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Stem Cell Donation – What advice can be given to the donor?

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Abstract

Haemopoietic stem cell transplantation (HSCT) is widely used to treat patients with a range of haematological and non-haematological disorders. Both bone marrow and peripheral blood stem cell collection are associated with morbidity and, very rarely, mortality. We investigated the information that exists to adequately inform donors about the relative merits of each procedure. We carried out a systematic review analysing data from 6 prospective randomised controlled trials of related donors and discuss here the merits and drawbacks of this approach. Registry data mostly describes patient outcome but stem cell donor registries collect and report information on unrelated donors which could easily be extended to related donors. Further well-designed, randomised studies are required.

Keywords

Stem Cell donation; peripheral blood; bone marrow; granulocyte; colony-stimulating factor; stem cell donor registries

Background

Haematopoietic stem cell transplantation (HSCT) is a widely used therapy, the numbers of which have increased dramatically during the last 20 years; an estimated 45-50,000 HSCTs are carried out annually worldwide (Horowitz and Confer, 2005). However, there continues to be debate about the optimal source of stem cells for allografting and, although most transplants use peripheral blood stem cells (PBSC) collected by apheresis after administration of granulocyte-colony stimulating factor (G-CSF - filgrastim, lenograstim), bone marrow (BM) is still used for many patients and the use of umbilical cord blood (UCB) cells is growing rapidly (Gratwohl et al, 2008). The choice of stem cell source is, in part, determined by the recipient's diagnosis, disease stage, age, the intended conditioning regimen and other factors, and is one component of treatment decisions aimed at minimizing the risks of graft rejection, graft-versus-host disease (GvHD) and other complications that contribute to transplant-related mortality (TRM) (McGlave et al, 2000; Rodrigues et al, 2009; Schmitz et al, 2006). Other important factors include the logistics of collecting HSC from unrelated donors compared to the relative ease of access to cord blood banks, and

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availability of operating room time and staff for BM harvests (Barker et al, 2002). An important consideration must also be the risk of the donation procedure for the donor, since, although HSC donation has an excellent safety record, even for healthy related or unrelated donors, it is not without risk of morbidity or, rarely, mortality (Horowitz and Confer, 2005; Halter et al, 2009). Against this background, an increasing proportion of donors are now unrelated volunteers. In 2005, 41% of allogeneic stem cell transplants reported to the European Group for Blood and Marrow Transplantation (EBMT) used unrelated donors, of whom about 70% donated peripheral blood stem cells (Gratwohl et al, 2007).

Donors and Standards for Donor Selection, Assessment and Management

The techniques for BM harvest or G-CSF primed PBSC collection are described in detail elsewhere (Confer, 2004). Each procedure has specific and well recognised side effects, most of which are transient and have little or no long term implications for the donor. However, severe adverse events have been recorded; these include pelvic fractures with BM donation, sepsis with either modality of donation (Switzer et al, 2001; Buckner et al, 1984) and splenic rupture during PBSC mobilisation/collection (Anderlini et al, 1996, Balaguer et al 2004; Dincer et al 2004; Falzetti et al, 1999; Nuamah et al, 2006). A recent survey of 338 HSCT transplant teams in 35 primarily European countries that included 51,024 allogeneic HSCT (27,770 BM and 23,254 PBSC) performed between 1993 and 2005 reported 5 donor deaths (1 BM; 4 PBSC) and 37 severe adverse events (Halter et al, 2009) These included a subarachnoid haemorrhage in a donor on aspirin therapy for coronary heart disease and with a post-procedural platelet count of 82×10^{9} /l. Another report described a related donor with a cerebrovascular malformation and treated hypertension who recovered following surgery for a subdural haematoma that occurred after PBSC collection (Pei et al, 2008). Of note though, none of 2408 PBSC donors reported by the US National Marrow Donor Program (NMDP) developed intracranial bleeding (Pulsipher et al, 2009). The report by Halter et al (2009) probably underestimated the frequency of adverse events, as the survey covered a long period of time during which there was no systematic effort to maintain a comprehensive tally of such events, especially in related donors.

