Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective EBMT-PDWP study

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Abstract

We prospectively investigated factors influencing the safety of hematopoietic stem cell (HSC) collection in 453 pediatric donors. The children in the study donated either bone marrow (BM) or peripheral blood stem cells (PBSC), 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, although differences between the groups undergoing BM vs PBSC donation preclude direct risk comparisons of the two 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. We conclude that PBSC and BM collections are safe procedures in children. Children <4 years were at higher risk than older children for allotransfusion following BM harvest, and a higher risk of complications from CVC placement prior to apheresis.
Introduction

The number of allogeneic hematopoietic stem cell transplants (HSCT) in children is increasing and the outcome of this therapy is continuously improving. HLA-matched siblings are considered to be the best donors for medical and biological reasons, and economic and logistical issues, including availability before and after transplantation.

Worldwide, children under 18 years are not allowed to donate HSC for unrelated recipients. Sibling donors have been recruited in 39%-48% of all childhood transplantsations so far. According to data from the European Group for Blood and Transplantation (EBMT) registry, between 1999-2002, 39% of all pediatric patients were grafted from their HLA matched sibling donor, while this proportion was higher in previous years. According to a recent EBMT estimate, about 600-700 children in Europe become HSC donors for their siblings every year (data not published).

In pediatrics, bone marrow (BM) is the primary graft source, despite the increase in transplantations with peripheral blood and umbilical cord blood. In the USA, between 2004-2008, BM accounted for 51%, peripheral blood for 27% and cord blood for 22% of all allogeneic transplants in patients younger than 20 years from any donor. In Europe, between 1999-2002, pediatric recipients transplanted from any donor received BM in 64%, peripheral blood in 30%, and cord blood in 6% of the cases.

Based on experience gained over the past 30 years, the use of BM from a HLA-identical sibling donor is considered the standard of care worldwide for children undergoing HSCT. Nevertheless, an increasing use of allogeneic peripheral blood stem cells (PBSC) among matched sibling pediatric transplants was reported to the Pediatric Blood and Marrow
Transplant Consortium between 1994-2002, which accounted for over 23% of all pediatric HSC collections.\textsuperscript{12,13} In the same period, PBSCs were collected from 4% of pediatric matched sibling donors in EBMT centers.\textsuperscript{4}

There are significant procedural differences between donating BM and PBSC. BM donation is regarded as safe, but it does entail a general or spinal anesthetic and discomfort at the harvest site.\textsuperscript{14} PBSC donation requires the donor to receive granulocyte colony-stimulating factor (G-CSF) and 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.\textsuperscript{15} A number of reports on the safety and efficacy of HSC donation in large groups of adult donors have been published recently.\textsuperscript{16-19} However, data on pediatric donors are relatively scarce, especially with respect to BM harvest.\textsuperscript{12,20} Severe complications, including thrombosis and splenic rupture, have occurred in the much larger group of adult donors.\textsuperscript{19} To date, no studies comparing the risks of BM and PBSC donation in children, unlike those relating to adult studies, have been reported.\textsuperscript{14,21}

The EBMT Pediatric Diseases Working Party (PDWP) set up a prospective multicenter observational, non-interventional study in order 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 (AEs) and 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 HSC between 2005-2009 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 finally closed. Early center 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. Prior to HSC collection a medical examination was carried out in order 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.

*Bone marrow harvest*

BM was harvested under general or epidural anesthesia from posterior or anterior iliac crests, according to standard practice. Following 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 upon recovery.

*PBSC donation*

All PBSC collections were performed after mobilization with G-CSF, which was administered once or twice daily subcutaneously, scheduled for 4 days. The first leukapheresis was usually performed on the morning of day 5, using an automated
continuous-flow cell separator with a peripheral vein access or after placement of a CVC. Some PBSC donors received a general anesthesia for CVC placement while the others had conscious sedation; the decision being undertaken institutionally according to local policy and the clinical situation. If the target yield of cells was not achieved, G-CSF was administered for one or two 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 EBMT/JACIE rules, taking donor medical history, physical examination and blood sample testing took place within 30 days preceding the collection.\textsuperscript{22,23} Performance status was assessed at hospital admission and 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 AEs were recorded at every step, i.e. 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, thrombotic complications), and hospital stay (duration before and after BM harvest). Pain was measured as: mild (analgesics not required), moderate (non-narcotic 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, complications after catheter placement including pain, thrombotic events), PBSC collection (number and duration of apheresis procedures, 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, drug administration), and hospital stay (duration before and after collection). Additionally, data regarding any other medical problem associated with mobilization or stem cell harvest, and the interventions required, were recorded. Specific data related to donor safety were assessed locally.

