Subsequent donation requests among 2472 unrelated hematopoietic progenitor cell donors are associated with bone marrow harvest

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ABSTRACT

Approximately 1 in 20 unrelated donors are asked to make a second donation of hematopoietic progenitor cells, the majority for the same patient. Anthony Nolan undertook a study of subsequent hematopoietic progenitor cell donations made by its donors from 2005 to 2011, with the aims of predicting those donors more likely to be called for a second donation, assessing rates of serious adverse reactions and examining harvest yields. This was not a study of factors predictive of second allografts. During the study period 2591 donations were made, of which 120 (4.6%) were subsequent donations. The median time between donations was 179 days (range, 21-4016). Indications for a second allogeneic transplant included primary graft failure (11.7%), secondary graft failure (53.2%), relapse (30.6%) and others (1.8%). On multivariate analysis, bone marrow harvest at first donation was associated with subsequent donation requests (odds ratio 2.00, P=0.001). The rate of serious adverse reactions in donors making a subsequent donation appeared greater than the rate in those making a first donation (relative risk=3.29, P=0.005). Harvest yields per kilogram recipient body weight were equivalent between donations, although females appeared to have a lower yield at the subsequent donation. Knowledge of these factors will help unrelated donor registries to counsel their donors.

Introduction

Allogeneic hematopoietic progenitor cell transplantation is now an established treatment for many hematologic malignancies, bone marrow failure syndromes and metabolic diseases.[1] Its development from an experimental novelty in the 1950s and 1960s to first-line therapy today is the consequence of many factors, including the establishment of experienced transplant centers, advances in supportive care, antimicrobial therapy and transfusion technology, and the formation of unrelated adult donor registries and cord blood banks now able to offer over 20 million donors and cord blood units worldwide to those without an HLA-identical sibling donor.[2] Along with increasing use of haplo-identical donors,[3] this expansion of available donor options means that, at least in the developed world, very few patients in need of a transplant should go without one.

Despite this progress, transplant failure remains a devastating complication, whether through graft rejection or failure of the graft-*versus*-malignancy effect, leading to disease relapse.[4] Outcomes in these circumstances can be very poor, with dire prospects of long-term survival in both groups.[5] The 1-year survival rate in patients with primary graft failure is particularly dismal (11% in one study).[6] In these groups of patients, a second allograft is a reasonable option for clinicians hoping to rescue hematopoietic function or re-establish disease control.[7-15]

The number of second or subsequent allogeneic transplants performed varies by country: data published by the British Society for Bone Marrow Transplantation show that 'non-first' allografts accounted for 7% of all transplants in the UK and Northern Ireland in 2010.[16] Anthony Nolan has consistently found the rate of second hematopoietic progenitor cell donations requested from its unrelated adult donors to be between 4% and 7% each year (internal audit).

A few studies have addressed second allografts from the perspective of the donor. Early reports focused on transplant yields and donor hematologic indices. A small study of 16 donors by Stroncek in 1991 showed a significant difference in red cell transfusion requirements and a slight reduction in hemoglobin levels between first and second-time bone marrow (BM) donors.[17] In 1997 Stroncek published again on second time donors, this time focusing on 19 volunteer peripheral blood stem cell (PBSC) donors.[18] Harvest yields were found to be equivalent between first and second donations, and routine blood counts were also unchanged. No difference in adverse reactions between first and second donations was reported, but numbers were, of course, too low to ascertain anything other than a very large difference. In 1997 Anderlini *et al.* published similar findings on harvest yields and adverse events in a study of 13 PBSC donors, concluding that second PBSC collections were 'feasible, similarly tolerated and (able to) provide comparable apheresis yields'.[19]

Later (and larger) studies supported these results. The Spanish,[20] German[21] and Japanese[22] registries reported the experience of 46 PBSC, 67 PBSC and 137 BM donors, respectively. All three studies showed similar rates of adverse reactions between first and second donations, but inferior harvest yields from the second donation. Finally, the National Marrow Donor Program recently reported follow-up from 43 donors who had donated twice to their recipient.[23] Again, rates of adverse reactions were found to be comparable between first and second donations.

