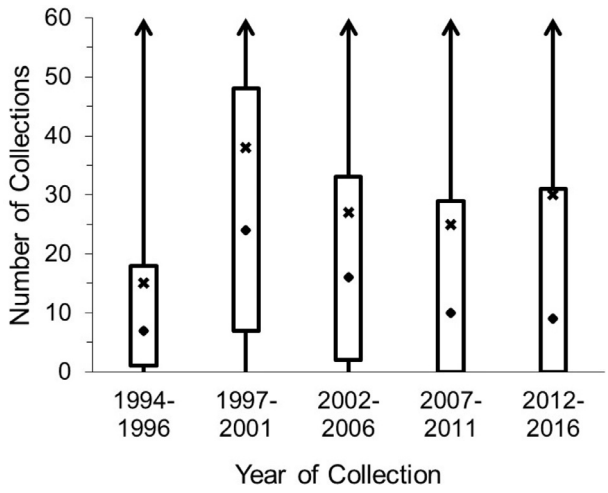

Figure 4. Number of collections per year by era, with mean (x) and median (◆) values. The maximum number of collections performed per year in the era is represented numerically, with the box representing the 25th and 75th percentiles. The arrows indicate the maximum number of collections per era, which are >60 (230 for 1994-1996, 477 for 1997-2001, 479 for 2007-2011, and 920 for 2012-2016) and are not represented, to more accurately depict the difference in quartile values across eras.

Table 3
Multivariate Model Using Linear Regression on Log TNC Concentration

Variable	Relative Effect (Relative Change in TNC Concentration)	95% CI	*P* Value
Collection year			
1994-1996	1.00		<.001
1997-2001	.92	.90-.93	<.001
2002-2006	.89	.87-.90	<.001
2007-2011	.87	.86-.89	<.001
2012-2016	.83	.81-.84	<.001
Donor race			
Caucasian	1.00		<.001
Hispanic	.98	.96-.99	.003
African/African American	.85	.84-.87	<.001
Asian Pacific Islander	.90	.88-.92	<.001
Native American	1.04	.99-1.09	.083
Multiple race/other	.97	.95-.99	.014
Unknown/declined to answer	.92	.87-.97	.003
Donor sex			
Male	1.00		<.001
Female	1.04	1.03-1.06	<.001
Number of collections per center			
<30	1.00		<.001
≥30	1.02	1.01-1.04	<.001
Donor age at collection			
18-29	1.00		<.001
30-39	.98	.97-.99	<.001
40-49	.92	.91-.93	<.001
50+	.89	.87-.91	<.001
Donor weight, kg			
≤69	1.00		<.001
69-71	1.04	1.01-1.07	.004
71-83	1.07	1.05-1.09	<.001
83+	1.14	1.12-1.16	<.001

BM products. This decline in BM quality has persisted even though centers have been using more optimal donors in recent eras. Further studies are needed to elucidate the factors responsible for this significant decrease in BM quality and, critically, to determine the impact of this declining BM quality on transplantation outcomes, to ensure that BM remains a high-quality source of HSCs for HCT.

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