Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective European Group for Blood and Marrow Transplantation Pediatric Diseases Working Party study

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We investigated prospectively factors influencing the safety of hematopoietic stem cell (HSC) collection in 453 pediatric donors. The children in the study donated either BM or peripheral blood stem cells (PBSCs) according to center policy. A large variability in approach to donor issues was observed between the participating centers. Significant differences were observed between BM and PBSC donors regarding pain, blood allotransfusion, duration of hospital stay, and iron supplementation; however, differences between the groups undergoing BM vs PBSC donation preclude direct risk comparisons between the 2 procedures. The most common adverse event was pain, reported mainly by older children after BM harvest, but also observed after central venous catheter (CVC) placement for PBSC collection. With regard to severe adverse events, one patient (0.7%) developed a pneumothorax with hydrothorax after CVC placement for PBSC collection. The risk of allotransfusion after BM harvest was associated with a donor age of < 4 years and a BM harvest volume of > 20 mL/kg. Children < 4 years were at higher risk than older children for allotransfusion after BM harvest and there was a higher risk of complications from CVC placement before apheresis. We conclude that PBSC and BM collection are safe procedures in children. (*Blood*. 2012; 119(12):2935-2942)

Introduction

The number of allogeneic hematopoietic stem cell (HSC) transplantations in children is increasing and outcome afterward is continuously improving.[1-4] HLA-matched siblings are considered to be the best donors for both medical and biological and economic and logistical reasons, including availability before and after transplantation.[1,5-9]

Worldwide, children under the age of 18 years are not allowed to donate hematopoietic stem cells (HSCs) for unrelated recipients. To date, sibling donors have been recruited in 39%-48% of all childhood transplantations.[4,10] According to data from the European Group for Blood and Transplantation (EBMT) registry, between 1999 and 2002, 39% of all pediatric patients were grafted from an HLA-matched sibling donor, whereas this proportion was higher in previous years.[4] According to a recent EBMT estimate, approximately 600-700 children in Europe become HSC donors for their siblings every year (data not published).

Despite the increased use of peripheral blood and umbilical cord blood, BM is the primary graft source in pediatric patients. In the United States between 2004 and 2008, BM accounted for 51%, peripheral blood for 27%, and cord blood for 22% of all allogeneic transplantations in patients younger than 20 years from any donor.[10] In Europe between 1999 and 2002, pediatric recipients undergoing transplantations from any donor received BM in 64%, peripheral blood in 30%, and cord blood in 6% of cases.[4]

Based on experience gained over the past 30 years, the use of BM from an HLA-identical sibling donor is considered the

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standard of care worldwide for children undergoing HSC transplantation.[11] Nevertheless, an increasing use of allogeneic peripheral blood stem cells (PBSCs) among matched-sibling pediatric transplantations was reported to the Pediatric Blood and Marrow Transplant Consortium between 1994 and 2002, which accounted for more than 23% of all pediatric HSC collections.[12,13] In the same period, PBSCs were collected from 4% of pediatric matched-sibling donors in EBMT centers.[4]

There are significant procedural differences between donating BM and PBSCs. BM donation is regarded as safe, but it does entail a general or spinal anesthetic and discomfort at the harvest site.[14] PBSC donation requires the donor to receive G-CSF and to undergo apheresis, potentially with central venous catheter (CVC) placement under general anesthesia. Many concerns have been raised regarding the short- and long-term safety of G-CSF administration in children.[15] Several reports on the safety and efficacy of HSC donation in large groups of adult donors have been published recently.[16-19] However, data on pediatric donors are relatively scarce, especially with respect to BM harvest.[12,20] Severe complications, including thrombosis and splenic rupture, have occurred in the much larger group of adult donors.[19] To date, no studies comparing the risks of BM and PBSC donation in children have been reported.[14,21]

The EBMT Pediatric Diseases Working Party set up a prospective multicenter observational, noninterventional study to assess the current practice on donation procedures in pediatric (< 18 years) siblings undergoing HSC collection. The secondary objective of the study was to describe any adverse events or complications of BM harvest and PBSC collection and to identify factors contributing to the improvement of safety of HSC collection in pediatric donors.