In this National Marrow Donor Program cohort (a combination of both PBSC and BM donors), it was noted that in the 60% of donors who donated BM the first time, 77% went on

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to donate PBSC a second time. This may simply be a reflection of changing trends in hematopoietic progenitor cell harvest (PBSC harvest has become much more common in recent years)[1], or may reflect the view that transplantation with peripherally harvested stem cells carries a lower risk of graft failure.[24]

By contrast, little work has been published looking at donor attributes at first donation that may be associated with an increased likelihood of being requested to give a subsequent HPC donation. One study from the United Kingdom of 144 patients diagnosed with primary graft failure following transplantation suggested that the use of BM as the HPC source, female donors and HLA-mismatched grafts increased the risk of primary graft failure (and, consequently, a request for a subsequent donation).[25]

In order to develop the evidence, and provide a sounder base for informed consent from its own unrelated donors, Anthony Nolan undertook a study of all second donations made by its HPC donors from 2005 to 2011. The objectives were to identify those donor and patient characteristics known by the registry at first donation that may be associated with a subsequent request for another HPC donation, to examine the safety of subsequent donations, and to compare harvest yields between first and subsequent donations. Importantly, this study was not aimed at examining patient factors predictive of the need for a second allograft.

Methods

Data collection

Data were obtained retrospectively from records kept by Anthony Nolan for the period 2005-2011, during which time 2591 HPC donations were made by 2472 unrelated adult donors to 2493 recipients.

During this study period, 145 requests for subsequent donations were made, of which 25 (17.4%) were later cancelled by the transplant center. There were three types of subsequent donation requests encountered in this study: 118 requests (group A, 81.4%) were to the same donor for the same patient as the initial donation; 21 (group B, 14.5%) were to a donor who had previously donated, but for a different patient and in six cases, patients requested (group C, 4.1%) a subsequent donation from a different donor.

For the purposes of assessing an association between donor and patient characteristics at initial donation and the need for a subsequent donation (whether from the same or a different donor), all patients for whom there was a request for a subsequent donation were reviewed (i.e. excluding those donors in group B whose donations were being used for a first transplant for the recipient). For the purposes of assessing harvest yields and adverse events related to a second donation, all donors who had donated more than once were reviewed (i.e. excluding the group C donors who had donated only once).

Thirteen (8.9%) of the donors who made a subsequent donation during the study period made their initial donation before 2005. As the statistical analysis relied on comparator data from those donors who made only a single donation, this sub-group was excluded from all analyses, since comparator data from before 2005 were not obtained.

Donor factors considered in this analysis included degree of HLA match (10/10 allele-matching being the ideal), cytomegalovirus (CMV) antibody status, gender, age and route of donation at first donation. Patient factors considered in the analysis included patient age, gender and disease type. The year of first donation was also included to account for changes in preference for HPC source in recent years. These characteristics are readily available in the donor registry. Other patient characteristics, including disease status at transplant and conditioning regimen intensity are generally not shared with the registry and were, therefore, unavailable for this study.

Serious adverse reactions were defined according to standard criteria published by the Serious Events and Adverse Reactions (SEAR) committee of the World Marrow Donor Association (WMDA).

The study protocol was reviewed by the Institutional Review Board at Anthony Nolan, which deemed that ethical approval was not necessary.

Statistics

Univariate analyses of donor and patient factors influencing subsequent HPC donation requests were performed using a χ^2 test for binomial variables and logistic regression for multinomial categorical variables (e.g. disease). Multivariate analysis was performed using binary logistic regression. A time-dependent cumulative hazard plot for subsequent HPC donation requests was modeled using the Kaplan-Meier method, and Cox regression analysis was performed to compare the hazard of subsequent donation requests between PBSC and BM as the route of initial donation. Rates of serious adverse events between first time and subsequent HPC donors were also compared using a χ^2 test. Harvest yields between first and subsequent donations were compared using a paired t-test.

Results

Donor and patient characteristics

Table 1 summarizes donor and patient characteristics for two groups. The first group comprises donations from donors who made only a single donation during the study period (n=2373). The second group includes donations from donors who were subsequently requested to donate HPC again for the same recipient (n=111).

For the single donation-only group, the median age of the patients was 46 years (range, 0-74), and 15% were pediatric donors. Acute leukemia accounted for almost half (47.6%) of the transplant indications; non-malignant indications accounted for 9.5%. Of these donations, 22.6% were by BM harvest. The median age of the donors was 35 years, and the majority of donors were male (76.8%) and CMV-negative (67.7%), reflecting donor selection practices. The numbers of donations were slightly higher in the latter half of the study period than in the former, reflecting an increase in usage of unrelated donors in general.

Subsequent donation requests

The median time to a subsequent donation request for the same recipient was 179 days (range, 21 to 4016 days; interquartile range 306) from the day of the first transplant. Seventy-three percent of requests were made within 1 year of the first donation, and 91% within 2 years. Figure 1 shows a cumulative hazard curve (limited to 1000 days) with an event defined as the registry receiving a subsequent donation request. The median age of those requiring a subsequent donation was 42 years (range, 0-68) and 87.4% were adults.

Indications for a second allogeneic transplant included primary graft failure (11.7%), secondary graft failure (53.2%), disease relapse (30.6%) and other (1.8%). This last group included two cases of secondary acute myeloid

leukemia and one case of refractory BK virus and CMV infection on a background of mixed donor chimerism. In three cases (2.7%), the indication for second allograft could not be established.

