G-CSF in Healthy Allogeneic Stem Cell Donors

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Keywords
CD34+ cells · Donors · G-CSF · Hematopoietic stem cells · Leukapheresis product

Summary
Mobilization of peripheral blood stem cells (PBSC) in healthy volunteers with granulocyte colony-stimulating factor (G-CSF) is currently carried out at many institutions worldwide. This report presents the experience of the Dresden center regarding donor evaluation and mobilization schedule. Data regarding efficacy, short- and long-term safety of G-CSF treatment gained from 8,290 PBSC collections in healthy donors are outlined. These results are discussed against the background of the available evidence from the literature. Although established as a standard procedure, G-CSF application to allogeneic donors will always be a very delicate procedure and requires the utmost commitment of all staff involved to ensure maximum donor safety.

Introduction

Allogeneic transplantation of hematopoietic blood stem cells (HSC) became a routine clinical procedure during the 1990s. It is a promising treatment option for patients with life-threatening diseases of the hematopoietic and immune systems [1, 2]. Initially, HSC were obtained from bone marrow (BM) only [3]. In the mid-1990s, mobilization of HSC from BM into peripheral blood was also applied in healthy donors [4–6]. These cells could easily be collected with common blood cell separators. The method evolved very quickly into an alternative to BM collection, and soon became the most widely used way to harvest HSC from healthy allogeneic donors. In contrast to BM collection, peripheral blood stem cell (PBSC) donation does not require hospitalization and is generally assumed to be less physically demanding for the donor. However, application of mobilizing agents is stringently required for successful HSC mobilization. The standard substance, which is almost exclusively used in healthy donors worldwide, is recombinant human granulocyte colony-stimulating factor (rhG-CSF). Two preparations – filgrastim and lenograstim – are available and have been approved for PBSC mobilization for about 15 years in Germany. Currently, more than 20,000 healthy donors worldwide receive rhG-CSF for PBSC mobilization every year [7]. At the Dresden University Hospital, PBSC collections have been performed since 1996. In the two collection facilities associated with the university hospital, 8,290 allogeneic PBSC collections from 8,005 donors (i.e. 285 second collections) have been documented in a database up until May 2012. This paper presents the data of our own group, and summarizes the current knowledge regarding the short- and long-term effects of G-CSF treatment in healthy stem cell donors.

Donor Eligibility

HSC donors should generally fulfill the requirements of the German Guidelines of Hemotherapy for apheresis donors [8]. Donor evaluation comprises primarily the following elements: i) detailed medical history, supported by a standardized questionnaire; ii) physical assessment with special consideration of peripheral veins; iii) electrocardiogram (ECG) at rest; iv) ultrasound examination of the upper abdomen with measurement of spleen diameter; and v) laboratory examinations including complete blood count with differential, clinical chemistry (liver enzymes, electrolytes, metabolic parameters, serum protein electrophoresis), urinalysis, infectious disease markers (hepatitis A/B/C, HIV, human T-cell lymphotropic virus type (HTLV) I/II, syphilis, toxoplasmosis, Epstein-Barr virus (EBV), cytomegalovirus (CMV)), ABO, rhesus (Rh)
number of colony-forming units (colony-forming units granulocyte/macrophage (CFU-GM), burst-forming units-erythrocyte (BFU-E)) reached their maximum. Studies with even higher G-CSF doses [20] indicate that this peak may occur 1 day earlier. On the other hand, there is some evidence that G-CSF doses higher than 10 $g/kg$ are associated with more frequent side effects [21, 22]. Our group used a median dose of 7.5 $g/kg$ lenograstim (6.8–8.5 $g/kg$) during a period of 4.5–5.5 days. In this protocol, the peripheral CD34+ count on day 5 of G-CSF application varied between 6 and 285/μl in 3,928 unrelated PBSC donors [23] (fig. 1). The median total yield from the first leukapheresis was 5.88 (0.16–27.39) $\times 10^8$ CD34+ cells (fig. 2). A single leukapheresis was sufficient to collect the CD34+ cell dose required in 3,072 donors (78.2%).