Endpoints and potential risk factors

For BM harvest, the variables regarding donor outcome included incidence and severity of pain, anemia, blood allo-transfusion, cardiovascular disturbances (tachycardia, bradycardia, 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 >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, 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.

Serious adverse events (SAE) were defined as events which were fatal, immediately life-threatening or which caused permanent disability, drug overdose, or those which resulted in prolonged hospitalization due to the need for medical intervention.11,16

Statistical methods

Three age groups (0-4, 4-8, and 8-18 years) and three weight groups (<20 kg, 20-40 kg, and >40 kg) were considered to assess any possible association between complications and age or weight. In order to compare differences between groups, the chi-square test or Fisher’s exact test were used for categorical variables and the Mann-Whitney U test for continuous variables. Hazard risk (HR) and 95% confidence intervals (95%CI) around a single proportion were calculated using exact binomial formulas. A multivariate logistic regression, using the step-wise model selection method, was used to evaluate potential risk factors that might influence donor outcome variables.24 A p-value below 0.05 was regarded as significant. The statistical analyses were performed with the SPSS software version 17.0 (SPSS Inc, Chicago, IL).

Results
**Demographic data**

A total number of 453 children and adolescents donating HSC for their siblings from 38 EBMT centers were enrolled into the study. In addition to parental consent for donation, court or local Ethical Committees approval for the donation procedure was obtained in 22% and 29% of the cases, respectively. BM was donated in 69% and PBSC in 31% of the cases. The criteria used by transplant centers for PBSC collection in children were: discrepancy between donor and recipient body weight, parents’ decision, or in accordance with clinical trials (pediatric centers), or transplant 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, 25% between 4-8 years and 62% over 8 years. According to weight stratification, 20% of the donors were below 20 kg, 43% between 20-40 kg, and 37% over 40 kg. Donor and recipient characteristics are summarized in Table 1.

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

**Hematological issues**

Hemoglobin levels were lower after BM than after PBSC collection, and a hemoglobin concentration below 5 mM was more often observed in the BM group. The median value of lowest hemoglobin concentration reported after BM harvest was 6.7 mM (range, 3.5-9.8) vs 7.1 mM (range 3.8-9.5) after PBSC collection (p<0.0001). A hemoglobin concentration below
5 mM was noted in 28 (9.9%) of the BM donors and in 5 (3.5%) of the PBSC donors (p<0.041, HR=2.65, 95%CI=1.05-8.0). In 15/28 donors with a hemoglobin concentration <5 mM 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 due to the inconsistent administration across participating centers. No thrombotic events were reported after the collection.

In the multivariate logistic regression model, after excluding the donors that 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 5 mM with a 36-fold higher risk, in comparison to donors who had had <20 mL/kg BM collected (Table 3). Children under 4 years were at a 5-fold higher hazard risk of post-BM harvest hemoglobin <5 mM than those aged 4-8 years (p=0.062).

Eighty-four BM (27%) and 9 (6%) PBSC donors (p<0.0001, HR=5.3, 95%CI=2.5-11.8), at a median age of 6.5 years (range 0.7-16.8) and median weight 21.5 kg (range 8-73), received red blood cell 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<0.0001) higher in comparison to PBSC collection. The 88 donors who underwent autologous blood collection, usually within 3 weeks prior to the harvest, had a median age of 10 years (range 4-18), median weight 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 ml/kg) of autologous blood was collected.

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

**Anesthesia complications**

All but one BM and 37 PBSC (26%) donors underwent general anesthesia, while 2 donors, one 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 only but not for the apheresis procedure itself. Of the 81 PBSC donors who had catheter placement, 46% required general anesthesia while the majority of the remaining donors received conscious sedation.