The main disease categories in the group of patients requiring a subsequent donation included acute myeloid leukemia (32.4%, n=36), acute lymphoblastic leukemia (11.7%, n=13), myelodysplasia (11.7%, n=13), non-Hodgkin's lymphoma (10.8%, n=12), aplastic anemia (9%, n=10) and chronic myeloid leukemia (6.3%, n=7); 83.8% of

Table 1. Univariate analysis of donor and patient characteristics at first donation.

Characteristic	Single donation episode only n. (%)	Donation episodes for which a further donation was requested for the same patient n. (%)	Odds ratio for subsequent donation request	95% CI	P
Patient age, years					
Median/range	46/0-74	42/0-68	-	-	-
<46*	1183 (49.9%)	61 (55.0%)	-	-	-
≥46	1190 (50.1%)	50 (45.0%)	0.81	0.56-1.19	0.293
Adult*	2016 (85.0%)	97 (87.4%)	-	-	-
Pediatric (≤17 years)	357 (15.0%)	14 (12.6%)	0.81	0.46-1.44	0.482
Patient gender					
Male	1442 (60.8%)	69 (62.2%)	1.06	0.72-1.57	0.769
Female*	931 (39.2%)	42 (37.8%)	-	-	-
Disease					
Aplastic anemia	102 (4.3%)	10 (9.0%)	2.23	1.07-4.60	0.032
Acute lymphoblastic leukemia	311 (13.1%)	13(11.7%)	0.95	0.50-1.81	0.876
Acute myeloid leukemia*	818 (34.5%)	36 (32.4%)	-	-	-
Chronic lymphocytic leukemia	124 (5.2%)	5 (4.5%)	0.92	0.35-2.38	0.857
Chronic myeloid leukemia	114 (4.8%)	7 (6.3%)	1.40	0.61-3.21	0.433
Hodgkin's lymphoma	92 (3.9%)	2 (1.8%)	0.49	0.12-2.09	0.3337
Infection	5 (0.2%)	2 (1.8%)	9.09	1.70-48.5	0.010
Inherited disease	98 (4.1%)	6 (5.4%)	1.39	0.57-3.39	0.467
Myelodysplastic syndrome	264 (11.1%)	13 (11.7%)	1.12	0.59-2.14	0.734
Myeloma†	75 (3.2%)	0 (0%)	-	-	-
Myeloproliferative neoplasm	67 (2.8%)	5 (4.5%)	1.70	0.64-4.46	0.285
Non-Hodgkin's lymphoma	283 (11.9%)	12 (10.8%)	0.963	0.49-1.88	0.998
Other (non-malignant)†	20 (0.8%)	0 (0%)	-	-	-
Malignant	2148 (91.3%)	93 (83.8%)	-	-	-
Non-malignant	225 (9.5%)	18 (16.2%)	2.03	1.20-3.42	0.007
Route of initial donation					
Bone marrow	537 (22.6%)	43 (38.7%)	2.14	1.44-3.17	<0.001
Peripheral blood stem cells*	1817 (76.6%)	68 (61.3%)	-	-	-
Unknown	19(0.8%)	0 (0%)			
Donor age, years					
Median/range	35/18-59	37/20-59			
≤30*	880 (37.1%)	38 (34.2%)	-	-	-
>30	1494 (62.9%)	73 (65.8%)	1.13	0.76-1-69	0.547
Donor gender					
Male*	1823 (76.8%)	88 (79.3%)	-	-	-
Female	550 (23.2%)	23 (20.7%)	0.87	0.54-1.38	0.548
Donor CMV status					
Negative*	1605 (67.6%)	76 (68.5%)	-	-	-
Positive/equivocal	758 (31.9%)	35 (31.5%)	1.01	0.68-1.55	0.904
Unknown	10 (0.5%)	0 (0%)			
HLA mismatched					
0	1896 (79.9%)	89 (80.2%)	-	-	-
>0	382 (16.1%)	19 (17.1%)	1.06	0.64-1.76	0.823
Unknown	95 (4.0%)	3 (2.4%)			
Year of initial donation					
Goodness of fit	-	-	-	-	0.157
2005	313 (13.2%)	24 (21.6%)	1.29	0.71-2.37	0.406
2006	283 (11.9%)	18 (16.2%)	1.07	0.56-2.05	0.833
2007	357 (15.0%)	11 (9.9%)	0.52	0.25-1.09	0.084
2008	365 (15.4%)	15 (13.5%)	0.69	0.35-1.37	0.289
2009	335 (14.1%)	19 (17.1%)	0.96	0.51-1081	0.890
2010*	354 (14.9%)	21 (18.9%)	-	-	-
2011§	366 (15.4%)	3 (2.7%)	-	-	-

*Reference category; †Odds ratio not calculable due to zero events in the second donation group; §For those donating in 2011, insufficient time had elapsed for accumulation of second donation requests.

recipients were transplanted for a malignant condition.

