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Allogeneic Peripheral Blood Stem Cell Collection as of 2008

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Abstract

The rapid growth of the use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) to mobilize and collect allogeneic peripheral blood stem cells (PBSCs) for transplantation has made it a new international standard. While the procedure remains safe, older donors, donors with significant comorbidities and pediatric donors are now often employed. This brings a new set of challenges in the donor evaluation, medical clearance, informed consent and collection process. Rare and unexpected severe adverse events related to rhG-CSF administration and PBSC apheresis have been described. Proper PBSC donor counseling, evaluation and care have become even more important.

Keywords

Normal donors; granulocyte colony-stimulating factor; G-CSF; filgrastim; allogeneic stem cell transplantation

Introduction

The last decade has witnessed the rapid growth of the use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in allogeneic peripheral blood stem cell (PBSC) donors. Over 15,000 stem cell donors are harvested every year, and rhG-CSF mobilized PBSCs accounted for 75% of related and 50% of unrelated donor donations in North America alone in 2003 [1]. This manuscript provides a concise outline of the key features of PBSC collection as performed in most transplant or apheresis units worldwide as of 2008. As the non-glycosylated rhG-CSF form (filgrastim) is the product most often administered (at least in North America), the terms rhG-CSF and filgrastim will be used interchangeably in the text.

Allogeneic Peripheral Blood Stem Cell Collection

Normal PBSC donor evaluation and informed consent

Table 1 outlines the key diagnostic elements of normal PBSC donor evaluation. In general, these tests should reflect current Foundation for the Accreditation of Cellular Therapy

(FACT; www.factwebsite.org) standards for donor evaluation. They should also reflect current FDA regulatory requirements (www.fda.gov) for the United States or, for other countries, local regulatory requirements. The evaluation is primarily aimed at (1) identifying factors that could jeopardize donor safety and well-being during donation and (2) detecting infectious agents or diseases that could potentially be transmitted to the recipient.

While there is no clear-cut upper age limit in the related donor setting, older related donors deserve more attention, as they are far more likely to carry significant comorbidities (hypertension, diabetes, atherosclerotic vascular disease, degenerative joint disease, etc). Appropriate subspecialty consultations should be requested in these cases. This is likely to become a more pressing issue in the years ahead, as an increasing number of older recipients, whose siblings are of similar age, are now considered candidates for allogeneic stem cell transplantation [2,3]. Younger donors (i.e. pediatric) present an entirely different set of challenges, primarily related to venous access as well as donor consent (frequently requiring the involvement of a third party to minimize the potential for a conflict of interest) [4]. There is also more hesitation in administering growth factors to healthy pediatric donors, in view of the possible potential for long-term adverse events (see below). In the unrelated donor setting, the age range is between 18 and 55-60 years, depending on the national registry in question.

Normal donors with positive testing for hepatitis B and C can still be employed as donors if no suitable alternative donor can be identified. Under these circumstances the recipient needs to be counseled about the long-term risk for acute and chronic hepatitis transmission. Likewise, normal donors with a past history of treated malignancy may still be considered as donors, although a five-year cancer-free period is usually advised and appropriate recipient counseling is indicated. These two categories of donors should be told that they will also be deferred from regular blood donation. All donors should be notified about their test results, and appropriate follow-up with their personal physician(s) should be arranged as clinically indicated.

An emerging issue is the potential conflict of interest related to donor work-up, medical evaluation and ultimately informed consent in the related donor setting. It has become clear that in many cases, at least in the U.S., physicians directly or indirectly involved in the care of the recipient are also involved in the PBSC donor evaluation and clearance process (Anderlini P & O'Donnell P; personal communication, 2007). Ideally, at least some degree of separation between donor and recipient care should be implemented in the related donor setting, as it is accomplished effectively through unrelated donor registries.

Cytokine administration to normal donors

RhG-CSF (primarily filgrastim, but also lenograstim) is ordinarily employed for this purpose, although occasionally recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) and other agents such as AMD3100 (a CXCR4 antagonist) have been used [5,6]. The filgrastim dose usually ranges from 5-16 mcg/kg subcutaneously daily, given once or in two divided doses for 4-7 days [7,8].