G-CSF Dosing and Factors Affecting Mobilization Efficacy

The dose-response relationship of G-CSF has been studied by many different groups (see overview in [14]). A wide range of dosages (3–20 $μg/kg$) has been applied to healthy PBSC donors (table 1). Even at a G-CSF dose as low as 3 $μg/kg$, CD34+ cells could be detected, but the amount was not sufficient for clinical application [15]. Due to the large individual variation of mobilization efficacy, the number of donors included in some of these studies is limited. Furthermore, it has to be considered that CD34 measurement was not well standardized when those reports were published. There also have been large variations in the leukapheresis procedures. Altogether, only 3 investigators could detect significant differences of PBSC mobilization at different G-CSF-dosages [16, 17]. Sekhsaria et al. [18] could only find significant differences in individual donors who consecutively received both G-CSF doses (5 and 10 $μg/kg$). The two prospective studies by Stronccek et al. [15] and Grigg et al. [19] revealed a peak of peripheral CD34 values after 4–6 days of G-CSF application at a maximum daily dose of 10 $μg/kg$. At the same time, the number of colony-forming units (colony-forming units granulocyte/macrophage (CFU-GM), burst-forming units-erythrocyte (BFU-E)) reached their maximum. Studies with even higher G-CSF doses [20] indicate that this peak may occur 1 day earlier. On the other hand, there is some evidence that G-CSF doses higher than 10 $μg/kg$ are associated with more frequent side effects [21, 22]. Our group used a median dose of 7.5 $μg/kg$ lenograstim (6.8–8.5 $μg/kg$) during a period of 4.5–5.5 days. In this protocol, the peripheral CD34+ count on day 5 of G-CSF application varied between 6 and 285/μl in 3,928 unrelated PBSC donors [23] (fig. 1). The median total yield from the first leukapheresis was 5.88 (0.16–27.39) $\times 10^8$ CD34+ cells (fig. 2). A single leukapheresis was sufficient to collect the CD34+ cell dose required in 3,072 donors (78.2%).
Table 1. Efficacy of various G-CSF dosages in healthy PBSC donors