Methods

Study cohort

Children who donated HSCs between 2005 and 2009 in participating EBMT centers were included in the study. Only data relating to first donations were analyzed. All consecutive donors were enrolled in the study, although some centers decided to complete their participation before the study was closed. Early withdrawal did not impact the outcome of the analysis (data not shown). Donor data were collected before donation, at each collection procedure, and before discharge from the hospital. Before HSC collection, a medical examination was carried out to assess suitability and the absence of transplantation-transmissible infectious diseases. Recipient data regarding demographics, weight, blood group, and HLA matching were also collected. The decision regarding stem cell source was made institutionally. Local ethical committees at each participating institution approved this research protocol, and informed consent for participation in the study was obtained from all parents in accordance with the Declaration of Helsinki.

BM harvest

BM was harvested under general or epidural anesthesia from posterior or anterior iliac crests according to standard practice. After the harvest, intravenous analgesics were given according to local guidelines. Depending on the hemoglobin concentration, the harvested BM volume and the hemodynamic stability of the donor, autologous, or allogeneic blood transfusions were given during or after the procedure. Donors were scheduled for discharge on recovery.

PBSC donation

All PBSC collections were performed after mobilization with G-CSF, which was administered subcutaneously once or twice a day for 4 days. The first leukapheresis was usually performed on the morning of day 5 using an automated continuous-flow cell separator with peripheral vein access or after placement of a CVC. Some PBSC donors received a general anesthesia for CVC placement and others had conscious sedation; this decision was undertaken institutionally according to local policy and the clinical situation. If the target yield of cells was not achieved, G-CSF was administered for 1 or 2 additional days and additional leukaphereses were performed on the following 1-2 days. Apheretic collections were planned to process the donor blood volume based on recipient body weight whenever possible.

Donor assessments

According to Joint Accreditation Committee–International Society for Cellular Therapy and EBMT rules, donor medical history collection, physical examination, and blood sample testing took place within 30 days before BM or PBSC collection.[22,23] Performance status was assessed at hospital admission and at discharge using the Lansky/Karnofsky score. Full blood counts were checked before the first harvest procedure and after each stem cell collection.

For all BM harvest procedures, all modalities and adverse events were recorded at every step: anesthesia (type, duration, complications, including allergic reactions, cardiovascular events, sore throat, and vomiting), blood transfusions (need for allogeneic and/or autologous transfusion), BM collection (duration and severity of pain, analgesic administration, lumbar stiffness, mechanical injury, anemia, need for iron supplementation, infections, and thrombotic complications), and hospital stay (duration before and after BM harvest). Pain was measured as mild (analgesics not required), moderate (nonnarcotic analgesics required), or severe (narcotics required). Iron supplementation was introduced institutionally, sometimes as a routine practice.

Similarly, for PBSC collections, procedure modalities, complications, and toxicities were recorded before the first harvest procedure and after each stem cell collection. These data included G-CSF priming (details regarding growth factor administration modalities and doses; WBC count before apheresis; pain, fever, or other flu-like symptoms during G-CSF priming; and reactions at G-CSF injection sites), vascular access placement (type of catheter; time and complications of anesthesia, if needed, including allergic reactions, cardiovascular events, vomiting and mechanical injury; and complications after catheter placement including pain and thrombotic events), PBSC collection (number and duration of apheresis procedures and complications during and after collection, including pain, symptomatic hypocalcemia, thrombocytopenia, decrease of hemoglobin concentration, need for blood or platelet transfusion, infection, thrombotic events, bleeding, cardiovascular problems, and drug administration), and hospital stay (duration before and after collection). In addition, data regarding any other medical problem associated with mobilization or stem cell harvest and any interventions required were recorded. Specific data related to donor safety were assessed locally.

End points and potential risk factors

For BM harvest, the variables regarding donor outcome included incidence and severity of pain, anemia, blood allotransfusion, cardiovascular disturbances (tachycardia, bradycardia, and hypotension), complications after anesthesia, and prolonged hospital stay (> 2 days after BM harvest). The variables considered potential risk factors for BM harvest complications included donor gender, age, weight, donor/recipient (D/R) weight ratio, duration of anesthesia > 90 minutes, and a collected BM volume of > 20 mL/kg.

For PBSC collection, the variables regarding donor outcome included complications after anesthesia for CVC placement, incidence of pain during G-CSF administration and collection, incidence of symptomatic hypocalcemia (paresthesia, tingling of lips, tongue or fingers, and lip smacking and abdominal pain during the apheresis procedure), number of aphereses, and prolonged hospital stay (> 1 day after PBSC collection). The variables considered potential risk factors for PBSC collection complications included donor gender, donor age, donor weight, D/R weight ratio, WBC count before apheresis, and number of aphereses.