There is evidence supporting a dose-response effect with regard to CD34+ cell mobilization [9]. Most allogeneic donors are mobilized with 10 mcg/kg for 5 days [10-14]. Doses as high as 20 mcg/kg daily have been employed. There is some evidence suggesting that a twice-daily rhG-CSF (lenograstim, filgrastim) administration schedule may be more effective than a once-daily schedule. It has also been suggested that the glycosylated form of rhG-CSF (lenograstim) may be biologically more active than the non-glycosylated form (filgrastim) for PBSC mobilization [15]. The pegylated form of G-CSF is currently being investigated for allogeneic PBSC mobilization [16].

Filgrastim-related adverse events can be divided into common “expected” ones (usually mild-to-moderately severe) and uncommon “unexpected” ones (occasionally serious or even life-threatening). Most common or “expected” side effects are mild to moderate, with bone pain, myalgia, malaise and nausea being the most frequently occurring (Figure 1) [17]. Many donors describe their symptoms collectively as “flu-like symptoms”. The severity of the symptoms, particularly the bone pain, usually peaks between day 4 of day 6 of filgrastim administration (Figure 2). It is important to note that the bone pain and other mild-to-moderate symptoms related to G-CSF are readily treated with common analgesics, such as acetaminophen and that the symptoms resolve within 4 days after discontinuation of the G-CSF administration [14, 18-19].

“Unexpected” rare but more severe and potentially life-threatening rhG-CSF-induced adverse events in PBSC donors have been reported. The most impressive has undoubtedly been splenic rupture, usually necessitating emergency splenectomy [14,20].

A measurable splenic enlargement occurs in many donors receiving rhG-CSF. Studies have reported a spleen size increase of about 10% to 13% on average in these individuals. The spleen size returned to baseline up to 10 days after G-CSF administration was stopped. There have been at least four cases of splenic rupture reported in healthy adult donors who received G-CSF. Three of the donors had to have splenectomy and the remaining donor was treated with conservative measures ([14]. Splenic trauma (even a minor one) immediately after the PBSC donation period could conceivably represent a predisposing factor. Donors should be told to avoid contact sports for a short period of time after donation [19]). While this is a very serious event, the incidence is estimated to be between 1 in 5000 to 1 in 10,000 donors [21].

The management of normal PBSC donors with hemoglobin S has caused some controversy. There have been reports of donors with complex hemoglobinopathies including hemoglobin S that have developed serious and occasionally fatal sickle cell crises after they received G-CSF [22,23]. Conversely, limited experience with healthy donors with isolated sickle cell trait (hemoglobin AS) suggests that these donors are not at risk for vaso-occlusive complications following rhG-CSF administration. In this prospective, controlled study comparing sickle cell trait subjects with normal subjects, no serious adverse events were found in either group. Both groups were mobilized with 10 mcg/kg G-CSF for 5 days, and CD34 yield were similar in each group [22]. However, as a precautionary measure, donors who test positive for hemoglobin S by hemoglobin solubility test are currently excluded

from G-CSF- mobilized PBSC donation by the United States National Marrow Donor Program [21]. Individual U.S. centers have variable policies on this issue.

Other uncommon but potentially serious or life-threatening adverse events described in PBSC donors include unstable angina, myocardial infarction (in donors with coronary artery disease), stroke, capillary leak syndrome, acute gouty arthritis, and episcleritis/scleritis [24]. In addition to leukocytosis, filgrastim also causes a transient increase in serum alkaline phosphatase, transaminases, LDH levels [11].

As reported by Tassi et al [25], filgrastim also causes a mild-to-moderate decrease in platelet count from baseline in approximately 25% of healthy allogeneic donors. Platelet counts returned to normal within 4 to 8 months. The apheresis procedure itself causes an additional and more substantial platelet depletion, however, no complications related to thrombocytopenia have been reported [26]. The reinfusion of autologous platelet-rich plasma has been suggested to minimize this, but it is of limited efficacy and usually unnecessary.

