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Safeguarding the long-term health of hematopoietic stem cell donors: a continuous and evolving process to maintain donor safety and trust

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Hematopoietic stem cell transplantation (HSCT) is being used to treat a number of hematologic diseases, hematologic malignancies, congenital immune deficiencies, and inherited metabolic diseases. This therapy is not possible without people willing to donate hematopoietic stem cells (HSCs) to relatives and strangers. Assessing and protecting the safety of HSCT donors is a critical but difficult and evolving task.

HSCT was initially performed using marrow as a stem cell source. However, in the 1990's HSCs collected by apheresis from donors given hematopoietic growth factors to increase the concentration of HSCs in the blood emerged as an alternative. Granulocyte colony-stimulating factor (G-CSF) has become the standard agent for mobilizing HSCs from the marrow to the blood and G-CSF-mobilized peripheral blood stem cell (PBSC) concentrates have largely replaced marrow as a graft source for both autologous and allogeneic transplants (1).

While the collection of G-CSF-mobilized PBSCs rather than marrow from HLA-compatible related and unrelated donors avoids the inherent acute and sometimes chronic pain and the risk of general or spinal anesthesia and red cell transfusion associated with the marrow collection, there are potential problems with giving donors G-CSF and collecting PBSC concentrates. The apheresis procedure sometimes requires the placement of a central venous catheter which can be associated with bleeding, thrombosis, and infection and all donors are exposed to a short, 4- to 6-day, course of G-CSF. Although the complications associated with central venous line placement can be significant, most concerns associated with PBSC donation safety have been related to G-CSF. Most recipients have side effects ranging from bone pain, headache, arthralgia, malaise, fatigue, insomnia, nausea (2), and/or some electrolyte changes that are not clinically important (2). G-CSF administration results in transient splenic enlargement and rarely splenic rupture (3).

Since G-CSF could be a risk to the donor, unrelated donors given G-CSF have been under close follow-up since this growth factor was first used for transplants involving unrelated donors. A study of 2,048 NMDP donors found that complete donor recovery is almost universal and no late adverse events attributed to the donation were identified (4).

A major safety issue related to G-CSF administration is the possibility that it could cause long-term adverse effects, especially leukemia or hematopoietic malignancies by stimulating silent, malignant, or genetically abnormal clones. Administration of G-CSF to patients with congenital neutropenia is a risk factor for leukemia transformation; however, congenital neutropenia is itself a leukemia risk factor (5). One study of sibling stem cell donors given G-CSF found that two of 200 donors developed acute myeloid leukemia four and five years after their donation (6). Anderlini et al (7) found no increased risk of hematologic malignancy in 281 G-CSF treated donors followed for a median of 3.2 years. Nagler et al found transient epigenetic alterations resulting in loss of synchrony in allelic replication timing and a study by Amariglio and colleagues found transient gene expression changes in lymphocytes from healthy subjects given G-CSF (8,9). However, several larger follow-up studies did not confirm these findings. Among 9,785 unrelated donors given G-CSF, the National Marrow Donor Program (NMDP) found 20 cases of cancer, but no reports of leukemia or lymphoma (10) and the European Group of Blood and Marrow Transplantation reported five hematologic malignancies among 16,431 healthy subjects given G-CSF (11). Hirsch et al studied 22 healthy subjects before they were given a 5-day course of G-CSF and periodically during 12 months after follow-up and found no evidence of aneuploidy or replication asynchrony (12). Olnes et al found no abnormalities in chromosomes 7 and 8 or aneuploidy (13) in 35 healthy PBSC and 35 healthy granulocyte donors given G-CSF.

Although these studies did not demonstrate an increased risk associated with G-CSF administration to healthy subjects, continued vigilance and follow-up are needed since it could take 10 or more years of follow-up to document an increase in risk (11). The NMDP is currently following and evaluating unrelated donors given G-CSF and this should continue.

