Allogeneic Blood Stem Cell Transplantation: Considerations for Donors

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Allogeneic transplantation of cytokine-mobilized peripheral blood stem cells (PBSCs) is now being increasingly performed, but safety considerations for hematologically normal PBSC donors have not been fully addressed. Progenitors are generally mobilized for collection from normal donors using recombinant human granulocyte colony-stimulating factor (rhG-CSF). Although the short-term safety profile of rhG-CSF seems acceptable, experience remains limited and its optimal dose and schedule have not been defined. Minimal data exist regarding long-term safety of rhG-CSF, primarily derived from experience in patients with chronic neutropenia or cancer. An “ad hoc” workshop was recently convened among a group of investigators actively involved in the field of allogeneic stem cell transplantation to discuss the safety issues pertaining to normal PBSC donors. There was agreement on the following points: (1) On the basis of available data, it appears that rhG-CSF treatment and PBSC collection have an acceptable short-term safety profile in normal donors. However, the need for continued safety monitoring was recognized. (2) rhG-CSF doses up to 10 μg/kg/d show a consistent dose-response relationship with the mobilization (and collection) of CD34+ progenitor cells, and this dose is acceptable for routine clinical use. Whether higher doses are superior (or cost effective) remains to be determined, and they may produce more severe side effects. The potential risks of marked leukocytosis (arbitrarily defined as a leukocyte count of more than 70 × 10⁹/L) have been a concern, and rhG-CSF dose reduction is performed by many centers to maintain leukocyte counts below this level. (3) Transient post donation cytopenias, involving granulocytes, lymphocytes, and platelets, may occur and are at least partly related to the leukapheresis procedure. These are generally asymptomatic and self-limited; follow-up blood counts are not necessarily required. Reinfusion of autologous platelet-rich plasma should be considered for donors with expected postdonation thrombocytopenia (platelet count < 80 to 100 × 10⁹/L). (4) Donors should meet the eligibility criteria which apply to donors of apheresis platelets, with the exception that pediatric donors may also be considered. Any deviation from these criteria should have supporting documentation. There is insufficient information at this time to clearly establish definite contraindications for PBSC collection in a hematologically normal donor. Potential contraindications include the presence of inflammatory, autoimmune, or rheumatologic disorders, as well as atherosclerotic or cerebrovascular disease. (5) The creation of an International PBSC Donor Registry is desirable to facilitate monitoring the long-term effects of the procedure. Individual institutions or donor centers are encouraged to establish their own PBSC donor follow-up system, preferably with a standardized approach to data collection.

The last few years have witnessed a dramatic increase in the use of cytokine-mobilized allogeneic peripheral blood stem cell (PBSC) transplants. National and international programs for unrelated donors have also begun supplying allogeneic PBSCs for transplantation. Most centers have used recombinant human granulocyte colony-stimulating factor (rhG-CSF) to mobilize progenitors. The collection of granulocytes from rhG-CSF–treated normal donors for granulocyte transfusions is now an established practice in many blood banks. Although rhG-CSF has been widely used for treatment of patients with neutropenic disorders, the short- and long-term effects of PBSC mobilization and collection in normal donors are not well defined.

On December 7, 1996, an “ad hoc” workshop was held involving representatives invited from centers active in performing allogeneic blood stem cell transplantation worldwide. More than 40 transplant teams were represented as well as the International Bone Marrow Transplant Registry (IBMTR), the National Marrow Donor Program (NMDP), and the European Group for Blood and Marrow Transplantation (EBMT). The meeting was organized and convened by the University of Texas M.D. Anderson Cancer Center to address issues relating to donor safety. The goals of the meeting were to:

1. Establish an international PBSC donor registry.
2. Develop guidelines for transfusion practice.
3. Develop guidelines regarding the schedule of blood product transfusions.

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meeting were to review currently available data on donor effects of rhG-CSF–stimulated PBSC collection, discuss PBSC donor eligibility criteria and management, and to assess potential long-term effects on the donor.

