Bone Marrow Transplantation (2011) 46, 1409–1412

www.nature.com/bmt

SPECIAL REPORT

WMDA guidelines for subsequent donations following initial BM or PBSCs

DL Confer[1], BE Shaw[2,3] and DH Pamphilon[4], on behalf of the clinical working group of the WMDA

[1]*National Marrow Donor Program, Minneapolis, MN, USA;* [2]*Anthony Nolan Trust, London, UK;* [3]*Section of Haemato-Oncology, Royal Marsden Hospital, Surrey, UK and* [4]*NHS Blood and Transplant Bristol Centre, Bristol, UK*

Unrelated donor SCT activity is increasing, and in 5–10% of cases a subsequent donation of stem cells or donor lymphocytes may be requested. Second donations of stem cells are not associated with an increased chance of donor complications, but the yield of CD34+ cells may be lower in some donors. It is acceptable practice for any registry to request subsequent donations and it is recommended that donors should be counselled about this possibility before their first donation. Guidance is provided on the requirements for further medical assessment, the procedures used to agree requests, frequency and timing of donation and timing and duration of donor follow up.
Bone Marrow Transplantation (2011) **46,** 1409–1412; doi:10.1038/bmt.2010.323; published online 7 February 2011
Keywords: haematopoietic cell transplantation; BM; PBSC; subsequent donations; DLI

Introduction

This document contains recommendations based on documentation supplied by the National Marrow Donor Program (NMDP), the UK Donor Registries and the World Marrow Donor Association (WMDA) Quality Assurance, Donor Registries and Clinical Working Groups. It has been reviewed and agreed by the WMDA Clinical Working Group (CWG).

Overall, between 5–10% of donors may be asked to provide a subsequent donation of haematopoietic progenitor cells (HPCs) or therapeutic cells (TCs); the latter are usually requests for donor lymphocytes, however, novel strategies mean that other products (for example, MSCs) may increasingly be requested. Eight percent of NMDP donors who have provided a BM (HPC, marrow) or PBSC (PBSC or HPC, apheresis) donation to a patient will subsequently give one or more additional products to that same patient. Currently, the most common subsequent donation is donor lymphocytes collected by leukapheresis, followed by PBSC, BM and whole blood (but other products may also be requested). These additional products are currently administered most often for immune modulation (for example, to increase donor chimerism or graft-versus-tumor effect) or to increase donor-derived hematopoiesis (for example, to treat poor graft function or to regraft following rejection).

Stroncek *et al.*, in 1991[1] reported on 16 donors at the University of Minnesota who provided BM on two occasions for sibling recipients. The time between donations ranged from 36 days to more than 3 years (average 292 days). There was no difference in donor experiences or BM yield between the two donations. However, donors harvested within 60 days of first donation were more likely to require allogeneic blood transfusion. Anderlini *et al.*,[2] reported on 13 normal donors who had provided PBSC on two occasions. The second donations in these cases occurred 1 to 13 months (median = 5) after the first donation. There were no differences in the donor experiences or the product characteristics between the first and second donations. Stroncek *et al.*,[3] reported on 19 volunteers who donated PBSC on two occasions 1 year apart. They found that pre-mobilization blood counts were not different between the two donations. PBSC yields and donor experiences were also similar with regard to the initial and subsequent donations.

Two recent reports evaluated the mobilisation and collection of PBSC after two cycles of G-CSF administration. One group reviewed data from 46 donors in the Spanish National Donor Registry and found that, although the side effects of repeat G-CSF 10 μg/kg per day were similar, with 26 and 26 donors developing some toxicity after the first and second cycles, respectively, the yields of CD34+ cells were significantly lower (5.15 versus 3.16×10^6/kg; $P = 0.05$) and 29/46 donors gave fewer CD34+ cells after the second donation.[4] The second study reviewed data from 67 healthy donors and noted that non-haematological side effects were again comparable, but that a significantly lower yield of CD34+ cells was obtained on day 5 in female donors (5.0 versus 3.23×10^6/kg; $P = 0.008$) but not in male donors (5.96 versus 5.36×10^6/kg; $P = 0.24$).[5]

When considering late haematological effects of donation, Storek *et al.*,[6] evaluated T, B and NK cells in the peripheral blood of nine sibling PBSC donors at 1 year after their first donation. Their sole finding was a modest lowering of monocyte counts at 1-year post donation, of uncertain clinical significance. All other cell populations including naïve CD4+ and CD8+ T cells were normal.