Those responsible for HSC donor safety must also be alert to new potential threats to donor safety and all new potential risk factors must be subjected to the same comprehensive investigation as G-CSF. Other agents are now being used to mobilize stem cells and much less is known about these agents than G-CSF. Plerixafor is approved for use in combination with G-CSF to mobilized PBSCs for autologous transplants. It mobilizes stem cells by a different mechanism than G-CSF; inhibition of the binding of CXCR4 on stem cells to CXCL12 on stromal cells. Because of the differences in the mechanism of mobilization, the combination of G-CSF and plerixafor is being used increasingly in subjects donating HSC for autologous use, particularly in those who respond poorly to G-CSF alone (14,15). Plerixafor has also been used in a pilot study as a single agent for mobilizing PBSCs for allogeneic transplantation (16). There is no specific reason to believe that plerixafor alone or in combination with G-CSF will present a risk to the long-term safety of healthy subjects, but experience with plerixafor is relatively limited. As a result, plerixafor should only be used in healthy subjects as part of studies which evaluate both short- and long-term effects on donors.

Another new concern for HSC donors involves the availability of generic or biosimilar forms of G-CSF. Most of the available data concerning the safety of G-CSF is from healthy subjects given filgrastim or lenograstim, its glycosylated form. Biosimilar agents are similar to filgrastim and lenograstim but not identical, and three such agents are available in the European Union. It is not certain if these biosimilar agents will have the same safety profile as filgrastim and lenograstim (17). The World Marrow Donor Association has recommended that these alternative agents not be for HSC mobilization in healthy subjects unless the

donor is followed in a study addressing long-term safety of these agents (17). We agree and believe that they should not yet be used at all in unrelated donors.

For those of us involved with safeguarding unrelated donors, the safety of related HSC donors is also of concern. While large studies have found that the donation of HSC by unrelated donors is almost completely free of long-term complications, this is likely due, in part, to the fact that they are healthy. Donating HSCs is likely equally as safe for healthy related donors. The troublesome issue is that related donors are not necessarily healthy. The process of selecting unrelated donors is well defined and tightly controlled to ensure only healthy subjects donate. However, subjects with health problems are sometimes permitted to donate stem cells for relatives. There is also an upper age limit for the eligibility for unrelated donors, but not for related donors. Collecting marrow or G-CSF-mobilized PBSCs from unhealthy or older donors may increase their risk of long-term complications. While in some situations using unhealthy or older donors may be unavoidable, it should be done only after evaluating other alternatives and with the proper informed consent. For related donors, this may not always be the case. A recent study has found that related donors often are evaluated by the same transplantation physician caring for the recipient (18). In this situation, the team evaluating and determining the eligibility of the related donor has a conflict of interest and they may be biased. This may result in placing the donor unnecessarily at increased risk. In establishing the NMDP, great care was taken to separate the evaluation of donors from the transplant team (19). Mechanisms are needed to ensure that risks encountered by all related donors are appropriately evaluated and that their safety is always considered.

While considerable attention has focused on PBSC donors given G-CSF, bone marrow is still used for some allogeneic transplants and donating marrow is not completely free of long-term complications; 0.7% of 9,245 NMDP marrow donors experienced prolonged serious complications related to mechanical injury due to tissue damage during the collection (20). Continued study of marrow donors is needed to monitor and reduce the incidence of serious adverse events.

Stem cell donors are at very low risk of long-term problems. However, this was only made possible through the development of standards concerning donor evaluation, stem cell mobilization, and stem cell collection; strict adherence to these standards; and comprehensive donor follow-up (19). As technology changes, standards and practices may require modification. Continued study and follow-up of subjects is needed of both related and unrelated donors. Stem cell donation is very safe, but continued commitment and vigilance is required to keep it safe and will be required as long as HSCs are collected for transplantation. This is particularly important because healthy subjects are being asked to donate stem cells for other uses. Bone marrow is being collected for mesenchymal stromal cell production and a variety of other cell types are being collected for induced pluripotent stem cell production. Since many healthy subjects will not likely distinguish different types of stem cell donations, it is critical to all stem cell fields that the confidence and trust of all donors is maintained.

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