**SHORT-TERM SAFETY PROFILE OF rhG-CSF IN NORMAL PBSC DONORS**

There are considerable data regarding the short- and long-term effects of rhG-CSF in patients with hematologic diseases or cancer. Patients with chronic neutropenia have generally tolerated the drug well for many years. There is now a growing amount of data on the short-term safety of rhG-CSF in normal PBSC (and granulocyte) donors, which has recently been reviewed. The doses used have been as low as 2 to 3 μg/kg/d or as high as 24 μg/kg/d. The most commonly reported adverse effects include bone pain, headache, fatigue, and nausea. Other side effects, such as noncardiac chest pain, insomnia, night sweats, fluid retention, and dizziness, have been reported less frequently. These adverse effects are at least partly dose-related and ordinarily resolve within a few days of rhG-CSF discontinuation. Severe side effects requiring rhG-CSF discontinuation have been uncommon (1% to 3% of donors). rhG-CSF–induced laboratory abnormalities include transient increases (about twofold to threefold) of alkaline phosphatase and lactate dehydrogenase, and, less commonly, decreases in serum electrolytes. On the basis of these data, it appears that rhG-CSF has an acceptable short-term safety profile in the vast majority of normal donors. Overall experience remains relatively limited, however, particularly at doses > 10 μg/kg/d and there is a need for continued short-term safety monitoring.

**OPTIMAL rhG-CSF DOSE AND SCHEDULE OF ADMINISTRATION**

The optimal rhG-CSF dose and schedule would ensure the collection of an “adequate” CD34+ cell number while minimizing donors’ cytokine exposure and side effects. This dose has not been established, however, partly because the optimal CD34+ cell dose required for engraftment and overall transplant outcome is unknown. It has been shown that, at least for rhG-CSF doses up to 10 μg/kg/d, a consistent dose-response relationship exists between rhG-CSF dose and degree of mobilization of CD34+ progenitor cells. Although rhG-CSF doses up to 24 μg/kg/d have been successfully used, experience with these doses remains limited and it is unclear whether higher doses will prove superior or cost effective. Higher rhG-CSF doses may produce more severe side effects. Additional evaluation of higher rhG-CSF doses is encouraged within the context of clinical trials. A dose of 10 μg/kg/d has been recently recommended by investigators with the EBMT and the NMDP (Stroncek D., personal communication, 1997).

The kinetics of the increase of granulocytes and CD34+ cells after rhG-CSF stimulation differ. Whereas a leukocytosis is usually evident within 4 to 6 hours of rhG-CSF administration, a substantial increase in circulating CD34+ progenitor cells does not occur until day 3 of rhG-CSF. The peak usually occurs on day 5 or 6, followed by a decline even with continued rhG-CSF administration. The correlation between the preapheresis leukocyte count and apheresis yield of CD34+ progenitor cells is weak, and a very high leukocyte count is not a prerequisite for an acceptable stem cell collection. In primates, an rhG-CSF–induced 15- to 28-fold increase in leukocyte count was found to be associated with cerebrovascular events related to neutrophilic infiltration of the brain parenchyma. Dose reduction of rhG-CSF has been recommended by several investigators to avoid development of “excessive” leukocytosis, which has arbitrarily been defined as a leukocyte count of more than 70 × 10^9/L. The impact of a reduced rhG-CSF dose intensity on PBSC mobilization efficiency is uncertain, and a correlation between degree of leukocytosis and toxicity has not been established in humans.

A twice-daily administration schedule has been used by some groups. The rationale for a twice-daily schedule is based on the fact that the elimination half-life of rhG-CSF after subcutaneous or intravenous administration is only about 3 to 4 hours. The biologic half-life of rhG-CSF is known to be significantly longer, however. Mobilization and transplantation results appear similar with either daily or twice-daily rhG-CSF administration schedules.

**EFFECTS OF PBSC APHERESIS**

PBSCs are usually collected by continuous-flow apheresis after cytokine treatment. The total blood volume processed per apheresis procedure is usually twice the donor’s total blood volume. Large volume stem cell apheresis processing 3 up to 6 times the donor’s total blood volume has been reported. Typically, 3 to 5 × 10^8 total nucleated cells per kilogram are collected per run with mononuclear cells encompassing between 60% and 90% of cells collected. Anticoagulation is usually performed with acid citrate dextrose-A (ACD-A) alone (regional anticoagulation), but can be combined with heparin to limit the total ACD-A intake during large-volume leukapheresis. Calcium chloride replacement is preferred when using ACD-A alone in large volume leukapheresis to maintain acceptable levels of ionized calcium. In normal PBSC donors it is common practice not to place a central line but rather to use the peripheral vein approach to avoid the risk(s) involved with catheter placement. Inadequate peripheral venous access has been reported in 4% to 8% of cases. Minor electrolyte imbalances (magnesium, potassium) have also been noted, and they may require electrolyte supplementation.

