Factors predicting peripheral blood progenitor cell collection from pediatric donors for allogeneic transplantation

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Background and Objectives. Although several studies have reported on the use of children as donors for peripheral blood progenitor cells (PBPC), no specific characteristics have been identified as predictors of PBPC collection in this population. In this study we analyzed predictive factors for PBPC collection in pediatric donors.

Design and Methods. We retrospectively analyzed factors predicting the yield for a target CD34+ cell dose of $\geq 4\times10^6$/Kg donor or recipient body weight, in 105 aphereses from 76 healthy pediatric donors (36 boys and 40 girls) included in the Spanish National Donor Registry. Mobilization consisted of granulocyte colony-stimulating factor (G-CSF) in single doses of 10 μg/kg per day subcutaneously for 4 or 5 days. Apheresis started after the fourth dose of G-CSF.

Results. Median age and body weight were 10 years (range 1-18) and 42 kg (range 9-89), respectively. The median number of CD34+ cells/kg recipient body weight was 4.22 (range 0.1-32). On multivariate analysis variables that had a significant negative impact on the CD34+ cell yield, considering the recipient's body weight were the total blood volume processed (regression coefficient (RC): 0.41, 95% CI: 0.21-0.81; p=0.01) and day of apheresis other than first (RC: 0.16, 95% CI: 0.07-0.34; p<0.0001). When considering donor's body weight the variables that positively influenced collection were younger age (RC: 6.79, 95% CI: 1.57-29.25; p<0.01) and large volume leukapheresis (RC: 3.33, 95% CI: 1.13-9.77; p<0.02).

Interpretation and Conclusions. Our data suggest that pediatric donors mobilized by G-CSF may donate sufficient numbers of CD34+ cells for allogeneic transplantation. The variables that influenced the yield were the donor's age, blood volume processed and the first day of the apheresis.

Key words: pediatric donors, children, transplantation, mobilization, apheresis.

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Over the last decade, mobilized peripheral blood progenitor cells (PBPC) have become an increasingly used alternative to bone marrow for allogeneic transplantation.[1] Recombinant human granulocyte colony-stimulating facttor (G-CSF) at a dose of 10 μg/kg/day for 4 or 5 days is the mobilization regimen most frequently used in normal adult donors.[2-4] In the short-term this mobilization regimen appears to be safe and well tolerated. Donor's age and the G-CSF schedule have been found to be factors that affect CD34+ cell mobilization and collection in healthy donors.[5-7]

Few studies about pediatric donors have been published.[5-10] In a recent study reported by our group,[5] mobilization using G-CSF in children was as safe and effective as in adults, although the children had a higher mobilization effect than did adult donors. However, no specific characteristics have been identified as predictive factors for PBPC collection when children are used as donors for allogeneic transplantation.

In an attempt to understand better the factors, if any, that may affect collection of CD34+ cells from pediatric donors, we retrospectively analyzed the yield of CD34+ cells from 76 healthy children included in the Spanish National Donor Registry.

Design and Methods

Data from the Spanish National Donor Registry were collected using a standardized, validated data sheet, once the data had been reviewed, by the different participating hospitals, as has been reported elsewhere.[4] The closing date of this study was October 2002. Data on donors younger than 18 years old were considered for this analysis. The donors' parents or guardians provided informed consent for mobilization and apheresis. Donors were exclusively mobilized by means of G-CSF at a dose of 10 μg/kg/day for 4 or 5 days administered subcutaneously in single daily doses. PBPC apheresis was usually started after the fourth dose of G-CSF using a continuous-flow blood cell separator and either a small-volume collection chamber (CS3000, Baxter Healthcare, Irvine, CA, USA) or an apheresis system (Spectra, COBE BCT, Lakewood, CO, USA). Large-volume leukapheresis (LVL) was defined as processing at least three times the donor's blood volume.[11] The apheresis characteristics are shown in Table 1.

Statistical analysis was performed using the StatView program (Abacus Concepts, Inc., Berkeley, CA, USA). A target CD34+ cell dose of $\geq 4\times10^6$/Kg donor or recipient

Table 1. Apheresis characteristics (n=105).

Age group	*0-4*	*5-9*	*10-14*	*15-18*	*p value*
(Number of aphereses)	(18)	(28)	(26)	(33)	
Donor age					
median (range)	3 (1-4)	7 (5-9)	12 (10-14)	17 (15-18)	
Donor weight					
median (range)	13.5 (9-18)	30 (19-50)	45.5 (29-84)	60 (42-89)	0.0001
Recipient weight					
median (range)	22 (14-47)	49 (9-85)	50 (7-71)	66 (22-95)	0.0001
Blood volume processed (mL/Kg)					
median (range)	303 (117-513)	214 (100-588)	202 (85-391)	125 (113-275)	0.0001
% of large volume leukapheresis	77.7	62.5	73.3	30	0.01
Day of apheresis					
First	15	20	19	22	
Second	3	8	6	9	
Third	0	0	1	2	0.7
CD34+ cells $\times 10^6$/Kg recipient body weight					
median (range)	5.2 (1.48-22.5)	4.22 (1.03-16.05)	5.18 (1.07-23.36)	4.35 (0.1-17)	0.6
CD34+ cells $\times 10^6$/Kg donor body weight					
median (range)	8.5 (2.8-50.9)	7.2 (2.4-41.8)	3.95 (1.7-14.2)	3.4 (1.1-15.7)	0.0001
Pre-apheresis WBC count ($\times 10^9$/L)					
median (range)	36.6 (21.6-56.7)	42.6 (25.8-68.5)	44.4 (13.2-23.8)	38.1 (27.6-74.9)	0.8