Correspondence: Dr DL Confer, National Marrow Donor Program, 3001 Broadway St NE, Suite 100, Minneapolis, MN 55413, USA.
E-mail: dconfer@nmdp.org
Received 4 March 2010; revised 6 October 2010; accepted 25 October 2010; published online 7 February 2011

Table 1 The median ECOG performance scores reported by first and second donation marrow and PBSC donors by week of Form 77 submission following donation

	Median ECOG performance score			
	Marrow donations		*PBSC donations*	
Week of submission	*First*	*Second*	*First*	*Second*
1	1 (26)	1 (9)	0 (17)	0 (34)
2	1 (22)	1 (7)	0 (4)	0 (14)
3	0 (17)	0 (5)	0 (1)	0 (3)
4	0 (9)	0.5 (2)	—	—
5	0 (4)	1 (1)	—	—
6	0 (1)	0 (1)	—	—
7	0 (1)	0 (1)	—	—
8	0 (1)	—	—	—

The number in parentheses is the number of forms received at each time point.

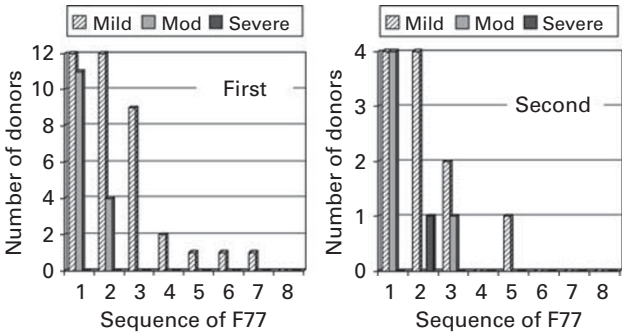

Figure 1 Site pain reporting among marrow donors. Pain at the site of BM collection was reported as mild, moderate or severe on each form 77 (F77) submitted weekly until full recovery. Left panel is reporting from first donation marrow donors ($n=26$). Right panel is reporting from second donation marrow donors ($n=9$).

The NMDP recently evaluated 43 donors who had provided two hematopoietic cell products (BM or PBSC) for their respective recipients (personal communication). Among the 43 donors, marrow was the first donation product for 26 (60%), while for 17 (40%) the first donation product was PBSC. Among the marrow donors, six (23%) gave marrow a second time and 20 (77%) gave PBSC. Three of 17 (18%) PBSC donors gave marrow for their second donation, while 14 (82%) gave a second PBSC product. Overall, PBSC as a second donation product outnumbered marrow 34–9 (79% PBSC versus 21% marrow). A median of 110 days (range 3–421) elapsed between the two donations.

The NMDP requires Form 77 (assessing donor recovery) to be submitted weekly until the donor reports full recovery. Routine follow-up forms were evaluated. Marrow donors submitted more forms than PBSC donors, which is an expected result because marrow donors take longer to recover than PBSC donors. From the first donation, the median number of forms submitted for marrow donors was three (range 1–8) and, for PBSC donors, one (range 1–3).

These numbers were identical for the second donation submissions with one exception: a BM donor who submitted eight forms with the first donation, submitted seven forms with the second donation. ECOG performance status for marrow and PBSC donors was also evaluated (Table 1). For marrow donors only, site pain was reported on form 77 for the first and second donations (Figure 1).

These limited NMDP data confirm that marrow donors have more symptoms and recover more slowly than PBSC donors. The experiences with a second donation, however, are very similar to a first donation.

WMDA data collected by the donor registries working group in 2006/2007 showed that 28 of 42 responding registries (67%) allowed a further stem cell donation to the same patient, but only 14/38 (33%) permitted a donation for another patient. The maximum number of donations allowed by registries was 1, 2 and $>/=4$ by 12, 27 and 2 registries, respectively. A subsequent survey by the quality assurance-working group gave the following information:

(1) Second donation permitted for another patient.
Yes 12/21 registries (57%)
Yes 3/21 registries (in specific cases only) (14%)
No 6/21 registries (29%)
(2) Second donation permitted for the same patient
BM 21/21 (100%)
PBSC 14/21 irrespective of type of first donation (67%)
PBSC 6/21 only if first donation was marrow (29%)
Not permitted 1/21 (5%)

The numbers of requests for TC-T (donor lymphocytes) are increasing over time. The British Society for Blood and Marrow Transplantation (BSBMT) reported 302 TC-T infusions in UK patients in 2006, an increase of almost two-fold since 2001 (160) (http://www.bsbmt.org/pages/48-2006_Activity_by_Indication).