<table>
<thead>
<tr>
<th>Author, year [ref.]</th>
<th>Donors, n / study design</th>
<th>Daily G-CSF dose</th>
<th>Substance</th>
<th>Administration period, days</th>
<th>Efficacy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2000 [16]</td>
<td>17 vs. 23 historical control</td>
<td>2 × 5 μg/kg, 1 × 5 μg/kg</td>
<td>filgrastim</td>
<td>4–6</td>
<td>2.8 × 10^6/kg CD34, 1.7 × 10^6/kg CD34 in first apheresis p = 0.049</td>
<td>mixed population: healthy donors and patients with non-malignant diseases, median age 8 and 13 years</td>
</tr>
<tr>
<td>Grigg et al., 1995 [15]</td>
<td>3 groups (10/5/10) prospective</td>
<td>1 × 3 μg/kg, 1 × 5 μg/kg, 1 × 10 μg/kg</td>
<td>filgrastim</td>
<td>10 (first apheresis day 6)</td>
<td>10 μg/kg significantly more effective than lower doses</td>
<td>at 10 μg/kg all donors reached ≥50 GM-CFC × 10^4/kg in first apheresis, peak on day 5 of G-CSF application</td>
</tr>
<tr>
<td>Stroncek et al., 1996 [19]</td>
<td>102 donors, various dosages prospective</td>
<td>2; 5; 7.5; 10 μg/kg</td>
<td>filgrastim</td>
<td>5 (apheresis day 6), 10 (apheresis day 11)</td>
<td>CD34 yield correlated with G-CSF dosage; difference in CD34 yield between 7.5 μg/kg and 10 or 5 μg/kg not significant</td>
<td></td>
</tr>
<tr>
<td>Dreger et al., 1994 [5]</td>
<td>9 donors, 6 vs. 3 prospective</td>
<td>10 μg/kg, 5–6 μg/kg</td>
<td>filgrastim</td>
<td>5 (first apheresis day 5)</td>
<td>better yield at 10 μg/kg</td>
<td></td>
</tr>
<tr>
<td>Höglund et al., 1996 [79]</td>
<td>4 × 6 prospective</td>
<td>3; 5; 7.5; 10 μg/kg</td>
<td>lenograstim</td>
<td>6 (first apheresis day 5)</td>
<td>mobilization depended on G-CSF dosage</td>
<td></td>
</tr>
<tr>
<td>Sekhsaria, 1996 [18]</td>
<td>32 donors prospectively randomized</td>
<td>10 μg/kg, 5 μg/kg</td>
<td>filgrastim</td>
<td>5–6</td>
<td>better yield at 10 μg/kg</td>
<td></td>
</tr>
<tr>
<td>Majolino, 1996 [20]</td>
<td>11 donors retrospective</td>
<td>2 × 8 μg/kg, 2 × 5 μg/kg</td>
<td>filgrastim</td>
<td>4 (apheresis day 4), 5 (apheresis day 5)</td>
<td>equivalent CD34 yield in both groups</td>
<td>80% of donors reached target in first apheresis in both groups</td>
</tr>
<tr>
<td>Engelhardt et al., 1999 [17]</td>
<td>75 donors prospective</td>
<td>2 × 12 μg/kg (n = 30), 1 × 10 μg/kg (n = 25)</td>
<td>filgrastim</td>
<td>4 (apheresis day 4), 5 (apheresis day 5)</td>
<td>3.7 × 10^6/kg CD34, 2.0 × 10^6/kg CD34 P &lt; 0.05</td>
<td>90% of donors reached target (4 × 10^6/kg) in 1 or 2 aphereses; 64% of donors reached target (4 × 10^6/kg) in 1 or 2 aphereses</td>
</tr>
<tr>
<td>Author</td>
<td>Donors, n</td>
<td>Sibling/unrelated</td>
<td>Age, median, (range), years</td>
<td>G-CSF preparation, daily dose</td>
<td>Factors affecting mobilization of CD34+ cells and apheresis yield</td>
<td></td>
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<tr>
<td>De la Rubia et al., 2002 [29]</td>
<td>261</td>
<td>sibling and unrelated</td>
<td>38 (2–72)</td>
<td>filgrastim, lenograstim 10 μg/kg</td>
<td>positive influence: divided G-CSF dose, WBC on day 5 of G-CSF</td>
<td></td>
</tr>
<tr>
<td>Suzuya et al., 2005 [30]</td>
<td>59</td>
<td>sibling</td>
<td>16 (3–63)</td>
<td>lenograstim, filgrastim nartograstim 10 μg/kg</td>
<td>negative impact: female gender, age &gt; 38 years no influence: baseline CBC, G-CSF preparation, G-CSF dose</td>
<td></td>
</tr>
<tr>
<td>Ings et al., 2006 [24]</td>
<td>400</td>
<td>263 siblings, 137 unrelated</td>
<td>41 (12–74), 37 (20–59)</td>
<td>filgrastim, lenograstim 10 μg/kg</td>
<td>positive influence: WBC, platelet count at baseline no influence: BMI, age no influence: G-CSF preparation</td>
<td></td>
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<tr>
<td>Vasu et al., 2008 [31]</td>
<td>639</td>
<td>sibling</td>
<td>40 ± 13</td>
<td>filgrastim, 10–16 μg/kg/day</td>
<td>no influence: G-CSF preparation</td>
<td></td>
</tr>
<tr>
<td>De Lavallade et al., 2009 [32]</td>
<td>129</td>
<td>sibling</td>
<td>51 (19–70)</td>
<td>filgrastim, median 8.9 μg/kg</td>
<td>positive influence: weight, G-CSF dose no influence: age no influence: sex, weight and comorbidities</td>
<td></td>
</tr>
<tr>
<td>Richa et al., 2009 [33]</td>
<td>195</td>
<td>sibling</td>
<td>52 (17–71)</td>
<td>filgrastim 10 μg/kg</td>
<td>negative influence: age</td>
<td></td>
</tr>
<tr>
<td>Al-Ali et al., 2011 [34]</td>
<td>167</td>
<td>sibling</td>
<td>47 (18–74)</td>
<td>filgrastim 2 × 5 μg/kg</td>
<td>negative influence: age (donors &gt; 50 years mobilized less well) no statement regarding other variables</td>
<td></td>
</tr>
<tr>
<td>Hölig et al., 2013 [80]</td>
<td>4,393</td>
<td>465 sibling, 3,928 unrelated</td>
<td>48 (2–73), 34 (18–61)</td>
<td>lenograstim 7.5 μg/kg</td>
<td>positive influence: BMI, baseline platelet count, male sex, divided G-CSF dose negative impact: female sex, smoking, alcohol consumption, age (in sibling donors only)</td>
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WBC = White blood cell count; CBC = complete blood count; BMI = body mass index; DLI = donor lymphocyte infusion.
In the majority of donors (99.5%), enough CD34+ cells could be collected in 1 or 2 aphereses. Only in 0.45% of the donors (n = 18), the CD34 yield was less than 2 × 10^6/kg recipient body weight in 2 leukaphereses, carrying a high risk of graft failure in the recipients [23]. Donors not mobilizing adequate numbers of CD34+ cells after G-CSF administration are called ‘poor mobilizers’ and can be found in proportions between 2 and 5% in the literature [24–27]. In related donors, the fraction with poor response to G-CSF application was 2% in our experience. The remarkable variability in the response to G-CSF creates significant uncertainty for allogeneic transplantation programs. It would be valuable to prospectively identify the donors with poor mobilization in order to target them selectively with different priming strategies [28]. Since the 1990s, many groups have investigated the influence of several factors on the mobilization ability of healthy donors. Table 2 shows the key data published by other groups [24, 29–34] and the results of our study. As compared to the literature, we analyzed the largest group of donors treated with a uniform G-CSF dosage. Several analyses, including our own, revealed a better mobilization in male than in female donors. Higher body weight or higher body mass index of the donors enhanced mobilization efficacy in all studies investigating this parameter. Platelet count at baseline also significantly influenced PBSC mobilization in some studies. Data of most groups showed no or only a minor impact of donor age on mobilization efficacy. This finding is clinically relevant with regard to an increasingly older patient population with sibling donors of comparable age. Another important result is the advantage of divided G-CSF doses over single daily doses. Summarizing these data, a reliable prediction of CD34+ cell mobilization in an individual donor cannot be made on the basis of demographic parameters or blood counts at baseline. The mobilization ability of an individual donor is very likely related to genetic polymorphisms. This assumption is supported by the results of second PBSC mobilizations in the same donors. All studies published including our own data showed a fair consistency between the first and second mobilization result [35–37]. CD34+ counts after the second G-CSF cycle in our donor population were reduced by about 10% compared with values after the first mobilization, but were all still in the same order of magnitude. First evidence of a genetic background determining stem cell mobilization was provided by Benboubker et al. [38] who reported an association between the CXCL12–3'A allele and a better mobilization result in healthy stem cell donors. This result could be confirmed by Bogunia-Kubik et al. [39] and Ben et al. [40]. Martin-Antonio et al. [41] reported the same finding and observed associations between mobilization ability and even more polymorphisms, including VCAM-1 und CD44. An analysis of our group could not show a significant association of the CXCL12–3'A allele with more efficient stem cell mobilization in 463 unrelated donors (Schmidt J, Bornhäuser M et al., submitted).