PBSC collection in normal donors

When to start Apheresis?—PBSC apheresis is ordinarily started between day 4 and day 6 of rhG-CSF administration. While not always performed in normal PBSC donors, evaluation of circulating CD34+ cell concentration is helpful in predicting the yield of the first day of apheresis. There is well-documented correlation between peripheral blood (PB) CD34+ count and CD34+ cell yield [27]. The minimum PB CD34+ cell count threshold predicting for a sufficient CD34+ cell yield is believed to be in the 8-10/microliter range [27]. Other parameters that have been reported to predictive of CD34 yield by apheresis in some studies are circulating peripheral blood leukocyte counts and mononuclear cell counts, platelet counts one day prior to or on the day of stem cell harvest, and the presence of immature myeloid forms (i.e. myelocytes, metamyelocytes, etc) in the PB [28, 29]. The final adequacy of the product is determined by the CD34+ cell count of the PBSC apheresis product. While the collection target is normally $4-5 \times 10^6/\text{kg}$ recipient, a minimum number of CD34+ cells required to ensure prompt engraftment after allogeneic transplantation, while quite variable, is probably in the range of $2 \times 10^6/\text{kg}$ body weight of the recipient.

Apheresis Instruments

Instruments that are commonly used for collection of platelets and granulocytes can also be used for collecting PBSC. All these instruments have a computer controlled programs specific for each procedure and require specialized collection kits. The instruments vary in the extracorporeal volume of the kits, need for single versus dual venous access, product volume, red cell and platelet loss, and collection efficiency. With better collection efficiency, the required cell dose can be collected in shorter time periods with lesser volume processed and in fewer numbers of procedures [30].

The number of PBSCs collected with an apheresis procedure depends on the percentage of progenitor cells in peripheral blood, the total blood volume processed, and the collection

efficiency of the instrument [30]. Conventionally 2 to 3 blood volumes are processed or the procedure may alternatively be conducted for a fixed period of time such as 4-6 hours.

Vascular Access

A continuous blood flow of 60-100 ml/min in adults is required for stem cell collection. This should ideally be established through the peripheral antecubital veins if they are large enough to accommodate a 16-18 gauge stainless steel needle for draw and at least a 19 gauge needle for return. Venipuncture complications include pain, nerve damage, hematoma and infection. If a central venous catheter is required a stiff, dual lumen dialysis-type catheter placed in the subclavian, femoral, or internal jugular veins can provide adequate blood flow. Side-effects and risks associated with central venous catheters include thrombosis, infections, bleeding, and pneumothorax [31]. Femoral venous catheters will limit a person's mobility and carry some risk of infection and bleeding, but are usually preferred in normal donors to avoid the risk of pneumothorax or hemothorax. Catheter patency is maintained by installation of heparin solution. Heparin induced thrombocytopenia and thrombosis are serious complications of heparin use; therefore some centers employ only normal saline flushes to maintain catheter patency. The percentage of donors who requires central or femoral venous catheters inserted varies according to the center, but is in the 5-20% range [32]. Middle-age women seem to be at particular risk for this [11].

Anticoagulation

The most commonly used anticoagulant for apheresis procedures is citrate or ADC-A, in a ratio of 1:12 to 1:15. The citrate binds with calcium resulting in a temporary decrease in the blood ionized calcium level. Donors may experience signs and symptoms of citrate reaction that include paresthesia, headache, light-headedness, nausea, and chest tightness [33]. These symptoms can usually be alleviated by reducing the blood flow rate or by replacing calcium orally or intravenously. Infusion of calcium via the return line reduces the incidence of citrate related effects by 65-90% [33]. Infusion of calcium does have the potential to cause cardiac arrhythmias. This should be done carefully, using calculated doses specific for each donor, with the aid of an infusion pump that controls rate of infusion. A combination of heparin and ACD-A or heparin alone may be used as an anticoagulant to reduce citrate toxicity. However, administration of heparin is also not without adverse effects like systemic anticoagulation and risk of bleeding [10].

Other complications of apheresis

Apheresis-related adverse events are well described in the literature and include the following:

1. Loss of red blood cells with anemia if rinseback cannot be performed at the end of stem cell collection
2. Transient thrombocytopenia, as platelet counts are expected to decrease by about 20-30% after each procedure.
3. Vasovagal effects/reactions - diaphoresis, nausea, hypotension, tachycardia, or bradycardia

4. Air embolus - most apheresis instruments have a built in alarm that detects air in the return line
5. Adverse effects related to venipuncture – severe pain, nerve damage, local hematoma, infiltration, arterial puncture (in cases of central access), infection
6. Machine malfunctions - hemolysis, clot or leak, inability to return blood. [10, 34].