Complications of anesthesia after BM harvest included vomiting (11.8%), sore throat (7.1%), decrease of blood pressure (6.4%), tachycardia (4.2%) and bradycardia (0.6%). In one case (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 one mild cardiovascular complication, corresponding to CTCAE grade <2. Donors with a D/R<0.75 were more likely to become anemic (14% vs 7%, p=0.114) or have >20 mL/kg harvested (56% vs 31%, p<0.001) 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 6/6 (100%) of the children younger than 4 years, 13/22 (59%) in those 4-8 year-old, and 62/112 (55%) in those older than 8 years (p=0.096). With reference to weight, CVC were placed in 10/13 (77%) of the donors weighing <20 kg, in 35/57 (61%) of donors between 20-40 kg, and in 36/70 (51%) of the donors weighing >40 kg (p=0.181). Complications of anesthesia after CVC placement for PBSC collection included vomiting (2 cases), decrease of blood pressure (1 case), tachycardia (2 cases) and bradycardia (1 case). No CVC-related complications occurred, except for one case of pneumothorax with hydrothorax reported in a 5-year old child after PBSC collection (1/140; 0.7%). This case was the only SAE reported among all the donors.

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 of complications than those older than 8 years (p=0.044) (Table 4). Other variables, such as donor weight, D/R weight ratio, gender and WBC>50 G/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 2h-14 days) and was treated by a median of 2 doses of non-narcotic 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 old had a 3.3-fold higher risk of pain than those <4 years and children >8 years had a 5-fold higher risk of pain than those <4 years. 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 105/140 (75%) were performed in 3/39 (7.7%) centers, while 27/39 (69.2%) centers performed no more than one 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/day, 118 (84.3%) received 10 µg/kg/day, and 6 (4.3%) 12-20 µg/kg/day. Subcutaneous injections were given to 110 donors (79%) in hospital, at home to 11 (8%), in both places to
14 (10%) donors. Data relating to 5 cases (3%) are missing. The median WBC before the first collection was 46 (range 6-205) G/L. Muscle/bone pain, headache, abdominal or back pain were reported in only 12 donors (9%) during G-CSF treatment. Donors reporting pain received oral analgesics, with good or complete pain relief. Pain decreased soon after G-CSF discontinuation and was not reported after the last collection. Only two donors (1.4%) had fever and none complained of nausea or vomiting during G-CSF priming. The dose of G-CSF had no impact on occurrence of adverse events. No risk factors predicting pain during G-CSF administration were found in the multivariate logistic regression (Table 4).

Aphereses

PBSCs were harvested via peripheral venous lines in 59 donors (42%) and by CVC in 81 (58%). The median duration of each procedure was 4 hours (range 2-6 hours). One apheresis procedure was sufficient for 45 donors (32%), two aphereses were required for 80 (57%) donors, while 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=0.015) for donors with a D/R weight ratio <0.75 compared to 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=0.028) and WBC<50 G/L at the time of collection (HR=3.9, p=0.004) (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 hours). Nine (6.4%) of the PBSC donors required non-narcotic analgesic administration for a median of one 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<0.0001) 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<0.0001) were spent in hospital (Table 2). A number of donors were required to stay for extra hospital nights as a routine in some centers. In the multivariate logistic regression analysis no factor significantly contributed to prolonged hospital stay after BM or PBSC collection (Tables 3 and 4).

Discussion

This report is, to our knowledge, the first prospective study reporting and analyzing the side effects of BM and PBSC collections in the pediatric population. The study 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. Due to 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, one (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. Possibly, the use of femoral veins would decrease the risk of pneumothorax. Previous reports have shown that life-threatening complications in donors under 20 years undergoing BM harvest were rare (0.39%) and mainly related 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-fold and 2-fold higher, respectively, when compared to 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 allo-transfusion. 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 four, and their adoption should reduce the risk of cardiovascular complications.
In children the standard HSC collection for transplantation is by means of multiple BM needle aspirations. However, PBSC collection by apheresis, after G-CSF stimulation, has been increasingly adopted in recent years. Studies in adults suggest that the safety of BM and PBSC procedures is comparable. In contrast to adults, there are currently only a few reports which describe favorable outcomes for pediatric patients transplanted with sibling PBSC (reviewed in Peters et al). 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. 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. As 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 in a prospective manner, 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 exceptionally performed 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 PBSCT, and an even worse outcome was reported when compared to BMT, primarily due to chronic GVHD. 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.\textsuperscript{31,32} It should be mentioned that in adults, peripheral blood transplants clearly lead to a higher rate of chronic GVHD.\textsuperscript{33,34}