Of those recipients of a second donation 44.2% received BM for their first allograft, but only 12.8% received BM for their second. In detail, 10.5% received BM on both occasions, 33.7% received BM for the initial allograft and PBSC for the subsequent, 2.3% received PBSC for the initial allograft and BM for the subsequent, and 53.5% received PBSC for both allografts.

Donor and patient characteristics associated with subsequent donation requests

A summary of the univariate analysis of donor and patient characteristics associated with subsequent donation requests is shown in Table 1. There was no statistically significant effect of year of initial donation, patient age (either </>46 years or pediatric/adult), patient gender, donor age, donor gender, donor CMV status or HLA match. However, the route of donation had a significant effect: those being called for second donation were more likely to have donated BM for their first donation (OR=2.14, P<0.001). In addition, those donating to patients with non-malignant conditions (OR=2.03, P=0.007), and in particular aplastic anemia (OR=2.23, P=0.032) had a significantly higher likelihood of being asked to make a second donation.

Multivariate analysis

Only route of donation and patient disease were considered in multivariate analysis, as the other variables examined did not have a statistically significant effect or trend with subsequent donation requests. Because of this heterogeneity of disease groups in the study cohort, and the relatively small numbers in individual disease groups, patient disease divided into malignant and non-malignant was used in the multivariate analysis.

On multivariate analysis, donation of BM was again found to be a significant influence (OR=2.00, P=0.001), but the effect of non-malignant disease retained only a statistical trend (OR=1.62, P=0.08).

Bone marrow versus peripheral blood stem cells

In order to explore further the association of graft choice at initial donation with a subsequent donation request, baseline characteristics were compared (Table 2). As would be expected, when compared to PBSC, those donating BM were more likely to have been children (28.4% *versus* 10.6%, P<0.001), and to be donating to recipients with non-malignant diseases (20.1% *versus* 5.7%, P<0.001). Patient and donor gender, donor CMV status, age and degree of HLA mismatch did not differ between the two groups. There was a significant decrease in the provision of BM annually during the study period, coupled with a reciprocal increase in PBSC provision, reflecting global graft selection practices.

Further analyses were performed to examine whether there was an association between BM donation and subsequent donation requests for each indication for a second allograft (Figure 2). Because of the time-dependent nature of graft selection, a Cox regression model was used to compare the two graft sources. This showed a trend for an association between donation of BM for the first transplant and a subsequent donation request because of primary graft failure (Figure 2B, HR=2.84, P=0.06) and a statistically significant association with a request because of secondary graft failure (Figure 2C, HR=2.34, P=0.001), but not because of disease relapse (Figure 2D, HR=1.27, P=0.524).

In view of the preference for BM for both pediatric malignant and non-malignant indications, the analysis was repeated for adult malignancies alone (Figure 3). Again, overall, those donating BM at their initial donation were more likely to be requested to make a second donation

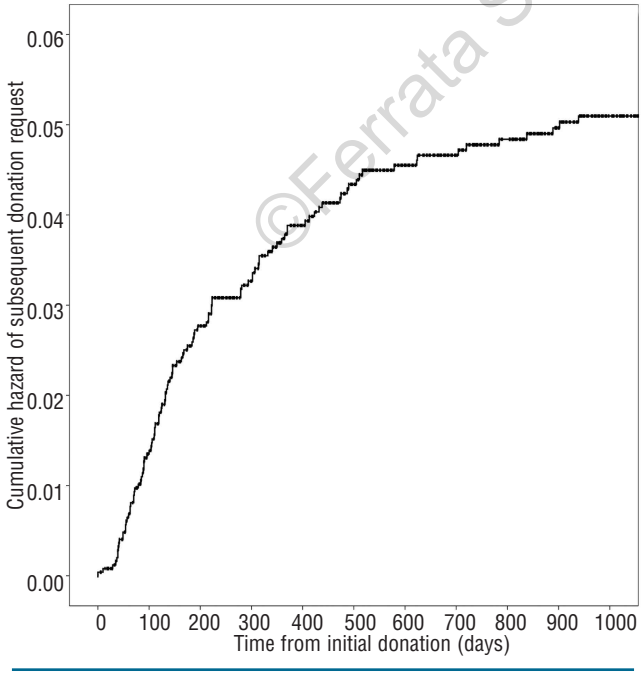

Figure 1. Kaplan-Meier cumulative hazard plot of subsequent donation requests. Time=0 equates to the date of the initial donation, and an event is defined as being requested to make a subsequent HPC donation.