PBSC collection

The peripheral blood CD34+ cell count in normal subjects under unstimulated conditions is very low (<5/mcL), but it increases 15- to 35-fold following 4-5 days of rhG-CSF administration. Leukocyte count and peripheral blood CD34+ cell count usually peak between day 5 and day 7 of filgrastim administration (Figure 3), and apheresis is usually started between day 4 and day 6. These collections are usually long (4-5 hours) procedures with 15-20 liters of blood processed [18].

As stated, the target and minimum CD34+ cell dose to be collected are normally 4-5 and 2×10^6 CD34+ cells/kg recipient, respectively. In about two thirds of donors the target dose can be reached with one collection, with most of the others requiring a second collection [18]. Filgrastim administration stops once the collection is completed, and filgrastim-related side effects ordinarily resolve within a few days. A follow-up assessment of the donor 24-48 hour following donation is usually performed. In view of published evidence suggesting transient rhG-CSF-induced hypercoagulability in PBSC donors [35,36], and the known thrombosis risk related to prolonged air or car travel, normal donors may be advised not to travel for at least 48 hours following the completion of their collection. In addition, if significant post-collection thrombocytopenia has developed, thrombocytopenic precautions may be recommended for up to a week following collection. The reinfusion of autologous platelet-rich plasma to ameliorate thrombocytopenia, while feasible in these cases, is usually unnecessary. Contact sports should probably be avoided for several days following donation to minimize the chance of splenic trauma and rupture. The stem cell product can be infused fresh or can undergo cryopreservation, and in the latter case it can be stored successfully for many years.

Factors affecting PBSC yield

The collection target is usually reached with one apheresis in 60-70% of donors, with most residual donors reaching the target cell dose with a second collection. Some groups of donors may frequently collect less than others, such as older donors [26]. Other factors that correlate with CD34+ cell yield are body mass index, blood withdrawal rate during collection, white blood count before mobilization, and platelet count before and during mobilization [37]. A small number of donors (up to 5%) prove to be poor mobilizers and fail to reach even the minimum CD34+ cell dose despite two or more collections [18]. In these cases a conventional marrow harvest may be considered.

Factors negatively affecting CD34+ cell yield include older age (> 55 years), female sex, a shorter duration of rhG-CSF administration and a low baseline platelet count. These donors are more likely to need a second collection [18,27,38].

Second PBSC collections

There is limited data regarding the efficacy and safety of repeated PBSC mobilization and collection of normal donors. It appears that the stem cell yield is reduced in the event of repeated mobilization and collections, particularly when the second collection takes place within 1-2 months of the first and with female donors. Still, an acceptable CD34+ cell dose can be collected in most cases [20,39].

Pediatric Donors

Normal pediatric PBSC donors present special and unique challenges. Issues surrounding this group of donors include venous access, effects of G-CSF and leukapheresis technique, as well as ethical considerations related to informed consent. A comprehensive review of over 200 pediatric PBSC donors by Pulsipher et al [4] found that most of the donors received G-CSF at an average dose of 10 microgram/kg subcutaneously once daily for four days, with the mean number of apheresis procedures of 1.4 required to reach target CD34 cell dose.

Short-term effects of G-CSF in this patient population are similar to those of adult donors, with bone pain, headache, and myalgias being the most frequently reported. Interestingly, pediatric donors report significantly fewer side effects compared to adult donors [38]. Less than 20% of pediatric donors require analgesics during G-CSF therapy [4].

To date, there have been no reports of long-term adverse side effects of G-CSF reported in pediatric donors, however this is an area where future research is needed to ensure long-term donor safety.

Pediatric donors may require a temporary central venous catheter, and donors of a progressively younger age seem to need this more consistently. Sedation (conscious sedation or general anesthesia) is usually required for catheter insertion. Complications from the catheter placement or sedation may occur, but so far these have mild and limited in this group of patients [4].

Side effects of the leukapheresis procedure in this population appear to be limited and mild, with hypocalcemia being the most common. The hypocalcemia resolves with calcium administration. The method of calcium supplementation varies from oral to intravenous [40].

Low-body weight donors, or donors that weigh less than 20-25 kilograms may need to be exposed to allogeneic blood during apheresis. It is common practice to prime the apheresis machine with packed red cells due to the ratio between donor and extracorporeal blood volume in pediatric donors. Generally, a unit of packed red blood cells is used to prime the machine when the extracorporeal volume exceeds 15% of patient's blood volume [41,42]. Some centers do not routinely complete the reinfusion procedure to minimize or avoid volume overload.