The CD34+ cell concentration in the donor’s peripheral blood is predictive for the yield of CD34+ cells in the apheresis product. Steady-state peripheral blood CD34+ cell concentrations in unperturbed hematopoietic condition are less predictive because of their low levels, approximately 0.1% of the total mononuclear cells, and the limited sensitivity of flow cytometry.

**POSTDONATION CYTOPENIAS**

A transient, postdonation reduction in the neutrophil count below baseline levels (sometimes resulting in an absolute neutropenia) has been described. The relative role of rhG-CSF and leukapheresis in this hematologic effect has not
been established, although a recent report suggests that the leukapheresis procedure itself is mainly responsible, possibly by removing large numbers of “mobilized” progenitors. Second PBSC collections have been performed successfully with yields comparable to the initial ones, indicating no long-lasting impact on the CD34+ progenitor cell pool. Transient lymphocytopenia after stem cell collection has also been reported. Because these donors were asymptomatic and the process was self-limited, routine follow-up blood counts are not necessarily indicated.

Platelet depletion is a recognized result of continuous-flow leukapheresis, particularly if two or more blood volumes are processed. rhG-CSF administration in normal donors may have a contributing role as well. Hemorrhagic complications in normal donors have not been reported. Because a 30% to 50% decrease in platelet count can be anticipated after completion of leukapheresis, the reinfusion of autologous platelet-rich plasma (sepsis blood) would need to be followed for 10 years or longer, and the risk of thrombotic or bleeding complications has been quite low. Second PBSC collections have been performed successfully in hematologically normal PBSC donors. However, it is conceivable that with increasing numbers of transplant procedures being performed, special circumstances may be identified that should recommend caution. Four possible scenarios in hematologically normal donors are presented below:

(1) PBSC donors with inflammatory conditions or disorders. One case of episcleritis and one case of iritis during rhG-CSF administration have been reported. This suggests caution in its use in donors with a history of inflammatory ocular disorders.

(2) PBSC donors with a history of venous thrombosis, predisposed to its development, or with known or suspected atherosclerotic vascular disease. Although few data exist on the effect of rhG-CSF on hemostasis in normal donors, a recent, preliminary report has suggested that “high-dose” (15 μg/kg/d) rhG-CSF may lead to a transient prethrombotic state. rhG-CSF has been reported to induce increase in platelet aggregation and platelet activity in normal donors.

These preliminary reports require further validation.

A case was discussed in which a normal donor (a 54-year-old woman) developed a cerebrovascular accident 2 days after completing an uneventful stem cell donation. She had no related symptoms or signs during the mobilization and collection procedure, and she never became thrombocytopenic during or after the collection. Another case was presented of a donor (a 64-year-old man) with a history of coronary artery disease who experienced a myocardial infarction after PBSC collection. In both instances, the relationship of the procedure to the event is uncertain. No other examples of vascular events have been reported, and the risk of thrombotic or bleeding complications has been quite low.

(3) PBSC donors with a history of autoimmune disorders, particularly if a prominent inflammatory component is present. Induction of granulocytosis with rhG-CSF may conceivably exacerbate inflammation associated with these disorders (eg, systemic lupus erythematosus with serositis/myalgia, rheumatoid arthritis, multiple sclerosis, etc). Mobilization and collection of PBSCs as part of clinical trials of autologous hematopoietic transplantation after high-dose chemotherapy is now being studied in selected patients with autoimmune disorders. The results of these studies will provide valuable data on the toxicity profile of rhG-CSF and apheresis in these individuals.

(4) PBSC donors with a history of malignancy treated with chemoradiotherapy (eg, Hodgkin’s disease). The possibility of a latent myelodysplastic state cannot easily be excluded in these cases. The risk of rhG-CSF treatment in these individuals is unknown. Similarly, PBSC donors with a strong family history for myelodysplasia or myeloid leukemia (ie, other family members affected in addition to the patient) may be at higher risk to develop hematologic malignancies.

These scenarios should not be viewed as documented contraindications to rhG-CSF administration. Individual physicians should decide, case by case, on the basis of available data, whether there is a serious risk of adverse events for the donor and whether the risk is likely to be higher with PBSC collection than with marrow harvesting. In general, the criteria used to screen and assess donation-related risks for healthy marrow and PBSC donors should be similar.

