

Possible harmful effects of short course granulocyte colony-stimulating factor in normal donors

The initial success of haematopoietic stem cell (HSC) transplants, intended to reconstitute a patient's bone marrow function after high dose or 'supralethal' chemotherapy or chemoradiotherapy, was based on the use of bone marrow derived from either a related or unrelated volunteer donor. However, in the late 1980s it became clear that an alternative was to collect HSCs was from peripheral blood following mobilisation with haematopoietic growth factors (HGFs), either granulocyte colony-stimulating factor (G-CSF) or granulocyte/macrophage colony-stimulating factor (GM-CSF).

To a large extent, the use of mobilised peripheral blood HSC has replaced marrow-derived stem cells as the preferred source of donor HSCs. The cells collected by prior treatment with cytokines include substantially more granulocyte/macrophage colony-forming units (CFU-GM), more CD34⁺ cells and more lymphocytes than an 'equivalent' marrow harvest.

Peripheral blood HSC grafts are particularly useful in the setting of reduced intensity conditioning allografts where transfusion of large numbers of CD34⁺ cells may be important. Whilst G-CSF and GM-CSF are very similar or identical to cytokines produced in the human body, investigators and clinicians have been aware since their first clinical use that their administration, even in a single short course, could possibly constitute a risk for healthy donors either in the short term or as a delayed effect. For this reason the healthy donors who receive them have been subjected to extensive follow-up evaluation and transplant centres and transplant registries on both sides of the Atlantic have attempted to maintain close contact with donors for many years after their respective donations. Thus the European Group for Blood and Marrow Transplantation reported five haematological malignancies from a database of 16 431 donors who had received G-CSF [A. Gratwohl (2004), personal communication] and the National Marrow Donor Program in the USA reported four cases of malignant disease out of 2370 donors followed for varying periods of time [D. Confer (2005), personal communication]. In both cases, the incidence of malignancy was deemed not to have differed significantly from what would have been expected in a normal population that was not exposed to HGFs (Bacher *et al*, 2005). Other smaller series failed to identify any increased risk of malignancy after G-CSF administration (summarised in Pulsipher *et al*, 2006). In summary of the available clinical data, it seems that the notion that HGFs cause or contribute to malignancy in a normal person is very far from established.

In contrast to the short-term treatment of HSC donors, G-CSF has been used for prolonged periods in patients with severe congenital neutropenia (Kostmann syndrome) and here there does seem to be some definite risk. After treatment for 6 years the projected risk of progression to myelodysplastic syndrome or acute myeloid leukaemia was 2.9%, though after treatment for 12 years the risk had risen to 8.0%. However, it is likely that such patients are constitutionally at risk of their disease progressing to overt malignancy, which could simply mean that G-CSF is a co-factor or expedites this progression. The observation may or may not have any relevance for normal persons exposed to G-CSF for a single 5-d course.

At Tel Aviv University, Nagler *et al* (2004) reported finding specific abnormalities in lymphocytes from normal people who had recently received G-CSF that were very similar to those seen in lymphocytes from persons with malignant diseases. Specifically, these abnormalities included loss of synchrony in allelic replication and aneuploidy. The abnormal timing of allele replication was a transient phenomenon but the aneuploidy persisted in the longer term. The authors stated that these changes were characteristic of changes seen in lymphocytes from patients undergoing chemotherapy for malignant disease.

The paper by Bennett *et al* (2006) that appears in this issue of the *British Journal of Haematology* reports five cases of leukaemia, three lymphoid and two myeloid, occurring in individuals who had received HGFs. Three patients had received a pegylated recombinant human megakaryocyte growth and development factor (rHuMGDF), which has now been withdrawn from the market, and two patients, who developed acute myeloid leukaemia, had received G-CSF in the course of donating HSCs to siblings who were undergoing treatment for acute leukaemia. However, as noted in the paper by Bennett, large-scale studies in both Europe and the USA have not found increased levels of haematological malignancy in G-CSF-treated donors.

There is no doubt that the use of HSC transplants has offered a potentially life-saving procedure to many patients. However, it must be recognised there are established and also unknown risks for the volunteer donor whatever method is used to harvest the HSC.

How then, should the bone marrow transplant community respond to this latest paper and the reported remote, but presumably finite, possibility that G-CSF could be harmful in the long-term? Most would agree that currently to abandon use of G-CSF for normal donors would not be justified. In the

meantime, five measures warrant consideration by organisations involved with the provision and use of donors worldwide:

1. The international transplant community and donor register organisations need to reach a consensus as to the long-term risks that donors are being subjected to and what risk is acceptable. Transplant centres and donor registries should ensure that they follow normal donors postdonation with as much precision as possible. The duration of follow-up should arguably be a minimum of 10 years and perhaps life-long. Such follow-up should apply equally to bone marrow donors.
2. Selected normal donors should be studied longitudinally with cytogenetic analyses of lymphocytes and other tests designed to detect persisting damage both to the lymphoid and, perhaps more importantly, to the myeloid lineage.
3. Donors should be exposed to the minimum amounts of cytokines, such that the maximal number of doses and the maximal number of courses are limited.
4. Consideration should be given to long-term (more than 1 year) insurance cover of donors following leucapheresis or marrow collection.
5. Prospective donors must be told of the somewhat uncertain situation regarding G-CSF for blood stem cell mobilisation so that they can balance the risks against those associated with bone marrow donation.

The continuation of this potentially life-saving treatment will depend upon the ability of the scientific community to monitor and evaluate on an on-going basis the level of risk associated with G-CSF administration, so that donors, both past and present, can receive and assess for themselves the best available evidence.

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