The procedure of PBSC collection in children carries the risk of pain related with G-CSF administration, the risks associated with CVC placement, the occurrence of hypocalcemia during apheresis and the risk of cardiovascular problems. The literature shows that cardiovascular problems occurred in 41\% of children <20 kg, but only in 2\% in older children and in 0\% of adults.\textsuperscript{20} In our analysis, younger donors had an increased incidence of complications during apheresis. By contrast, very few reports of complaints 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.\textsuperscript{16,17,20}

Pain during G-SCF priming was reported by only 9\% of the donors in our series. The low incidence of adverse events related to G-CSF administration in children, particularly in donors <20 kg bw, is a persistent finding in all published reports.\textsuperscript{12,20,35,36} Older pediatric donors and adults have a higher incidence of complaints related to G-CSF priming than younger children.

Currently, the use of children as PBSC donors is still not routinely recommended.\textsuperscript{15} The data presented in this study verify that PBSC harvest in children has a favorable short-term safety profile; except in younger donors, where 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 risk of 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, SAE 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, both for BM harvest and PBSC collection. In children below 4 years 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 further prospective study. The results of this report 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

data. A.B., G.D. and C.P. critically reviewed the manuscript. All the other authors provided donor data and approved the final version of the manuscript.

**Conflict of interest disclosure**

All the authors declare that they have no financial conflict of interest related to this study.