### Short-Term Side Effects of G-CSF Administration

The usual complaints, reported by a large proportion of healthy donors during G-CSF administration, are bone pain, headache and flu-like symptoms like malaise, nausea, subfebrile body temperature and night sweats [13, 23, 42]. Furthermore, muscle pain, insomnia, anorexia, and vomiting can occur less often. Frequency and severity of the most common side effects were described in two recent studies in unrelated donors [23, 43] (fig. 3). Both groups found a frequency of skeletal pain of about 90% of the donors, but the intensity was mild or moderate in the majority of cases. The incidence of flu-like symptoms differed between the reports, obviously due to differences in data collection. The study of Pulsipher et al. [43] represents the most comprehensive and detailed survey about G-CSF-induced side effects reported so far, and is the first to prospectively compare the experiences of unrelated BM and PBSC donors [43]. The incidence of pain was comparable in both groups, but PBSC donors had a significantly faster and higher probability of complete recovery from their complaints than BM donors.
Our own results and the data of Pulsipher et al. [43] revealed a higher intensity of pain in donors who were overweight or obese. Pain was also more frequently reported by female donors. Surprisingly, both studies recorded a lower probability of pain in older donors. In our program, related donors had a lower incidence and severity of pain, possibly due to the different psychological situation of this subgroup. Besides, the median age of siblings was 48 years compared to a median age of 34 years in unrelated donors, which might partially account for the lower incidence of pain in the related donor population. From a clinical point of view, all of the typical G-CSF-associated side effects normally respond quickly to non-steroid analgesics like acetaminophen or ibuprofen. With such medication, substantial impairment of the donor’s general condition can generally be avoided [13].