Table 2. Baseline donor and patient characteristics for initial BM and PBSC donations.

Characteristic	BM	PBSC	P
Patient age			
<46 years	376 (64.8%)	858 (45.5%)	**<0.001**
Adult	415 (71.6%)	1685 (89.4%)	**<0.001**
Patient gender			
Female	222 (38.3%)	745 (39.5%)	0.591
Disease			
Non-malignant	115 (20.1%)	106 (5.7%)	<0.001
Donor age			
>30 years	361 (62.2%)	1192 (63.3%)	0.654
Donor gender			
Female	138 (23.8%)	433 (23.0%)	0.681
Donor CMV status			
Positive/equivocal	188 (32.6%)	604 (32.1%)	0.824
HLA mismatches			
>0	95 (16.9%)	301 (16.7%)	0.882
Year of donation			**<0.001**
2005	134 (23.1%)	203 (10.8%)	
2006	76 (13.1%)	212 (11.2%)	
2007	99 (17.1%)	266 (14.1%)	
2008	89 (15.3%)	288 (15.3%)	
2009	75 (12.9%)	279 (14.8%)	
2010	55 (9.5%)	320 (16.8%)	
2011	52 (9.0%)	317 (16.8%)	

(Figure 3A, HR 1.92, *P*=0.03). While the numbers were too small to draw any conclusions about primary graft failure (Figure 3B, HR=2.35, *P*=0.242), there was a statistically significant association between use of BM and a subsequent donation request because of secondary graft failure (Figure 3C, HR=2.12, *P*=0.011). However, no such effect was seen in disease relapse (Figure 3D, HR=1.69, *P*=0.173).

Donor safety

Forty serious adverse reactions were reported from 2005-2011 in those donors making just a single donation (n=2379), a rate of 1.7%. Six serious adverse reactions (as defined by the WMDA) were reported in those donors making a subsequent donation (either for the same patient or a different patient, n=107), a rate of 5.6%. Although this rate of serious adverse reactions differed statistically from that in first-time donors (RR=3.29, *P*=0.005), overall numbers were small.

Serious adverse reactions in second-time donors included a forearm nerve injury from a tourniquet being left on too long (PBSC/PBSC, definitely related), sciatica for over 1 year after a second donation (PBSC/BM, probably related), severe thrombocytopenia <30x10^9/L (PBSC/PBSC, definitely related), pancreatic cancer 2 years after donation (PBSC/PBSC, unlikely to be related), central line requiring insertion under general anesthetic (BM/PBSC, definitely related), severe muscular edema in right leg (PBSC/PBSC, probably related) and a prolonged chronic fatigue-like syndrome post-donation (PBSC/PBSC, possibly related).

Comparison of harvest yields between donations

Harvest yields were only compared for those donors giving PBSC on both occasions. The main reason for excluding BM donors from this analysis was the small number of donors who donated BM on both occasions (n=11). In addition, there were differences in the units of harvest yield between donations: for some BM collections, the unit of yield used was total nucleated cells, whereas for others, CD34 count was used.

Fifty donors donated PBSC on both occasions, and data on harvest yields were available for 46 of these donors (38