body weight was considered for this study. The independent variables analyzed included donor age and sex, donor and recipient weight, baseline white blood cell (WBC), platelet and hemoglobin counts, maximum WBC count following G-CSF administration and blood volume processed. Non-parametric Mann-Whitney U tests and Fisher's exact tests were applied for continuous and categorical variables, respectively, in the univariate analysis. For multivariate analysis a stepwise logistic regression model was used. Age was included for this analysis as a continuous variable. Results were considered statistically significant if the *p* value was <0.05.

Results

A total of 105 aphereses performed in 76 healthy children (median 1; range 1-3) were included in this study. The median age of the donors was 10 years (range 1- 18), with 30 of them (40%) aged less than 10 years. There were 36 boys and 40 girls. Their median body weight was 42 kg (range 9-89). Two apheresis procedures were performed in 26 donors and three in 3 donors. The percentage of donors undergoing only one collection in the LVL group and in the standard leukoapheresis group was 82% and 58%, respectively.

Data regarding mobilization side effects have been published in part elsewhere[5] and are in accordance with those reported by others.[10] In all cases, symptoms were mild and managed with minor analgesics. G-CSF did not have to be discontinued in any donor because of toxicity.

The median number of CD34+ cells $\times 10^6$/kg recipient body weight was 4.22 (range 0.1-23.36). In the first apheresis the median number of CD34+ cells $\times 10^6$/kg recipient body weight was 5.55 (range 0.71-23.36), whereas it was 2.37 (range; 0.84-14.86) in the second one and 1.07 (range; 0.1-2.27) in the third (p=0.0035).

Sixty-one donors (58%) achieved the CD34+ cell dose of $\geq 4 \times 10^6$/kg donor body weight after only one leukapheresis. We found, on univariate analysis, that the factors affecting CD34+ cell collection considering donor´s body weight, were: age (r=0.4, p=0.0002), gender (girls vs boys) (RR: 1.46, 95% CI: 1.04-2.05; p=0.03), LVL vs standard leukapheresis (RR: 1.76, 95% CI: 1.12-2.76; p=0.008), and first procedure vs subsequent ones (RR: 1.55, 95% CI: 0.98-2.47; p=0.04). As greater blood volumes were processed in younger donors than older ones, we also considered the CD34+ cells per kg of donor body weight and per liter of blood volume processed in the procedure and found better collections from younger donors (Table 2). In multi-

variate analysis only younger age (RC: 6.79, 95% CI: 1.57-29.25; $p<0.01$) and large volume leukapheresis (RC: 3.33, 95% CI: 1.13-9.77; $p<0.02$) were found to be significant predictors of yield (Table 3).

When considering the recipient body weight, 57 leukapheresis procedures achieved the target dose ($\geq 4\times10^6$/Kg recipient body weight) after the first procedure (54.3%). Only 11 of the 76 donors could not finally produce the target number of CD34+ cells (14.5%). However, all patients underwent hematopoietic transplantation. Univariate analysis of the factors predicting the achievement of a CD34+ cell target of $\geq 4\times10^6$/Kg recipient body weight showed that the variables that had a positive influence were: volume processed expressed as mL/kg donor body weight (r=0.2; p=0.03), large volume leukapheresis (RR: 1.55, 95% CI: 1.02-2.37; p=0.03), first day of apheresis (RR: 1.65, 95% CI: 1.21-2.32; p=0.0003) and platelet count at the end of the apheresis procedure (r=0.2; p=0.04) in that donors with a lower platelet count at the end of apheresis were those who yielded higher numbers of CD34+ cells. In multivariate analysis only the volume processed (standard leukapheresis) and the day of apheresis (other than first) had a negative impact on CD34+ cell yield (Table 4).

Table 2. CD34 collection from pediatric donors related to body weight and blood volume processed.

Age group	*0-4*	*5-9*	*10-14*	*15-18*	*p°*
CD34+ cells/kg donor BW/Lbvp* $\times10^6$	2.0 (0.63-14.32)	0.94 (0.22-5.06)	0.37 (0.12-1.26)	0.32 (0.07-0.82)	0.0001

**Lbvp: liters of blood volume processed; °analyzed by Kruskall-Wallis test.*

Table 3. Multivariate analysis of factors predicting a CD34+ cell yield $\geq 4\times10^6$/kg considering donor´s body weight.