Table 1. Donor and recipient characteristics

Variable	Total	BM donors	PBSC donors	*P*
Donor	n = 453	n = 313	n = 140	
Female sex	206 (45.5%)	148 (47.3%)	58 (41.4%)	.154
Male sex	247 (54.5%)	156 (52.7%)	82 (58.6%)	
Median age, y (range)	9.6 (0.7-18.0)	8.3 (0.7-18.0)	12 (1.3-17.6)	< .0001
Median weight, kg (range)	32 (8-114)	29 (8-100)	42 (12-114)	< .0001
Age group				
< 4 y	58 (12.8%)	52 (16.6%)	6 (4.3%)	< .0001
4-8 y	114 (25.2%)	92 (29.4%)	22 (15.7%)	
> 8 y	281 (62.0%)	169 (54.0%)	112 (80.0%)	
Weight group				
< 20 kg	92 (20.3%)	79 (25.2%)	13 (9.3%)	< .0001
20-40 kg	194 (42.8%)	137 (43.8%)	57 (40.7%)	
> 40 kg	167 (36.9%)	97 (31.0%)	70 (50.0%)	
Recipient				
Median age, y (range)	9.8 (0.3-28)	8.2 (0.3-22.8)	14.3 (0.9-28)	< .0001
Median weight, kg (range)	30 (5-90)	25 (5-88)	45 (6-90)	< .0001
D/R				
Weight ratio, median (range)	1.08 (0.18-11)	1.16 (0.18-8.5)	0.95 (0.21-11)	.015
Weight ratio < 0.75	120 (26.5%)	77 (24.6%)	43 (30.7%)	.173
ABO major incompatibility				
No	358 (79.9%)	251 (80.2%)	107 (76.4%)	.394
Yes	95 (20.1%)	62 (19.8%)	33 (23.6%)	

Serious adverse events (SAEs) were defined as events that were fatal, immediately life-threatening, or caused permanent disability; drug overdose; or those that resulted in prolonged hospitalization because of the need for medical intervention.[11,16]

Statistical methods

Three age groups (0-4, 4-8, and 8-18 years) and 3 weight groups (< 20, 20-40, and > 40 kg) were considered to assess any possible association between complications and age or weight. To compare differences between groups, the χ^2 test or Fisher exact test were used for categorical variables and the Mann-Whitney *U* test for continuous variables. Hazard ratio (HR) and 95% confidence intervals (95% CIs) around a single proportion were calculated using exact binomial formulas. A multivariate logistic regression using the stepwise model selection method was used to evaluate potential risk factors that might influence donor outcome variables.[24] $P < .05$ was regarded as significant. Statistical analyses were performed with SPSS Version 17.0 software.

Results

Demographic data

A total number of 453 children and adolescents donating HSCs for their siblings from 38 EBMT centers were enrolled into the study. In addition to parental consent for donation, court or local ethical committee approval for the donation procedure was obtained in 22% and 29% of the cases, respectively. BM was donated in 69% and PBSCs in 31%. The criteria used by transplantation centers for PBSC collection in children were: discrepancy between donor and recipient body weight, parent decision, or in accordance with clinical trials (pediatric centers) or transplantation protocols (adult centers).

Among donors, 55% were male and 45% female. The median age at donation was 9.6 years (range, 0.7-18); 13% of the donors were under 4 years of age, 25% between 4 and 8 years, and 62% over 8 years. According to weight stratification, 20% of the donors were below 20 kg, 43% between 20 and 40 kg, and 37% over 40 kg. Donor and recipient characteristics are summarized in Table 1.

The results regarding end points such as pain, blood allotransfusion, length of hospital stay, or iron supplementation (Table 2) revealed significant differences between the 2 groups. Because the procedures for BM and PBSC collection varied considerably, the risk factors analysis could only be done separately for each group.

Hematologic issues

Hemoglobin levels were lower after BM than after PBSC collection, and a hemoglobin concentration below 5mM was more often observed in the BM group. The median value of lowest hemoglobin concentration reported after BM harvest was 6.7mM (range, 3.5-9.8) vs 7.1mM (range, 3.8-9.5) after PBSC collection ($P < .0001$). A hemoglobin concentration below 5mM was noted in 28 (9.9%) of the BM donors and in 5 (3.5%) of the PBSC donors ($P < .041$, HR = 2.65, 95% CI = 1.05-8.0). In 15 of 28 donors with a hemoglobin concentration < 5mM, blood transfusion was performed during the harvest. Transfused donors either had an autologous unit ready and the transfusion was planned or the patients were given an allogeneic blood transfusion. Erythropoietin was administered in 31 (10%) of the BM donors, mainly in 2 centers where it was a routine practice. Iron was supplemented in 74% of the BM and in 29% of the PBSC donors independently of the donor's age. However, no comparison can be made here because of the inconsistent administration across participating centers. No thrombotic events were reported after the collection.