Laboratory findings after G-CSF treatment are characterized by a typical leukocytosis, but also a mild decrease in platelet count and potassium concentration and an increase in uric acid, alkaline phosphatase, transaminases and lactate dehydrogenase levels [44].

G-CSF administration causes a slight spleen enlargement in the majority of healthy donors [45–47], which normally resolves within a few weeks. The magnitude of splenomegaly might be related to the daily dose and duration of G-CSF treatment [47]. An uncommon but potentially life-threatening complication is splenic rupture. There are at least 6 cases of this dreaded event in healthy donors after G-CSF application reported in the literature [48–53]. In these donors, the daily G-CSF dosage was between 10–20 μg/kg, in 3 cases mobilization was continued until day 6. Tigue et al. [54] assume an incidence between 1:5,000 and 1:10,000 for splenic rupture in healthy stem cell donors. Donors should be counseled to avoid contact sports and other risks for abdominal trauma during the time of G-CSF administration and about 1 week thereafter. In donors with preexisting splenomegaly, the G-CSF dose might be preventively reduced.

Pulmonary events such as interstitial pneumonitis, pulmonary infiltrates, and lung fibrosis are other rare but serious complications of G-CSF treatment. A few cases of acute respiratory distress syndrome (ARDS) after G-CSF application have been reported in healthy donors, the pathogenesis remains hypothetical [55–57]. In our study, we observed pulmonary infiltrates during or shortly after G-CSF treatment in 3 donors, but all suffered from concomitant bacterial or viral infections [58].

Another potential hazard of stem cell mobilization with G-CSF might be a transient state of hypercoagulability that could give rise to thrombotic complications, especially in older sibling donors [59–61]. There are some reports of increased plasma markers of endothelial activation and activated plasmatic coagulation, but findings are partially conflicting [62]. Vascular events among healthy stem cell donors during G-CSF treatment are rarely reported [54]. Among 8,290 healthy donors, we observed one young man (age 24 years) with deep vein thrombosis 1 day after stem cell collection and one 63-year-old female sibling donor with a cerebral insult 2 weeks after PBSC donation. This number does not imply a clinically significant thrombotic risk in healthy PBSC donors.

**Results from Long-Term Follow-Up after G-CSF Administration**

While follow-up of unrelated PBSC donors is routinely conducted by the registries, there is no ongoing large scale international registry prospectively monitoring related donors [13]. Because of that, available data might be biased by a significant number of unreported cases. In our study, the proportion of donors participating in the follow-up investigations 4 weeks after donation was 67%, but was reduced to 38.1% after 5 years. Altogether, our follow-up data included 16,242 donor years. The vast majority of PBSC donors consider their general condition excellent or good throughout the observation period (fig. 4).

Reports on the course of blood counts after PBSC collection are partly controversial. In our donor cohort, leukocyte
counts were significantly lower 4 weeks after PBSC collection as compared to baseline. During further follow-up, white blood cells gradually recovered. Lymphocyte counts returned to baseline values between 1 and 2 years after donation, but neutrophile counts remained slightly but significantly below the initial values throughout the follow-up period. With the exception of some [63], this effect was reported by the majority of the more recent studies [64, 65]. In the latest publication, the NMDP survey, Pulipher et al. [43] report also on a delayed normalization of leucocyte counts, resolving by year 3, the last point of follow-up. In this study, platelet counts and hemoglobin levels were slightly decreased from baseline after both BM and PBSC donation through year 3. This finding was not observed in our study and in the other previous reports [64, 65]. The mechanisms underlying these effects remain unclear. As Anderlini et al. [66] already stated in 1996, the relative contributions of mobilization and leukapheresis have not yet been elucidated. To analyze this phenomenon in more detail, we separately evaluated the hematologic recovery of ‘poor mobilizers’ (donating less than \(2 \times 10^6\) CD34+ cells/kg recipient weight in the first apheresis). These donors are characterized by lower baseline values, but also by a remarkably delayed normalization of leucocyte counts (fig. 5). Between years 2 and 5, white blood cells were still 9% lower than the baseline value. These observations cannot be easily explained. Conceivably, there might be distinct differences in the proliferation dynamics of the individual stem cell pools. A better understanding of the underlying mechanisms would be highly desirable and would help make a more informed decision about second donation requests from individual donors. Besides these clearly demonstrable effects on hematologic parameters, a clinical impact, e.g., an increased susceptibility to infections after PBSC donation, has never been reported in the literature. Altogether, it can be concluded that hematologic effects of G-CSF treatment are self-limiting and clinically acceptable.