The informed consent process of the minor donor presents unique issues and concerns. While the informed consent process varies, most minor donors are consented along with a parent or guardian. This situation may be complicated by a conflict of interest due to the

parent/guardian's interest in the PBSC recipient's welfare. Some centers often elect to have a third party involved in the informed consent process of minor donors. Studies have identified emotional stress, of the PBSC donor and their relatives, as an issue to be addressed with this group [43,44]. Some centers have special departments or entities to provide education, counseling, and support for pediatric donors and families.

Current data suggest that PBSC mobilization and collection in pediatric donors is relatively safe and efficient, however data are limited and additional research is needed.

The question of possible long-term adverse events

G-CSF receptors are primarily located on normal myeloid cells. There are no data to indicate that it may selectively stimulate leukemic myeloid blasts in normal PBSC donors [45]. However, whether even short-term rhG-CSF exposure can increase the risk of later development of myeloid malignancies (i.e. acute myeloid leukemia or myelodysplasia) in selected and possibly genetically predisposed PBSC donors has been a debated issue, an issue that can theoretically be solved only by long-term follow-up studies [46]. This theoretical concern is particularly acute in pediatric donors, in view of their much longer life expectancy. As leukemia is a rare event in the general population, it has been estimated that, in order to detect a 10-fold increase in leukemia risk in normal PBSC donors (a very substantial and unlikely risk increase), over 2,000 donors would have to be followed for ten years or longer [19,47]. To detect smaller (and more realistic) increases in risk, much larger numbers of donors would be required, and the monumental logistical challenges related to this endeavor are quite obvious. While unrelated donors are usually part of an established registry-based follow-up system, at the time of this writing there is no ongoing large-scale international registry prospectively monitoring large numbers of related PBSC donors in the long-term.

A few cases of leukemia in PBSC donors have been reported, although these publications have been criticized for selection bias and misleading statistical techniques [19,48, 49]. The National Marrow Donor program (NMDP) has recently provided some reassuring data on this issue. Among 4015 donors who have passed the first anniversary of their PBSC donation, the NMDP has accumulated 9785 years of follow-up (range 1-9 years, with 897 donors < 4 years). The incidence of cancer in this group was consistent with the age-adjusted US incidence of cancer in the adult population, with no reports of leukemia or lymphoma [50]. One can conclude that, based on the data currently available, there is no evidence of any measurable long-term leukemia risk for normal PBSC donors, although this issue should be part of the normal PBSC donor counseling and informed consent process.

Conclusion

The use of rhG-CSF for PBSC mobilization in normal donors has been adopted as an international standard of care and it is now widespread. While an accurate assessment would be problematic, it can be estimated that no less than 20,000 to 30,000 PBSC donors have received rhG-CSF [1], and the number is growing daily. Available evidence indicates that the procedure is remarkably safe, although rare serious adverse events have been described. However, it poses special challenges in older donors (particularly if comorbidities are

present) as well as in pediatric donors, challenges that only now are coming into focus. While present follow-up data are reassuring, the possibility of long-term adverse events related to PBSC donation (e.g. development of myelodysplasia or leukemia) cannot be ruled out, and needs to be included in the PBSC donor counseling and consent process. Efforts to establish long-term monitoring on normal PBSC donors should be supported by the international apheresis and transfusion medicine community.

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Figure 1. Adverse events related to filgrastim administration in normal PBSC donors (reproduced with permission of the National Marrow Donor Program)

Figure 2. Temporal profile of bone pain experienced by normal PBSC donors (reproduced with permission of the National Marrow Donor Program)

Figure 3. Leukocyte count during filgrastim administration in normal PBSC donors (reproduced with permission of the National Marrow Donor Program)

Table 1
Normal PBSC donor work-up

1	Physical assessment, medical history
2	EKG, CXR
3	Hematology, chemistry profile, coagulation profile, electrolytes, serum protein electrophoresis
4	Infectious disease screening panel (Hepatitis A, B, C, HIV, HTLV/II, syphilis, West Nile virus, CMV)
5	ABO, Rh typing
6	Urinalysis
7	Serum or urine pregnancy tests (for women of childbearing age)
8	Peripheral venous access assessment
9	Marrow aspiration/biopsy (if abnormal blood counts or otherwise clinically indicated)
10	Additional testing as clinically indicated