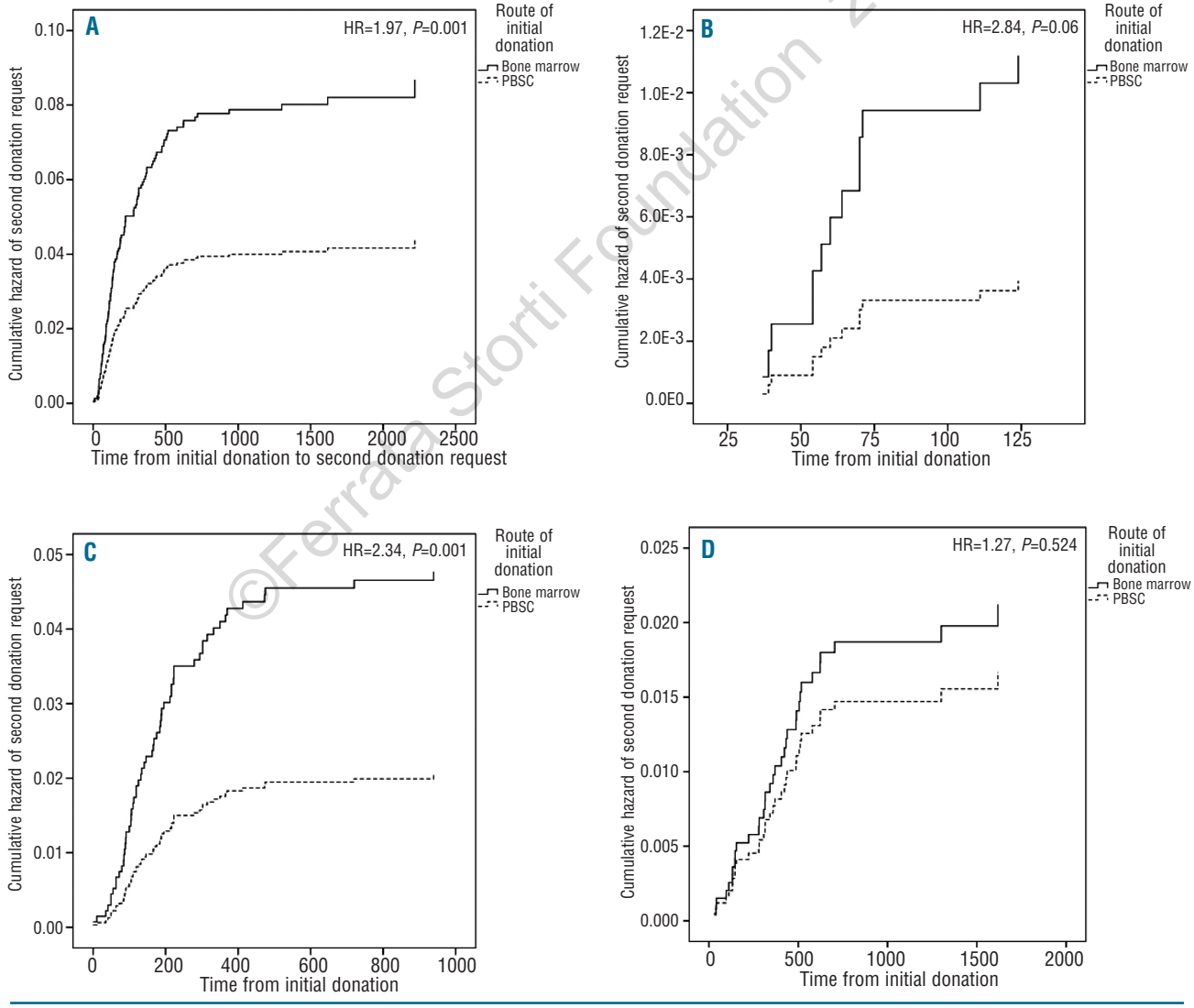

Figure 2. Cumulative hazard plots of subsequent donation requests for all donations during the study period. Time=0 is the date of initial donation, and an event is defined as being requested to make a subsequent HPC donation. Donors are categorized by whether their initial donation was BM or PBSC. (A) All indications for subsequent donation. (B) Subsequent donation request for primary graft failure. (C) Subsequent donation request for secondary graft failure. (D) Subsequent donation request for relapse.

male, 8 female). All had received at least 4 days of granulocyte colony-stimulating factor at a dose of 10 μg/kg once daily. Those requiring a second day of collection received a fifth dose following the first collection. The number of donors requiring a second day of collection did not differ significantly between first and second donations (21.2 *versus* 30.3%, *P*=0.134).

The mean total cell dose (CD34$^+$ cells x10^6) requested was 308 for the initial donation and 350 for the subsequent donation, and this difference was statistically significant (*P*=0.038). Likewise, requested dose per kg recipient weight was also greater at the subsequent donation (4.32 *versus* 4.97 CD34$^+$ cells x10^6/kg, *P*=0.017). However, there was no statistically significant increase in either total harvest yield (542 *versus* 574 CD34$^+$ cells x10^6, *P*=0.48) or yield per kg recipient weight (7.88 *versus* 8.38 CD34$^+$ cells x10^6/kg, *P*=0.41).

As a final test of equivalence of harvest yields between first and subsequent donations, the mean difference between harvest yield obtained and dose requested per kg recipient was calculated and found not to differ (+3.85 *versus* +3.93, *P*=0.92). Although a difference was seen when only female donors (n=8) were analyzed (+1.69 *versus* -0.58, *P*=0.049) this is likely to be explained by a proportionately higher requested dose for the subsequent donation compared to the first donation (4.67 *versus* 6.33 CD34x10^6/kg). A multivariate analysis was not attempted because of the small sample size.