In the multivariate logistic regression model, after excluding the donors who were transfused during the harvest, a collected BM volume > 20 mL/kg was the only risk factor significantly associated with the risk of a post-BM harvest hemoglobin below 5mM; this was associated with a 36-fold higher risk compared with donors who had had < 20 mL/kg of BM collected (Table 3). Children under 4 years of age had a 5-fold higher HR for post-BM harvest hemoglobin < 5mM than those 4-8 years of age ($P = .062$).

Eighty-four (27%) BM donors and 9 (6%) PBSC donors ($P < .0001$, HR = 5.3, 95% CI = 2.5-11.8) at a median age of 6.5 years (range, 0.7-16.8) and a median weight of 21.5 kg (range,

Table 2. Common end points after BM and PBSC collection

Variable	Total donors (N = 453)	BM donors (n = 313)	PBSC donors (n = 140)	*P*	HR (95% CI)
Pain (not related to G-CSF)					
No	237 (52.3%)	118 (37.7%)	119 (85.0%)	< .0001	
Yes (no analgesics)	50 (11.0%)	38 (12.1%)	12 (8.6%)		
Yes (nonnarcotic analgesics)	166 (36.7%)	157 (50.2%)	9 (6.4%)		
Blood allotransfusion					
No	368 (81.2%)	229 (73.2%)	131 (93.6%)	< .0001	5.3 (2.5-11.8)
Yes	85 (18.8%)	84 (26.8%)	9 (6.4%)		
No. of days spent in hospital after collection					
0	118 (26.1%)	12 (3.8%)	106 (75.7%)	< .0001	
1	265 (58.5%)	240 (76.7%)	25 (17.9%)		
2 or more	70 (15.4%)	61 (19.5%)	9 (6.4%)		
Iron supplementation					
No	156 (34.4%)	70 (22.4%)	86 (61.4%)	< .0001	6.9 (4.3-11.3)
Yes	273 (60.3%)	232 (74.1%)	41 (29.3%)		
No data	24 (5.3%)	11 (3.5%)	13 (9.3%)		

8-73) received a RBC allotransfusion. Autologous blood transfusion was given to 88 BM donors (28%). The risk for any blood transfusion after BM collection was 17.7-fold (95% CI = 8.4-38, $P < .0001$) higher compared with PBSC collection. The 88 donors who underwent autologous blood collection, usually within 3 weeks before the harvest, had a median age of 10 years (range, 4-18), a median weight of 38 kg (range, 12-80), and a median number of 2 collections (range, 1-3). Overall, a median of 10 mL/kg (range, 5-23) of autologous blood was collected.

In the multivariate logistic regression model, the risk of blood allotransfusion after BM harvest was associated with a donor age of < 4 years (HR = 5.2 and HR = 7.5 compared with children 4-8 and > 8 years of age, respectively) and volume of collected BM of > 20 mL/kg (HR = 4.8; Table 3).

Anesthesia complications

All but 1 BM donor and 37 (26%) PBSC donors underwent general anesthesia, whereas 2 donors, 1 in each group, had epidural anesthesia. The median durations of anesthesia for BM and PBSC donors were 90 minutes (range, 30-225) and 30 minutes (range, 8-105), respectively. PBSC donors underwent general anesthesia for CVC placement but not for the apheresis procedure itself. Of the 81 PBSC donors who had catheter placement, 46% required general anesthesia, whereas the majority of the remaining donors received conscious sedation.

Complications of anesthesia after BM harvest included vomiting (11.8%), sore throat (7.1%), decreased blood pressure (6.4%), tachycardia (4.2%), and bradycardia (0.6%). In one patient (0.3%), laryngospasm occurred after extubation. In the multivariate logistic regression model, only a D/R weight ratio was significantly associated with the risk of cardiac complications after BM harvest under anesthesia (Table 3). Children with a D/R weight ratio < 0.75 had a 3-fold higher risk of at least 1 mild cardiovascular complication, which corresponded to a Common Terminology Criteria for Adverse Events grade < 2. Donors with a D/R weight ratio < 0.75 were more likely to become anemic (14% vs 7%, $P = .114$) or have > 20 mL/kg harvested (56% vs 31%, $P < .001$) than those with a D/R ≥ 0.75, and the anemia then was more likely to lead to cardiovascular complications. Neither donor age < 4 years nor weight < 20 kg were risk factors for hypotension, tachycardia, or bradycardia during BM harvest.