The literature suggests that unstimulated leukapheresis product collections are low risk donations. McLeod *et al*.,[7] surveyed centres that had performed nearly 20 000 apheresis procedures. The overall incidence of adverse events was 2.2% with more than half (1.2%) being pain or haematoma at the venipuncture site. In 1994, Strauss[8] reviewed the issue of leukocyte depletion following repeated apheresis procedures. He concluded that, 'Clinically significant immunodeficiency is unlikely to be induced by lymphocyte depletion unless $>1\times10^{11}$ donor lymphocytes are lost over a relatively brief time (days to weeks), and/or the donor blood lymphocyte counts fall persistently below 500/μL (0.5×10^{9}/L).' Strauss further recommended that donors be deferred when the pre-apheresis lymphocyte count is less than 1×10^{9}/L. The level of lymphocyte removal cited by Strauss ($>1\times10^{11}$) is highly unlikely in the NMDP (or other unrelated donor) setting as it corresponds to processing >100 L of donor blood by leukapheresis within a few days or weeks.

A recent survey by the CWG of the WMDA (2009) investigated current policies around TC-T donations within registries. Practice in the 20 registries that responded was heterogeneous:

- The number of TC-T donations permitted varied from one to multiple donations (no limit).
- The minimum time period between the initial donation and a TC-T donation was between 3 weeks and 3 months (mode: 1 month).

- The minimum time period between two TC-T donations was between 2 weeks and 9 months (mode: 1 month).
- 7/20 registries felt that there should be a minimal lymphocyte count (in the donor) necessary before the donor would be accepted to donate TC-T.
- 17/20 registries allowed Transplant Centres to store 'excess' cells (for example in aliquots for TC-T), at the time of the initial stem cell donation, with no additional specific permission required.

Recommendations

This guideline is intended to outline where subsequent donations would routinely be considered appropriate (from the donor's point-of-view), as well as the frequency and timing of such donations. Requests that do not conform to this guideline may still be submitted. Transplant physicians may be required to provide a justification for such requests. Justifications are likely to be reviewed for approval by the Registry's medical director or a designee who may seek input from additional physicians, for example, donor centre medical director, medical director of the collection site or others. Some registries may use an expert advisory panel. Whenever appropriate, discussions should involve the transplant physician(s). The goal is to reach a mutually agreeable decision about the non-conforming subsequent donation request as rapidly as possible.

Donor counselling
The donor must be made aware of the possibility of subsequent donation requests before the first donation. The frequency of second donations of HPC and donor lymphocytes is in the range 5–10% and may increase further with the more widespread adoption of reduced intensity conditioning allografting. Some registries will assess the donor's willingness to be approached for a subsequent donation before or soon after the first donation. Donors may also be asked if they agree to storage of part of their donation for use as donor lymphocytes for the same patient. For many registries this is allowed as routine practice if 'excess' cells are collected. Alternately, this may be allowed only if it is considered very likely that the patient will require additional cells or if a subsequent donation would be logistically difficult. Some registries do not allow storage of 'excess' cells, and this should be communicated to the transplant centre. Donors should also be assured that cells not used will be discarded if/when necessary according to a robust discard policy. It is important to note this information in the donor-counselling checklist and also to inform the transplant centre if it is likely that the donor is not willing to give a further donation. This will allow the transplant centre to consider selecting another donor, at least where the need for a second donation would not be unexpected.

Donor consent
Any subsequent donation, whether falling within this guideline or not, requires the consent of the donor. Subsequent donations that occur in a research setting require IRB or Research and Ethics Committee (REC) approval(s) and, whenever the donor is a research subject, informed consent of the donor according to IRB/REC procedures. In all cases, the request for a subsequent donation originates with the transplant recipient's physician and is submitted initially to the Registry's coordinating centre.

Donor medical examination
The donor should be seen for a limited medical assessment before a second donation if a short interval (for example, $\leqslant 3$ months) has elapsed from the first donation to ascertain that they are still fully fit. Further blood tests will normally include a full blood count and tests for mandatory infectious disease markers. There may be national regulatory requirements, which have a more restrictive time period for infectious disease markers. If a longer interval (for example, >3 months) has elapsed, a full medical assessment should be undertaken according to the registry's usual procedures.

Donor follow-up
This is conducted by the medical and registry staff, for example, donor welfare officer, according to registry policy and procedures. This should normally be within the first week of donation, at 1-month post donation (or until resolution of all symptoms is reported), at 1 year and thereafter annually or bi-annually for up to 10 years (although in some countries this may be lifelong).

Procedure used for reviewing request
Requests for a second or subsequent donation must be submitted on the appropriate request form by the transplant physician caring for the patient to the registry where it is reviewed by the Medical Director or a designee. For straightforward cases for example, primary non-engraftment, early graft failure, relapsing chronic myeloid leukemia or acute leukemia, the Medical Director or designee may make a decision. Review by registry expert medical assessor(s) or an advisory group may be recommended for more controversial indications. Ordinarily a decision should be communicated to the transplant centre within 72 h. If the request is rejected, the transplant centre may appeal against this and an expert medical assessor(s) advisory group may be asked for their urgent review of these cases.