LONG-TERM SAFETY ISSUES

The issue of possible long-term effects remains open and difficult to address. Available data are largely limited to isolated case reports. Because long-term adverse effects are likely to be infrequent, a major logistical problem is the fact that long-term data on large numbers of cases will be required to detect an increased risk of rare events (eg, acute leukemia). It has been estimated that to detect a 10-fold increase in the leukemia risk, more than 2,000 normal donors would need to be followed for 10 years or longer, and the detection of a smaller risk increase would require an even larger sample size. In addition, because PBSC donors are primarily relatives of patients with malignancies, controls for any risk assessment should consist of comparable marrow donors not exposed to rhG-CSF. The issue of the long-term follow-up of healthy marrow donors has received little or no attention in the literature. A recent report as well as HLA-typing studies suggest that related HLA-identical marrow donors may have a risk of developing leukemia at least somewhat higher than the general population.

Data on the long-term effects of rhG-CSF in patients with severe congenital neutropenia and aplastic anemia have recently become available in which a number of cases of leukemia have developed. These diseases carry a predisposition to the development of acute leukemia regardless of rhG-CSF therapy. The risk of leukemia does not appear to be
increased in patients with cyclic or idiopathic neutropenia receiving long-term rhG-CSF therapy. There is no evidence that rhG-CSF can cause leukemia in normal individuals. rhG-CSF may stimulate proliferation of malignant myeloid cells if present and its effects in persons predisposed to the development of leukemia is unknown.

An International PBSC Donor Registry to monitor long-term effects of PBSC donors is desirable, and discussions regarding its logistics and feasibility are ongoing. This would require the cooperation of the majority of transplant teams and centers. It will be a costly, complex, and possibly low-yield effort, but it is of primary importance to ensure the long-term safety of normal PBSC donors. At this stage, we believe that individual institutions should establish a system for the follow-up of their own PBSC donors. This should include periodic (at least every 1 to 2 years) contacts with the donors. A standardized approach to data collection among different centers should be pursued.

**UNRELATED, HLA-MATCHED PBSC TRANSPLANTS**

The use of unrelated normal donors for rhG-CSF–mobilized allogeneic PBSC transplantation is controversial. The potential for adverse effects in donors as well as logistical difficulties in managing rhG-CSF mobilization and the potential need for multiple apheresis procedures complicate this process. At this time, bone marrow still remains the most common source of hematopoietic cells for unrelated donor transplants. There is considerable interest in the use of unrelated PBSC transplants and if the mobilization and procurement emerges as a safe and more “donor-friendly” stem cell collection procedure, this may allow a substantial expansion of the number of unrelated donors in national and international registries. The administration of rhG-CSF to unrelated PBSC donors should be studied with close monitoring for potential adverse events in the donors as well as its potential benefits to the recipients. Several unrelated donor programs have begun PBSC collections and, in personal communication, their experience will provide very valuable information.

**CONCLUSION**

rhG-CSF–mobilized PBSCs are being used increasingly as an alternative to marrow for allogeneic transplantation. Donor safety issues continue to be actively studied. The optimal rhG-CSF dose and schedule for PBSC mobilization need to be defined. Transient, self-limiting postdonation cytopenias have been noted, although they are usually asymptomatic. Postdonation thrombocytopenia related to apheresis represents a more significant potential risk but can be minimized by reinfusion of autologous platelet-rich plasma, mainly in donors undergoing multiple collections. As additional experience is gained, possible contraindications to rhG-CSF administration in selected PBSC donors may emerge. The criteria used to screen and assess donation-related risks for healthy marrow and PBSC donors should be similar. The use of rhG-CSF to collect PBSCs from unrelated donors for allogeneic transplantation requires study. There is a need for continued donor safety monitoring. The establishment of a PBSC donor registry to collect long-term safety data is appropriate to address potential adverse effects of the procedure. In the interim, individual institutions and donor centers are encouraged to establish a follow-up system for their own donors, preferably with a standardized approach to data collection.

**REFERENCES**

3. Lane T: Allogeneic marrow reconstitution using peripheral blood stem cells: The dawn of a new era. Transfusion 36:585, 1996
15. Dale DC, Bonilla MA, Davis MW, Nakanishi A, Hammond...


45. Bandarenko N, Brecher ME, Owen H, Wiley J, Shea T, Se-
rody J: Thrombocytopenia in allogeneic peripheral blood stem cell collections. Transfusion 36:668, 1996 (letter)
49. Parkkali T, Volin L, Siren MK, Ruutu T: Acute iritis induced by granulocyte colony-stimulating factor used for mobilization in a volunteer unrelated peripheral blood progenitor cell donor. Bone Marrow Transplant 17:433, 1996
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