In relation to age, among the PBSC donors, a CVC was placed in 6 of 6 (100%) children younger than 4 years, in 13 of 22 (59%) children 4-8 years of age, and in 62 of 112 (55%) children older than 8 years ($P = .096$). With reference to weight, CVCs were placed in 10 of 13 (77%) donors weighing < 20 kg, in 35 of 57 (61%) donors weighing between 20 and 40 kg, and in 36 of 70 (51%) donors weighing > 40 kg ($P = .181$). Complications of anesthesia after CVC placement for PBSC collection included vomiting (n = 2), decrease of blood pressure (n = 1), tachycardia (n = 2), and bradycardia (n = 1). No CVC-related complications occurred, except for 1 case of pneumothorax with hydrothorax reported in a 5-year-old child after PBSC collection (1 of 140; 0.7%). This case was the only SAE reported among all of the donors.

Table 3. Multivariate logistic regression of risk factors for complications of BM harvest

	Pain		Decrease of hemoglobin < 5mM		Blood allotransfusion		Cardiovascular complications after anesthesia		Hospital stay ≥ 2 d	
	P	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Donor age, y	.023		.148		.003		.828		.515	
< 4 vs 4-8	.018	0.30 (0.11-0.81)	.062	5.1 (0.92-22.4)	.002	5.2 (1.8-16.6)	.640	1.35 (0.39-4.54)	.645	1.38 (0.34-5.5)
< 4 vs > 8	.007	0.20 (0.06-0.65)	.132	7.2 (0.78-28.7)	.001	7.5 (2.2-24)	.972	0.97 (0.19-5.1)	.958	1.02 (0.46-2.27)
Donor weight, kg	.612		.520		.115		.357		.778	
< 20 vs 20-40	.649	0.81 (0.34-1.96)	.188	6.9 (0.38-25)	.130	2.1 (0.8-5.5)	.165	2.63 (0.67-9.7)	.440	1.63 (0.46-5.5)
< 20 vs > 40	.817	1.14 (0.38-3.44)	.215	10.9 (0.25-76)	.979	1.02 (0.3-3.8)	.215	3.12 (0.51-19.8)	.262	1.51 (0.72-3.12)
D/R weight ratio < 0.75	.527	1.28 (0.59-2.85)	.272	2.43 (0.49-12.5)	.926	1.04 (0.5-2.3)	.042	3.1 (1.04-8.3)	.902	0.95 (0.41-2.17)
Female vs male sex	.364	1.29 (0.74-2.26)	.519	0.68 (0.42-2.65)	.576	1.2 (0.6-2.3)	.251	1.65 (0.7-3.9)	.808	1.07 (0.6-1.91)
Duration of anesthesia > 90 minutes	.243	1.39 (0.8-2.42)	.415	0.521 (0.31-1.61)	.763	1.1 (0.6-2.1)	.422	1.43 (0.6-3.44)	.908	1.11 (0.18-6.68)
Collected BM volume > 20 mL/kg	.414	1.28 (0.71-2.33)	.006	36 (2.8-63)	< .001	4.8 (2.4-9.6)	.194	0.54 (0.21-1.37)	.671	1.72 (0.14-20.84)

Age was the only factor significantly associated with a risk of complications of anesthesia after CVC placement for PBSC collection in the multivariate logistic regression analysis. Donors younger than 4 years had a 33-fold higher HR for complications than those older than 8 years ($P = .044$; Table 4). Other variables, such as donor weight, D/R weight ratio, gender, and WBC $> 50 \times 10^9$/L before apheresis, had no prognostic value for complications related to CVC placement under anesthesia for PBSC collection.

Complications related to BM harvest

A median BM volume of 18.5 mL/kg of donor weight was collected (range, 2-66). No severe complications were observed after BM collection. The most frequent complication was pain requiring the administration of analgesics, which occurred in 157 (50.2%) donors. No narcotic drugs were necessary for any donor after BM harvest. Pain was reported at the collection site, including lumbar stiffness, in 28 (9%) donors and sore throat related to general anesthesia in 22 (7%) donors. Pain persisted for a median of 1 day (range, 2 hours-14 days) and was treated by a median of 2 doses of nonnarcotic analgesic (range, 1-20) for a median of 1 day (range, 1-5). No severe mechanical injury after BM collection was observed. Upper respiratory tract infections were observed after collection in 3 BM donors.