Discussion

This study presents an in-depth review of subsequent HPC donations in a large cohort of unrelated donors. We found that donors who donate BM appear to have greater odds of being requested to make a subsequent donation, when compared to those who donate PBSC. Although there was also a trend toward increased subsequent donation requests for non-malignant conditions, this effect of BM as graft choice persisted even when pediatric and non-

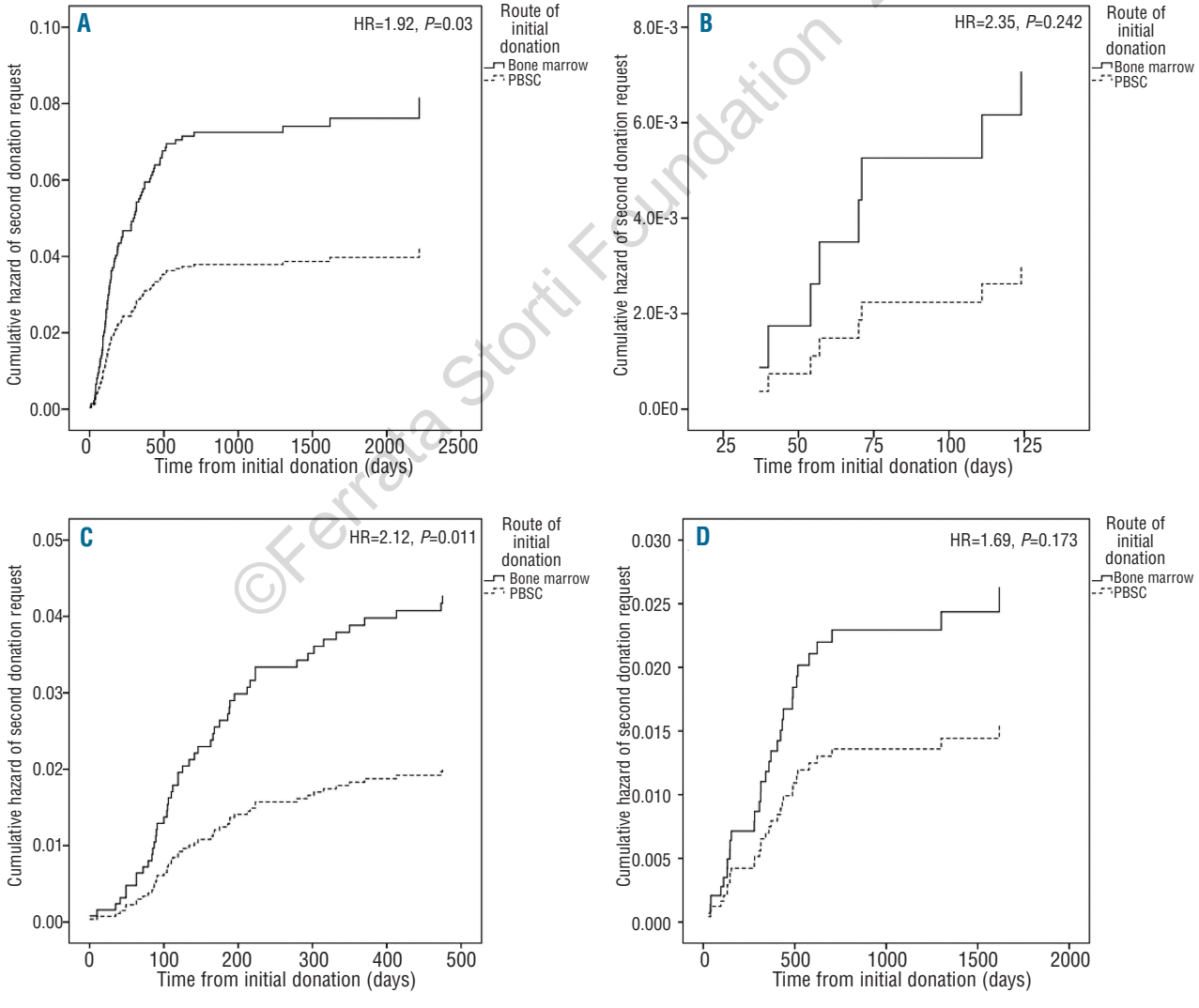

Figure 3. Cumulative hazard plots of subsequent donation requests for adult malignancies during the study period. Time=0 is the date of initial donation, and an event is defined as being requested to make a subsequent HPC donation. Donors are categorized by whether their initial donation was BM or PBSC. (A) All indications for subsequent donation. (B) Subsequent donation request for primary graft failure. (C) Subsequent donation request for secondary graft failure. (D) Subsequent donation request for relapse.

malignant cases were excluded from analysis. This effect appears to be predominantly attributable to graft failure, which has a well-documented association with BM as a graft source.[28]