Favorable category	*Regression coefficient*	*95% CI*	*p value*
Large volume leukapheresis	3.33	1.13-9.77	<0.02
Younger age	6.79	1.57-29.25	<0.01

Table 4. Multivariate analysis of factors related to CD34+ cell yield $\geq 4\times10^6$/kg considering recipient´s body weight.

Unfavorable category	*Regression coefficient*	*95% CI*	*p value*
Standard leukapheresis	0.41	0.21-0.81	0.01
Second or subsequent apheresis	0.16	0.07-0.34	<0.0001

Discussion

Although no definitive mobilization regimen has been established, the mobilization regimen employed in this series has been considered safe in adults[4] and children.[5] It allowed us to compare variables related to the apheresis since all donors in the series underwent the same mobilization regimen. Our results show that the use of large volume leukapheresis (LVL) as the method for collecting the PBPC and the first day of collection were the only variables that significantly affected the CD34+ cell yield. However, if we consider the same target with respect to donor body weight, younger age was also a variable that significantly influenced the CD34+ cell yield.

These data suggest that very small children mobilize better than older children do and that they may donate a high number of CD34+ cells for allogeneic transplantation. There are controversial data in the literature regarding the influence of age in CD34+ cell mobilization.[6,12,13] Although previous studies in adult donors have reported a negative impact of age on CD34+ cell mobilization and collection,[6,7] other series have not described the same effect.[12,13] No differences were observed in CD34+ cell mobilization between donors aged below 18 years and adult donors in a previous study reported by our group, although greater age was associated with a more frequent requirement for more than one apheresis.[5] In this pediatric donor series, the largest reported so far, the yield was related to donor's age when considering donor's weight. However, a relationship between donor´s age and CD34+ cell yield considering recipient´s body weight was not found (*data not shown*). This may be explained by significant differences between recipient and donor's weight, especially in those donors aged less than 5 years: a higher number of donors below this age yielded the CD34+ cell target with only one apheresis, whereas the number of second and third aphereses needed to reach the target cell collection increased for older donors (Table 1).

The other variable that influenced the collection was the volume of blood processed. In this study, LVL was related to better yields when considering either donor or recipient body weight. The relationship between platelet count at the end of apheresis and achievement of the target number of CD34+ cells probably reflects the volume processed and duration of apheresis.[11,14] Regarding secondary

effects of LVL, this procedure has been considered a feasible and safe approach for PBPC collection from children, even very small ones, undergoing autologous PBPC transplantation.[11,15-17]

In summary, our data suggest that younger age is also a variable to consider among pediatric donors for better collections, and that pediatric donors mobilized by G-CSF may donate sufficient number of $CD34^+$ cells for allogeneic transplantation using a single large volume leukapheresis.

Participating centers

Hospital "Niño Jesus" Madrid, (M.A. Díaz, J.Sevilla, M.G. Vicent), Hospital "La Fe", Valencia (J. de la Rubia, A.Verdeguer, M.A.Sanz), Hospital "Virgen del Rocio", Sevilla (I. Espigado), Hospital "La Paz" Madrid (R. Arrieta), Hospital "Carlos Haya" Malaga (M.J. Pascual), Hospital "Ramon y Cajal" Madrid (C. Zamora), Hospital "Gregorio Marañon" Madrid (D. Serrano), Hospital Universitario Salamanca (C. Cañizo), Hospital Son Dureta Mallorca (J. Bargay), Hospital Gral Murcia (F. de Arriba), Hospital Clinico Valencia (C. Arbona), Hospital " Sant Pau" Barcelona (S. Brunet) Spain.

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Pre-publication Report & Outcomes of Peer Review

Contributions

MAD, JS and MGV were responsible for the conception and design of the study, interpretation of its results and writing the manuscript. JS, AV, IE, MJP, CZ, RA, DS, CdC, CA, FdA, JB, SB and MAS selected the donors and provided clinical data. MAD, JS and JdR critically revised the content of the manuscript. MAD and JS created Tables 1, 2, 3 and 4. All authors gave significant contributions to drafting the article.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Luca Malcovati, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Malcovati and the Editors. Manuscript received May 7, 2003; accepted June 24, 2003.

In the following paragraphs, Dr. Malcovati summarizes the peer-review process and its outcomes.

What is already known on this topic

Collection of hematopoietic stem cell after mobilization with G-CSF from pediatric healthy donors is being recognized as a safe and effective procedure, increasingly used in the allogeneic transplant setting, but little is known about the factors affecting its results.

What this study adds

This study by Diaz *et al.* confirms the effectiveness of the peripheral blood progenitor cell collection from pediatric donors and identifies the variables predicting the results, providing valuable information for the clinical management of this procedure.