**References**


### Table 1. Donor and recipient characteristics

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<th>Variable</th>
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</tr>
<tr>
<td><strong>Age</strong> (median, range) yrs</td>
<td>9.6 (0.7-18.0)</td>
<td>8.3 (0.7-18.0)</td>
<td>12 (1.3-17.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Weight</strong> (median, range) kg</td>
<td>32 (8-114)</td>
<td>29 (8-100)</td>
<td>42 (12-114)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; 4 yrs</td>
<td>58 (12.8%)</td>
<td>52 (16.6%)</td>
<td>6 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>114 (25.2%)</td>
<td>92 (29.4%)</td>
<td>22 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 8 yrs</td>
<td>281 (62.0%)</td>
<td>169 (54.0%)</td>
<td>112 (80.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight groups</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; 20 kg</td>
<td>92 (20.3%)</td>
<td>79 (25.2%)</td>
<td>13 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>20-40 kg</td>
<td>194 (42.8%)</td>
<td>137 (43.8%)</td>
<td>57 (40.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>167 (36.9%)</td>
<td>97 (31.0%)</td>
<td>70 (50.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (median, range) yrs</td>
<td>9.8 (0.3-28)</td>
<td>8.2 (0.3-22.8)</td>
<td>14.3 (0.9-28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (median, range) kg</td>
<td>30 (5-90)</td>
<td>25 (5-88)</td>
<td>45 (6-90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Donor/recipient weight ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, range</td>
<td>1.08 (0.18-11)</td>
<td>1.16 (0.18-8.5)</td>
<td>0.95 (0.21-11)</td>
<td>0.015</td>
</tr>
<tr>
<td>Ratio &lt;0.75</td>
<td>1.08 (0.18-11)</td>
<td>1.16 (0.18-8.5)</td>
<td>0.95 (0.21-11)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>ABO major incompatibility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>358 (79.9%)</td>
<td>251 (80.2%)</td>
<td>107 (76.4%)</td>
<td>0.394</td>
</tr>
<tr>
<td>Yes</td>
<td>95 (20.1%)</td>
<td>62 (19.8%)</td>
<td>33 (23.6%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Common endpoints after BM and PBSC collection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total donors</th>
<th>BM donors</th>
<th>PBSC donors</th>
<th>P-value</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (not related to G-CSF)</td>
<td>n=453</td>
<td>N=313</td>
<td>n=140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>237 (52.3%)</td>
<td>118 (37.7%)</td>
<td>119 (85.0%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Yes (no analgesics)</td>
<td>50 (11.0%)</td>
<td>38 (12.1%)</td>
<td>12 (8.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (non-narcotic analgesics)</td>
<td>166 (36.7%)</td>
<td>157 (50.2%)</td>
<td>9 (6.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood allo-transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>368 (81.2%)</td>
<td>229 (73.2%)</td>
<td>131 (93.6%)</td>
<td>&lt;0.0001</td>
<td>5.3 (2.5-11.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>85 (18.8%)</td>
<td>84 (26.8%)</td>
<td>9 (6.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of days spent in hospital after collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>118 (26.1%)</td>
<td>12 (3.8%)</td>
<td>106 (75.7%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>265 (58.5%)</td>
<td>240 (76.7%)</td>
<td>25 (17.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>70 (15.4%)</td>
<td>61 (19.5%)</td>
<td>9 (6.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron supplementation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>156 (34.4%)</td>
<td>70 (22.4%)</td>
<td>86 (61.4%)</td>
<td>&lt;0.0001</td>
<td>6.9 (4.3-11.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>273 (60.3%)</td>
<td>232 (74.1%)</td>
<td>41 (29.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td>24 (5.3%)</td>
<td>11 (3.5%)</td>
<td>13 (9.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Multivariate logistic regression of risk factors for complications of bone marrow harvest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pain</th>
<th>Decrease of hemoglobin &lt; 5 mM</th>
<th>Blood allograft transfusion</th>
<th>Cardiovascular complications after anesthesia</th>
<th>Hospital stay ≥2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Donor age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 vs 4-8 [years]</td>
<td>0.018</td>
<td>0.30 (0.11-0.81)</td>
<td>0.062 (0.52-2.24)</td>
<td>0.002 (1.8-16.6)</td>
<td>0.646 (0.39-4.54)</td>
</tr>
<tr>
<td>&lt;4 vs &gt;8 [years]</td>
<td>0.007</td>
<td>0.20 (0.06-0.65)</td>
<td>0.132 (0.78-28.7)</td>
<td>0.001 (2.2-24)</td>
<td>0.972 (0.97-5.1)</td>
</tr>
<tr>
<td>Donor weight</td>
<td>0.612</td>
<td>0.520 (0.34-1.96)</td>
<td>0.188 (0.38-25)</td>
<td>0.130 (0.8-5.5)</td>
<td>0.168 (0.8-4.7)</td>
</tr>
<tr>
<td>&lt;20 vs 20-40 [kg]</td>
<td>0.649</td>
<td>1.1 (0.36-3.44)</td>
<td>0.215 (0.25-76)</td>
<td>0.979 (0.3-3.8)</td>
<td>0.215 (0.51-19.8)</td>
</tr>
<tr>
<td>&lt;20 vs &gt;40 [kg]</td>
<td>0.817</td>
<td>1.28 (0.59-2.85)</td>
<td>0.272 (0.49-12.5)</td>
<td>0.926 (0.5-2.3)</td>
<td>0.042 (1.04-8.3)</td>
</tr>
<tr>
<td>D/R weight ratio &lt;0.75</td>
<td>0.527</td>
<td>1.28 (0.74-2.26)</td>
<td>0.519 (0.42-2.65)</td>
<td>0.576 (0.5-2.3)</td>
<td>0.251 (1.07-3.9)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.364</td>
<td>1.29 (0.74-2.26)</td>
<td>0.519 (0.42-2.65)</td>
<td>0.576 (0.5-2.3)</td>
<td>0.251 (1.07-3.9)</td>
</tr>
<tr>
<td>Duration of anesthesia &gt;60 min</td>
<td>0.243</td>
<td>1.39 (0.8-2.42)</td>
<td>0.415 (0.31-1.61)</td>
<td>0.763 (1.1)</td>
<td>0.422 (1.43-3.44)</td>
</tr>
<tr>
<td>Collected BM volume &gt;20 ml/kg</td>
<td>0.414</td>
<td>1.28 (0.71-2.33)</td>
<td>0.006 (0.28-63)</td>
<td>&lt;0.001 (4.8)</td>
<td>0.194 (0.21-1.37)</td>
</tr>
</tbody>
</table>
Table 4. Multivariate logistic regression of risk factors for complications of PBSC collection