The question whether G-CSF exposure of healthy donors could increase the risk of later development of hematologic (especially myeloid) malignancies has been debated since the very beginning of allogeneic PBSC mobilization. During the last years, follow-up data from stem cell donor registries and several collection centers have been reported. The results of our follow-up study are shown in table 3. Malignancies have been reported in 28 donors (0.34%) during follow-up, 8 of these being hematologic malignancies. Referring to the standardized incidence ratio and the respective confidence interval, the incidences of acute myeloid leukemia (AML) and Hodgkin’s disease in the cohort of donors investigated turned out to be significantly different from the natural incidence in the German population. The incidences of the other malignant diseases did not differ significantly from the age- and gender-adjusted German population. Some groups did not observe any hematologic malignancies in PBSC donors [64, 67–69]. Some cases of AML have been published in related donors [9, 70]. The NMDP reported data of 4,015 unrelated donors who were monitored more than 1 year after their PBSC donation (9,785 donor years) with no cases of leukemia or lymphoma [71]. A retrospective follow-up survey of the German Bone Marrow Donor Registry (DKMS) evaluated all PBSC and BM donors donating through January 2009 [72]. This study
had a response rate of 81.3% of the donors and documented 55,229 observation years, of these 30,777 in PBSC donors. This analysis revealed no clustering of leukemia or lymphomas; however, a significantly increased incidence of malignant melanoma was shown in BM donors. Halter et al. [42] presented a retrospective multicenter EBMT study covering 51,024 first allogeneic hematopoietic stem cell donations (27,770 BM and 23,254 PBSC) [42]. In this survey, 20 hematologic malignancies were reported (8 in bone marrow donors, 12 in PBSC donors). The incidences in both groups were below the age-adjusted values of the control population and there have been no statistically significant differences between BM and PBSC donors. However, the authors state that there might be some underreporting because of the retrospective and heterogenic character of their data. Added together, there is still no sufficient evidence to definitely prove or disprove the hypothesis that G-CSF administration affects the risk of leukemia in healthy donors. According to calculations by Schmidt et al. [72], at least 90,000 donor years would be required to detect a duplication of leukemia risk. This figure illustrates the enormous logistical challenges facing sophisticated donor follow-up programs.

The major question, whether G-CSF promotes leukemogenesis via genetic or epigenetic alterations, cannot currently be answered. Mutations in the G-CSF receptor have been identified in patients with severe congenital neutropenia and have been shown to be characteristic for this disease [73]. These receptors provoke an excessive cell proliferation after stimulation with G-CSF and can thereby contribute to the development of leukemia. From in vitro investigations, Nagler et al. [74] reported epigenetic and genetic alterations in lymphocytes, changes in gene expression patterns in mononuclear cells, and DNA destabilization. These findings have raised much concern regarding the safety of allogeneic PBSC donors; however, some other studies published by the NMDP and other groups [75–78] could not confirm these data. Nevertheless, this issue has to be investigated carefully and thoroughly in future studies.

Conclusion

Mobilization of PBSC with G-CSF and leukapheresis has become a well-established procedure worldwide and is the predominating technique for the procurement of allogeneic hematopoietic stem cell transplants. Although G-CSF has a clear dose response relationship, the wide variety of mobilization efficacy remains a major challenge in the management of the individual donor. Parameters that allow prediction of mobilization potential would therefore be highly desirable. Short-term side effects as well as hematologic changes after G-CSF application are generally tolerable and do not pose serious risks for healthy donors. Long-term follow-up remains an ongoing endeavor and should be carried out with the most appropriate statistical instruments and the utmost accuracy to guarantee the safety of related and unrelated voluntary PBSC donors.

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References


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