Long-term safety of filgrastim (rhG-CSF) administration

This journal recently included an article by Bennett *et al* (2006) reporting five cases of haematological malignancy occurring in normal individuals following exposure to haematopoietic growth factors. Three cases described lymphoid malignancies (non-Hodgkin lymphoma and chronic lymphocytic leukaemia) occurring months to years after receipt of an investigational agent (pegylated, recombinant megakaryocyte growth and development factor). The two additional cases, however, were identified among 200 individuals who had received filgrastim (recombinant human granulocyte colony-stimulating factor; rhG-CSF, Neupogen®) as a mobilising agent for collection of peripheral blood stem cells (PBSC) for allogeneic transplantation. The transplant recipients for these latter two donors were their siblings, each with acute myelogenous leukaemia (AML). The donors themselves also developed AML 4–5 years following filgrastim exposure.

It is known that siblings of persons with leukaemia have a 2–5-fold increased annual incidence of leukaemia (Pottern *et al*, 1991; Shpilberg *et al*, 1994; Rauscher *et al*, 2002). In some families, multi-generational occurrence of leukaemia, in the absence of any known syndrome, e.g. Fanconi anaemia, suggests direct inheritance of susceptibility genes (Segel & Lichtman, 2004). Given these patterns, the contribution of filgrastim exposure to the development of acute leukaemia within families remains speculative.

Documenting the safety of filgrastim as a mobilising agent for PBSC donation has long been a matter of importance for the transplantation community, particularly in the context of donations made by volunteer, unrelated adult donors. Since 1997, the US National Marrow Donor Program (NMDP) has maintained an Investigational New Drug (IND) application accepted by the Food and Drug Administration for manufacture of PBSC products from unrelated donors. Filgrastim is administered for PBSC mobilisation at a total dose of *c.* 10 μg/kg donor weight per day for 5 d. Under the IND protocols, every donor provides informed consent for the research, which includes agreement for perpetual annual follow-up. Among 4015 donors who have passed the first anniversary of their PBSC donation, we have accumulated 9785 years of follow-up (range 1–9 years with 897 donors ≥4 years). Twenty cases of cancer have been reported, occurring in various organ systems, consistent with the age-adjusted US incidence of cancer in adults and in support of the applicability of data obtained from the NMDP follow-up system (Ries *et al*, 2006). There have been no reports of leukaemia or lymphoma in this donor cohort, which US statistics suggest should comprise 9% of all malignancies in this age group.

National Marrow Donor Program donor consent forms approved by the Institutional Review Board contain the following information:

Normal individuals are at risk for developing cancer, including leukaemia, lymphoma or other blood diseases throughout their lifetime. It is unknown whether filgrastim increases or decreases an individual's risk of developing cancer. The data being collected during follow-up will help establish if there are any positive or negative long-term effects from receiving filgrastim. Based on limited long-term data from healthy people who have received filgrastim, no long-term risks have been found so far.

The low occurrence of leukaemia and lymphoma in our cohort of volunteer, unrelated PBSC donors should provide reassurance to individuals who receive filgrastim for PBSC mobilisation and should encourage their participation in carefully designed programmes for follow-up monitoring. As data from these and other studies mature, a more complete assessment of overall donor safety will become available to all interested parties.

Disclosures

The authors are employees of the National Marrow Donor Program, a non-profit 501c3 US corporation.

Dennis L. Confer
John P. Miller

National Marrow Donor Program®, 3001 Broadway St NE, Suite 500, Minneapolis, MN, USA.
Email: dconfer@nmdp.org

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Long-term safety of filgrastim (rhG-CSF) administration: application of haematopoietic growth factors in healthy individuals

In light of the increasing frequency of peripheral blood stem cell transplantation (PBSCT) requiring the application of granulocyte colony-stimulating factor (G-CSF), the recent article regarding haematological malignancies in previously healthy individuals who received haematopoietic growth factors by Bennett *et al* (2006) and the editorial comment regarding the possible harmful effects of short course G-CSF in normal donors, by Goldman *et al* (2006), address a highly sensitive topic. Bennett *et al* (2006) reported on three out of 538 healthy volunteers who received pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) in the course of clinical studies and on two out of 200 stem cell donors who received G-CSF and subsequently developed haematological malignancies 1–5 years after growth factor administration. Long-term monitoring of healthy individuals who received human growth factors is essential and all cases suspicious for long-term effects deserve the utmost attention. However, in our view, the paper contains some sensitive points:

First, the titles of the original article and of the editorial give the impression that healthy individuals undergoing peripheral stem cell mobilisation take a significant risk. However, it should be noted that PEG-rHuMGDF, which was administered to cases 1–3, had already been withdrawn from clinical trials, in 1998. This is mentioned shortly in the discussion (Bennett *et al*, 2006), but should have been outlined clearly at the beginning of the article. Moreover, the title of the article by Bennett *et al* (2006) does not differentiate between the diverse growth factors that were applied to the patients, whereas the title of the editorial by Goldman *et al* (2006) deals exclusively with G-CSF.

Secondly, cases 4 and 5 had received G-CSF when donating stem cells for siblings with acute myeloid leukaemia (AML). Familial clustering of haematological malignancies is well known in AML (Smith *et al*, 2004) and in other entities, such as lymphoma. This is in line with the positive family history for AML in both the mother and brother of patient 4. These aspects should have led to a more cautious interpretation of the data. The importance of familial clustering is further enhanced by occasional reports on the transmission of haematological malignancies, such as AML, from related donors to recipients by allogeneic haematopoietic stem cell transplantation (HSCT) (Niederwieser *et al*, 1990).

Finally, the limited sample size of the study with only 200 individuals in the G-GSF cohort is a point of consideration. When compared with some of the large retrospective analyses that are cited by Bennett *et al* (2006), including up to 60 000 cases in the study of Pulsipher *et al* (2005) and more than 28 000 individuals in the study of Horowitz and Confer (2005), their study contains rather few G-CSF treated cases that may not be sufficient for far-reaching conclusions.

Progress in allogeneic HSCT in recent years was only possible following the establishment of allogeneic PBSCT and depends to a very large extent on the motivation of the donors and the support of the public. A renewed debate on the safety of this procedure might easily destroy the results of the tremendous efforts that were necessary to establish allogeneic PBSCT in the routine setting. In light of the large number of allogeneic PBSCT performed in the last 10 years without apparent harm to donors, caution should be exerted with respect to far-reaching conclusions based on the evaluation of 200 cases in a single study. Instead, analysis on possible