There has been much recent discussion within the transplant community of preferences regarding BM or PBSC as the route of donation. Traditionally, BM has been preferred for pediatric patients,[29] as well as those with non-malignant conditions in whom a graft-*versus*-disease effect is neither required nor desirable.[30] By contrast, PBSC is the preferred product for many adult malignancies.[15,31] The majority of studies supporting such practices are based on retrospective analyses of registry data, many of which are now outdated. There was a relative lack of randomized, prospective data until the recent publication of the results of a Blood and Marrow Transplant Clinical Trials Network (BMT CTN) study, which compared PBSC to BM as the source of HPC for transplantation in patients with acute leukemia, myelodysplasia, chronic myeloid or myelomonocytic leukemia, or myelofibrosis. Importantly, no difference in overall survival was found between the two groups given grafts from the different sources. However, as a route of donation, BM was associated with more death from graft failure compared to PBSC, but less death from acute or chronic graft-*versus*-host disease.[28] The authors concluded that specific patient characteristics might influence the choice of stem-cell source. Of note, they suggested that BM might be the HPC source of choice for patients who have had previous immunosuppressive chemotherapy (and are thus at lower risk of graft failure). As a result, it is possible that the use of BM may increase again, reversing the trend of the last few years.

For a transplant physician selecting a donor, the prime concern is the prognosis of their patient. It falls, then, to harvest centers and unrelated donor registries to consider the welfare of unrelated donors when making the final decision on harvest route. A number of donor factors must be taken into consideration, not least the health of the donor, including the presence of pre-existing medical conditions that may preclude a particular route of donation.[32]

Interestingly, there has been contradictory evidence on the relative safety of BM and PBSC donations. Halter *et al.* presented the results of a survey undertaken by the European Group for Blood and Marrow Transplantation (EBMT), finding higher rates of serious adverse events in PBSC donors than in BM donors.[33] This study was retrospective, voluntary, survey-based and the overall rates of serious adverse reactions were very low, suggesting a degree of under-reporting. In addition, the study period included the early years of PBSC donation, when clinicians were likely to be much more vigilant about PBSC harvest and, perhaps, less so about BM. By contrast, Miller *et al.* published a large study based on data from several thousand donors collected prospectively by the National Marrow Donor Program, finding rates of serious adverse events of 1.34% and 0.6% in unrelated BM and PBSC donors, respectively.[34] An update to this study, reporting outcomes in 9494 National Marrow Donor Program donors who donated between 2004 and 2009, was recently published. Although the serious adverse event data were not included in this initial publication, the study showed that BM donors took longer to recover following donation. In addition 3% of BM donors reported donation-related symptoms at 6 months after donation, compared to 0% of PBSC donors.[35]

Our own data add a different perspective to the BM *versus* PBSC debate, suggesting that BM donors may be more likely to be requested to make a second donation. In addition, although comparable harvest yields have been demonstrated, the safety profile of subsequent donations remains uncertain.

Of the serious adverse events that we encountered, one (pancreatic cancer several years after donation) was very unlikely to have been related to donation. Two others (severe, but asymptomatic, thrombocytopenia and the requirement for a central line under general anesthetic) although definitely related to the donation, did not result in harm to the donor. Excluding these three events from the analysis renders the difference between adverse events non-significant. Furthermore, our study was underpowered to detect a meaningful difference in adverse events between first and second donations: such a study urgently needs to be repeated in a far larger cohort of donors. There are a few other limitations in interpreting our results: data on disease status at transplant, disease phenotype and conditioning intensity were unavailable for the whole cohort, as were data on ABO blood group matching. Our study would, by design, include only those who were deemed healthy enough to merit a subsequent donation request, and thus it is possible that selection bias may confound the results. However, it is difficult to see how this might differ depending on whether the recipient received BM or PBSC. One further limitation is that there is likely to be a cohort of subsequent donations missed by the study, namely from non-UK transplant centers requesting a non-Anthony Nolan donor for the subsequent donation, when the first donation was provided by Anthony Nolan.

While we would not currently suggest that donor registries and harvest centers advise against BM as a route of donation, our findings have implications when counseling and consenting donors. Being requested for a second donation is considered an undesirable event in itself, carrying the additive risk of donation-related adverse events as well as inconvenience to the donor, who may need to give up time from work or family for donation.

This study also contributes to an interesting ethical dilemma: how should physicians and donor registries balance the respective risks to the patient and their unrelated donor? When does the potential increased benefit to a patient from a particular route of donation outweigh the chance of a higher risk of serious adverse reactions in the donor, including long-term disability, as well as the higher chance of being requested for a second donation suggested by our study? And by telling donors that a particular route of donation may be more beneficial for the patient, are we placing them under undue emotional duress to select a particular route of harvest that may be of greater detriment to their health?

These are difficult questions to answer, and further evidence and debate are required before a consensus opinion is achieved internationally. In the meantime, it is important for donor registries and harvest physicians to be as open as possible with donors about the existing evidence for both routes of donation, and allow donors to make an informed decision without undue emotional bias.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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