In the multivariate logistic regression model that assessed risk factors for pain after BM harvest, only donor age was statistically significant (Table 3). Children 4-8 years of age had a 3.3-fold higher risk of pain than those < 4 years of age, and children > 8 years of age had a 5-fold higher risk of pain than those < 4 years of age. Donor gender, donor weight, D/R weight ratio, duration of anesthesia, and high volume of collected BM were not significantly associated with an increased risk of pain after BM harvest.

Complications of PBSC collection

Distribution of PBSC collection. The majority of PBSC collections, 105 of 140 (75%), were performed in 3 of 39 (7.7%) centers, whereas 27 of 39 (69.2%) centers performed no more than 1 PBSC collection each. No correlation between the number of collections performed by a given center and specific complications was detected.

G-CSF priming in PBSC donors. G-CSF was administered almost exclusively once daily: 16 (11.4%) donors received 5 μg/kg/d, 118 (84.3%) received 10 μg/kg/d, and 6 (4.3%) received 12-20 μg/kg/d. Subcutaneous injections were given to 110 donors (79%) in the hospital, to 11 (8%) at home, and to 14 (10%) in both places. Data relating to 5 cases (3%) are missing. The median WBC before the first collection was 46 g/L (range, 6-205). Muscle/bone pain, headache, abdominal pain, or back pain was reported in only 12 donors (9%) during G-CSF treatment. Donors reporting pain received oral analgesics, which provided good or complete pain relief. Pain decreased soon after G-CSF discontinuation and was not reported after the last collection. Only 2 donors (1.4%) had fever and none reported nausea or vomiting during G-CSF priming. The dose of G-CSF had no impact on the occurrence of adverse events. No risk factors predicting pain during G-CSF administration were found in the multivariate logistic regression (Table 4).

Apheresis. PBSCs were harvested via peripheral venous lines in 59 (42%) donors and by CVCs in 81 (58%) donors. The median duration of each procedure was 4 hours (range, 2-6). One apheresis procedure was sufficient for 45 donors (32%), 2 aphereses were required for 80 (57%) donors, and the remaining 15 donors (11%) completed their donations after a third apheresis. In total, 220 apheretic procedures were performed in 140 PBSC donors. The risk for the third apheresis was 3.4-fold higher ($P = .015$) for donors with a D/R weight ratio < 0.75 compared with those with a D/R weight ratio > 0.75 (20.9% and 6.2%, respectively). Two variables were independent risk factors for additional apheresis requirement: a D/R weight ratio < 0.75 (HR = 3.7, $P = .028$) and WBC < 50 g/L at the time of collection (HR = 3.9, $P = .004$; Table 4). Thirty donors (21%) experienced symptomatic hypocalcemia. No risk factors were predictive of hypocalcemia during apheresis (Table 4). Thrombocytopenia < 70 g/L occurred in 4% of the donors, although no symptomatic thrombocytopenia was observed. One 6-year-old child with a platelet count of 51 g/L before the third apheresis received a platelet transfusion according to local safety guidelines. An upper respiratory tract infection was observed after collection in 1 PBSC donor.

Collection-related pain. Pain, including pain related to CVC placement during and after collection, occurred in 29 (21%) of the PBSC donors and persisted for a median of 3 hours (range, 0-72). Nine (6.4%) of the PBSC donors required nonnarcotic analgesic administration for a median of 1 day (range, 1-3). In the multivariate logistic regression analysis of risk factors for any pain during PBSC procedures, age below 4 years was significantly associated with an increased probability of pain after CVC placement Table 4).

Hospital stay after HSC collection

A median hospital stay of 1 day (range, 0-14) for BM and 3 days (range, 0-7) for PBSC donors ($P < .0001$) before collection was required and, overall, a median of 1 day (range, 0-7) for BM and < 1 day (range, 0-6) for PBSC donors ($P < .0001$) was spent in hospital (Table 2). Several donors were required to stay for extra hospital nights as a routine in some centers. In the multivariate logistic regression analysis, no factor contributed significantly to prolonged hospital stay after BM or PBSC collection (Tables 3-4).