Frequency of marrow or PBSC donation
A donor can routinely be asked to donate on two occasions (whether to the same or a different recipient), but a third or subsequent donation should be according to the policy within the individual registry and considered on an individual basis. Donors should ordinarily donate marrow or PBSC for a maximum of two patients, although rarely, and with the agreement of the registry medical director and appropriate consent of the donor, they may donate for more than two recipients. Registries may want to consider that rarely a donor who has donated via an unrelated registry is later asked to donate to a relative. In this case the

eligibility of the donor to donate will be determined by the transplant centre. Their eligibility to remain available on the unrelated register should be reviewed. Following donation for a first patient and then after an interval of 1–2 years during which time the donor remains available only for that recipient and therefore unavailable for any other, they may donate two or more further HPC donations for a second patient. The minimum time interval between donation to one patient and a subsequent donation to a second patient should be 12–24 months. This acknowledges that with the widespread use of reduced intensity conditioning transplantation, there is an increased likelihood of donor lymphocyte therapy and that this may be delayed up to 2 years from the time of transplant, although in most cases, it will occur within the first 2 years. This restriction would not apply where the first recipient has died. Individual registries may wish to set more restrictive policies. It is not possible to give specific advice as to how many donations of BM versus PBSC should be allowed, as there is no published data to support a recommendation.

Interval between HPC donations
A minimum period of 4 weeks should elapse between the first and second donations. Requests for donations before this would usually be reviewed on an individual basis.

Therapeutic cell (TC) donations
The total number of TC donations, which can safely be undergone, and the optimal interval between such donations, remains unclear. Provisionally it is recommended that one donation be routinely accepted. Second donations of TC to the same recipient will be dependent on individual registry policy and often at the discretion of the Medical Director (or designee). It should be borne in mind that some registries allow a total of only two donations of any sort. Thus, if the donor is donating to a second patient, donation of TCs may not be routinely allowed. It is currently not standard practice for a donor to donate TC to a patient for whom they have not given a HCT donation—this should only be considered in the context of a clinical research study. The minimum interval between two donations of TC should be established by the registry and would normally be 1–3 months. Registries should encourage transplant centres to cryopreserve aliquots of the initial collection (if there are surplus cells) before or after any manipulation as a source of TC to minimise the chance of re-access to the donor.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We would like to acknowledge the WMDA board for critical reading of the document and the unrelated donor registries for participating in the surveys.

References

1 Stroncek DF, McGlave P, Ramsay N, McCullough J. Effects on donors of second bone marrow collections. *Transfusion* 1991; **31**: 819–822.
2 Anderlini P, Lauppe J, Przepiorka D, Seong D, Champlin R, Korbling M. Peripheral blood stem cell apheresis in normal donors: feasibility and yield of second collections. *Br J Haematol* 1997; **96**: 415–417.
3 Stroncek DF, Clay ME, Herr G, Smith J, Ilstrup S, McCullough J. Blood counts in healthy donors 1 year after the collection of granulocyte-colony-stimulating factor-mobilized progenitor cells and the results of a second mobilization and collection. *Transfusion* 1997; **37**: 304–308.
4 De la Rubia J, Arbona C, Del Canizo C, Arrieta R, De Arriba F, Pascual MJ *et al*. Second mobilization and collection of peripheral blood progenitor cells in healthy donors is associated with lower CD34(+) cell yields. *J Hematother Stem Cell Res* 2002; **11**: 705–709.
5 Platzbecker U, Bornhauser M, Zimmer K, Lerche L, Rutt C, Ehninger G *et al*. Second donation of granulocyte-colony-stimulating factor-mobilized peripheral blood progenitor cells: risk factors associated with a low yield of CD34+ cells. *Transfusion* 2005; **45**: 11–15.
6 Storek J, Dawson MA, Maloney DG. Normal T, B, and NK cell counts in healthy donors at 1 year after blood stem cell harvesting. *Blood* 2000; **95**: 2993–2994.
7 McLeod BC, Price TH, Owen H, Ciavarella D, Sniecinski I, Randels MJ *et al*. Frequency of immediate adverse effects associated with apheresis donation. *Transfusion* 1998; **38**: 938–943.
8 Strauss RG. Effects on donors of repeated leukocyte losses during plateletpheresis. *J Clin Apher* 1994; **9**: 130–134.