<table>
<thead>
<tr>
<th></th>
<th>Pain after G-CSF administration</th>
<th>Number of aphereses &gt;1</th>
<th>Hypocalcemia after apheresis</th>
<th>Any pain during PBSC procedure</th>
<th>Cardiovascular complications after anesthesia</th>
<th>Hospital stay ≥1 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value (95% CI)</td>
<td>p-value (95% CI)</td>
<td>p-value (95% CI)</td>
<td>p-value (95% CI)</td>
<td>p-value (95% CI)</td>
<td>p-value (95% CI)</td>
</tr>
<tr>
<td><strong>Donor age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 vs 4-8 [years]</td>
<td>0.290 (0.39-24.8)</td>
<td>0.088 (0.68-285)</td>
<td>0.332 (0.07-2.43)</td>
<td>0.024 (1.7-812)</td>
<td>0.213 (0.30-195)</td>
<td>0.704 (0.11-24)</td>
</tr>
<tr>
<td>&lt;4 vs &gt;8 [years]</td>
<td>0.997 (0.11-9.7)</td>
<td>0.139 (0.44-292)</td>
<td>0.33 (0.07-1.92)</td>
<td>0.009 (1.7-51)</td>
<td>0.044 (1.1-690)</td>
<td>0.948 (0.9-0.94)</td>
</tr>
<tr>
<td><strong>Donor weight</strong></td>
<td>0.925 (0.26-4.5)</td>
<td>0.302 (0.64-8.3)</td>
<td>0.510 (0.12-3.7)</td>
<td>0.185 (0.43-49)</td>
<td>0.111 (0.6-96)</td>
<td>0.372 (0.39-34)</td>
</tr>
<tr>
<td>&lt;20 vs 20-40 [kg]</td>
<td>0.997 (0.03-19)</td>
<td>0.086 (0.12-3.7)</td>
<td>0.341 (0.12-1.85)</td>
<td>0.866 (0.35-3.44)</td>
<td>0.484 (0.19-2.21)</td>
<td></td>
</tr>
<tr>
<td>&lt;20 vs &gt;40 [kg]</td>
<td>0.431 (0.06-3.12)</td>
<td>0.028 (1.14-11.2)</td>
<td>0.635 (0.24-23.2)</td>
<td>0.009 (1.86-36.9)</td>
<td>0.392 (0.54-47.6)</td>
<td>0.162 (0.76-5.8)</td>
</tr>
<tr>
<td><strong>D/R weight ratio &lt;0.75</strong></td>
<td>0.46 (0.06-2.12)</td>
<td>0.052 (1.17-1.01)</td>
<td>0.097 (1.15-8.32)</td>
<td>0.959 (0.98-3.24)</td>
<td>0.785 (1.45-2.64)</td>
<td>0.380 (1.52-3.99)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.583 (0.64-4.58)</td>
<td>0.052 (0.17-1.01)</td>
<td>0.097 (1.15-8.32)</td>
<td>0.959 (0.98-3.24)</td>
<td>0.785 (1.45-2.64)</td>
<td>0.380 (1.52-3.99)</td>
</tr>
<tr>
<td><strong>WBC before apheresis &gt;50 G/L</strong></td>
<td>0.738 (0.62-4.28)</td>
<td>0.004 (0.00-0.64)</td>
<td>0.647 (0.00-0.23)</td>
<td>0.237 (0.04-2.13)</td>
<td>0.679 (0.01-1.17)</td>
<td>0.146 (0.17-5.73)</td>
</tr>
<tr>
<td><strong>Number of aphereses &gt;1 vs 1</strong></td>
<td>0.933 (0.27-11.06)</td>
<td>ND</td>
<td>ND</td>
<td>0.202 (0.25-6.1-10.72)</td>
<td>0.069 (1.36-11.45)</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND – not done
Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective EBMT-PDWP study

Jan Styczynski, Adriana Balduzzi, Lidia Gil, Myriam Labopin, Rose-Marie Hamladji, Sarah Marktel, M. Akif Yesilipek, Franca Fagioli, Karoline Ehlert, Martina Matulova, Jean-Hugues Dalle, Jacek Wachowiak, Maurizio Miano, Chiara Messina, Miguel Angel Diaz, Christiane Vermylen, Matthias Eyrich, Isabel Badell, Peter Dreger, Jolanta Gozdzik, Daphna Hutt, Jelena Rascon, Giorgio Dini and Christina Peters