Discussion

To our knowledge, the present study is the first prospective study reporting and analyzing the side effects of BM and PBSC collections in the pediatric population. We assessed the current practice and safety of these procedures in pediatric donors from 38 EBMT centers. Our analysis revealed considerable variability in details of HSC collection from pediatric donors concerning agreement for donation, stem cell source, volume of BM collection, indication for blood auto- and allotransfusion, selection of anesthesia, and policy regarding iron supplementation between the centers. Because of the procedural differences between centers, a general model risk factor analysis for BM and PBSC collection could not be performed. However, an analysis of safety of both harvest modalities was possible.

In our study, no SAEs were reported in the 313 children undergoing BM harvest. However, 1 (0.7%) SAE was reported in the 140 children undergoing PBSC collection; this child had a pneumothorax with hydrothorax after CVC placement under general anesthesia. It is possible that the use of femoral veins would have decreased the risk for pneumothorax. Previous reports have shown that life-threatening complications in donors under 20 years of age undergoing BM harvest are rare (0.39%) and mainly related

Table 4. Multivariate logistic regression analysis of risk factors for complications after PBSC collection

	Pain after G-CSF administration		No. of aphereses > 1		Hypocalcemia after apheresis		Any pain during PBSC procedure		Cardiovascular complications after anesthesia		Hospital stay ≥ 1 d	
	P	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Donor age, y	.538		.230		.192		.011		0.036		.735	
< 4 vs 4-8	.290	2.77 (0.39-24.8)	.088	14.2 (0.68-285)	.332	0.41 (0.07-2.43)	.024	48 (1.7-912)	0.213	8.34 (0.30-195)	.704	1.69 (0.11-24)
< 4 vs > 8	.997	0.56 (0.11-9.7)	.139	12.5 (0.44-292)	.428	0.33 (0.07-1.92)	.009	8.3 (1.7-51)	0.044	33 (1.1-890)	.948	0.9 (0.03-21)
Donor weight, kg	.925		.350		.341		.328				.254	
< 20 vs 20-40	.929	1.06 (0.26-4.5)	.302	1.6 (0.648.3)	.510	0.58 (0.12-3.7)	.185	5.8 (0.43-49)	0.111	8.3 (0.6-96)	.372	3.57 (0.39-34)
< 20 vs > 40	.997	0.26 (0.03-19)	.086	12.5 (0.7-96)	.341	0.50 (0.12-1.85)	.866	1.1 (0.35-3.44)			.484	0.74 (0.24-2.21)
D/R weight ratio < 0.75	.431	0.46 (0.06-3.12)	.028	3.7 (1.14-11.2)	.635	0.76 (0.24-2.32)	.009	7.9 (1.68-36.9)	0.392	1.58 (0.54-4.76)	.162	2.08 (0.76-5.8)
Female vs male sex	.583	1.52 (0.64-4.58)	.052	0.42 (0.17-1.01)	.097	1.15 (0.88-3.2)	.959	0.98 (0.38-2.49)	0.785	1.14 (0.45-2.84)	.380	1.52 (0.60-3.89)
WBC before apheresis > 50×10^9/L	.738	1.41 (0.62-4.28)	.004	0.25 (0.10-0.64)	.647	0.58 (0.09-2.13)	.237	11.45 (0.04-82.19)	0.679	0.81 (0.31-2.17)	.146	2.10 (0.77-5.73)
No. of aphereses > 1 vs 1	.933	1.97 (0.27-11.06)	ND	ND	.202	2.55 (0.61-10.72)	.469	1.93 (0.36-11.45)	ND	ND	.685	1.25 (0.42-3.71)

ND indicates not done.

to general anesthesia.[25] Several reports on adult donors have shown an incidence of life-threatening or debilitating complications of BM donation in 0.3%-0.4% of the donors.[11,25-27] Death has been reported as contributing to an overall risk of 0.003%-0.02% in adults after BM collection.[19,28] The risk of death and SAE after PBSC collection in adults was 4- and 2-fold higher, respectively, compared with BM harvest.[19] To date, no fatality has been reported after either BM harvest or PBSC collection in children.

Most HSC collections in our study were from BM, generally with moderate side effects. The current analysis revealed some unexpected observations, such as a high rate of BM harvest (> 20 mL/kg) resulting in severe anemia in the donors and the necessity for blood allotransfusion. Collection of > 20 mL/kg is therefore not an appropriate practice and should be discouraged. In general, an allogeneic blood transfusion in pediatric donors should be avoided unless an unexpected life-threatening event occurs. There is also no justification for using erythropoietin in this population. Such approaches should be the rule for pediatric donors, especially for those below the age of 4 years, and their adoption should reduce the risk of cardiovascular complications.

In children, the standard HSC collection for transplantation is by multiple BM needle aspirations. However, PBSC collection by apheresis after G-CSF stimulation has been used increasingly in recent years. Studies in adults suggest that the safety of BM and PBSC procedures is comparable.[29] In contrast to adults, there are currently only a few reports describing favorable outcomes for pediatric patients receiving transplantations with sibling PBSCs (reviewed in Peters et al[15]).

The use of G-CSF for stem cell collection in pediatric donors is a crucial issue. Despite potential concerns, none of the rare early complications described in adults after G-SCF administration (vascular events, splenic enlargement, or rupture) have been reported in children.[29] The long-term effects of G-CSF use in healthy children have not been reported. There are no reports on increased risk of cancer in donors of any age or a single case of cancer in healthy children treated with growth factors. G-CSF is not licensed for healthy children. Because many of the medications used in children are not licensed specifically for some pediatric conditions, precise information during the informed consent process and documentation of any side effects prospectively are necessary in this extremely vulnerable cohort. In some European countries, such as Austria and Italy, the use of G-CSF is not routinely allowed in healthy children, and therefore PBSC collections are only performed occasionally in pediatric donors. In our study, the majority of the PBSC collections were performed in only a few centers. We have shown that G-CSF–stimulated PBSC collection has an acceptable safety profile, and the single daily dose of 10 μg/kg seems to be optimal for efficient collection. Earlier studies had shown that pediatric patients received no benefit from PBSC transplantation, and an even worse outcome was reported compared with BMT, primarily because of chronic GVHD.[30] However, recent data do not confirm this experience but instead support the finding that PBSC transplantation in children leads to a faster engraftment without an increased risk of acute and/or chronic GVHD.[31,32] In adults, peripheral blood transplantations clearly lead to a higher rate of chronic GVHD.[33,34]

The procedure of PBSC collection in children carries the risk of pain related to G-CSF administration, the risks associated with CVC placement, the occurrence of hypocalcemia during apheresis, and the risk of cardiovascular problems. Studies show that cardiovascular problems occur in 41% of children < 20 kg, but only in 2% in older children and in 0% of adults during PBSC collection.[20] In our analysis, younger donors had an increased incidence of complications during apheresis; in contrast, very few reports of symptoms during G-CSF administration were received. Older children showed a similar pattern to that described in adults, with a higher incidence of adverse events related to mobilization and a lower incidence of apheresis complications, which were almost exclusively related to hypocalcemia.[16,17,20]

Pain during G-SCF priming was reported by only 9% of the donors in the present study. The low incidence of adverse events related to G-CSF administration in children, particularly in donors < 20 kg in body weight, is a persistent finding in all published reports.[12,20,35,36] Older pediatric donors and adults have a higher incidence of symptoms related to G-CSF priming than do younger children.

Currently, the use of children as PBSC donors is still not recommended routinely.[15] The data presented in the present study verify that PBSC harvest in children has a favorable short-term safety profile except in younger donors, in whom there is a higher risk from CVC placement and cardiovascular complications related to hypovolemia. Although extensive studies in adult sibling donors have not demonstrated any increased long-term complications such as increased cancer risk after short-term G-CSF administration for PBSC, sufficient long-term studies in children addressing this issue have not been performed.

In conclusion, SAEs in healthy pediatric donors are rare, with no statistical difference between BM and PBSC donation. The most common adverse event was pain, reported mainly by older children after BM harvest. In our study, children under 4 years belong to the highest risk group for complications for both BM harvest and PBSC collection. In children less than 4 years of age, the risk of anemia and the need for blood transfusion were observed after BM harvest, whereas pain after CVC placement and cardiovascular complications occurred during PBSC collection. Modifications in clinical practice could potentially diminish the risk of HSC collection in very small children. The question of whether BM harvest or PBSC collection is the better method, in terms of risk to the donor, should be clarified in a future prospective study. The results of the present study could be used as a tool to create a global approach to defining best practices, general recommendations, and specific standard operating procedures for stem cell harvest in different pediatric age groups.

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Authorship

Contribution: J.S. had primary responsibility for study design, data analysis, and interpretation; J.S. and L.G. wrote the manuscript; J.S., L.G., C.P., and G.D. designed the research; M.L., A.B., and J.S. analyzed the data; A.B., G.D., and C.P. critically reviewed the manuscript; and all other authors provided donor data and approved the final version of the manuscript.

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