Standards that relate specifically to unrelated donors were developed by the World Marrow Donor Association (WMDA) (www.worldmarrow.org). Standards developed by the Foundation for Accreditation of Cell Therapy (FACT) in the USA and the Joint Accreditation Committee of ISCT (Europe) and the EBMT (JACIE), termed the FACT-JACIE Standards (both voluntary accreditation systems) (FACT-JACIE, 2008), also contain detailed requirements for the selection, evaluation and management of donors and the reporting of adverse events. Other pertinent and legally-binding requirements are those of the National Competent Authorities in Europe who are required to implement the EU Directive on Tissues and Cells (2004/23/EC) and its associated Commission Directives (2006/17/EC and 2006/86/EC) (www.transfusionguidelines.org) via specific regulations and those of the US Food and Drug Administration (FDA) (www.fda.gov/cber/tiss.htm; www.fda.gov/cber/gene.htm

Evidence for the safety of donation: What clinical trials exist?

Counselling donors prior to HSC collection should be based on a good understanding of the different risks associated with both BM and PBSC collection. Randomized controlled trials (RCTs) that evaluate and compare the profiles of adverse events for donors randomized to PBSC or BM harvest might provide a first and more robust source of data to determine the relative benefits and harms of the two methods of HSC collection. In our recent systematic review (Siddiq *et al*, 2009), 6 relevant RCTs were identified from comprehensive searches of the Cochrane Central Register of Controlled Trials (Siddiq *et al* 2009), MEDLINE (1950-

Aug 2007), EMBASE (1974-Aug 2007), Current Controlled Trials, the National Research Register and the NHS Blood and Transplant's register of RCTs (Table I). All were substudies or constituent parts of larger RCTs and evaluated recipient outcomes after BM versus PBSC allogeneic transplantation. The six trials with 765 related donors (388 BM; 377 PB) provided a range of data on the adverse effects associated with HSC donation and comparative findings for the tolerability and safety of the two methods of donation. Both physical and psychological side-effects were reported as follows:

(i) pain prior to donation was experienced by PBSC donors only (due to G-CSF); (ii) more BM donors experienced pain at the donation site than PBSC donors; (iii) BM donors experienced more back pain and PBSC donors more generalized skeletal pain; (iv) BM donors had greater incidences of haemorrhage, anaemia and hypotension; (v) BM donors tended to have more days of restricted activity, higher mean discomfort scores and a greater number still had restricted activity at 14 days post-collection, whereas PBSC donors had greater difficulty functioning in the first 7 days after collection; (vi) BM donors were more likely to require hospitalisation post-donation; (vii) both BM and PBSC donors had fatigue, and reduced energy following the procedure; (ix) the overall number of donors reporting any adverse events, was greater in the BM group (56%) in comparison to the PBSC group (44%) but no life-threatening adverse events were reported.

With the exception of one episode of deep venous thrombosis, no immediate life threatening events were reported. Only three trials reported donor outcome data beyond 3 months; so the incidence of serious late effects could not be determined.

Although the results document that different short term morbidities are experienced by BM and PBSC donors, the data do not clearly indicate one method of collection as "safer" than the other.

Limitations of the findings from the systematic review

These clinical trials had merits but also difficulties including:

(i) Related Donors

Results from RCTs are limited to the participant group under evaluation and in all six trials described above, the donor was related to the recipient. Related donors may have stronger motivation leading to under-reporting of symptoms and acceptance of a greater level of morbidity than unrelated donors. Unrelated volunteer donors are generally rejected if they have any clinically significant medical problems at pre-donation evaluation; the criteria for exclusion may be less stringent for related donors. Consequently, pre-donation morbidity may differ significantly between related and unrelated donors and these 6 trials may not accurately estimate the relative risks to unrelated donors between the two methods of stem cell donation.

(ii) Incomplete understanding of psychological morbidity

Three RCTs reported data on this but all used different quality of life assessment tools. All donors in these three trials reported psychological morbidity but, given that they were related to the recipients and thus had a personal interest in the transplant outcome, it is possible that the donors might have minimized the effect the procedure had on their quality of life. Conversely, the fact that they were also dealing with a seriously ill relative may have affected their anxiety and energy levels. Additionally, the use of different assessment tools across the studies prevents comparison between them.

(iii) Sample size and the lack of long term follow-up of safety outcomes

Even allowing for a total of 765 donors (388 BM; 377 PBSC) across 6 included studies, the numbers may not be adequate to evaluate lower frequency adverse events, such as the theoretical concern that the use of G-CSF may induce myelodysplasia (MDS) or acute myeloid leukaemia (AML) in susceptible individuals (Pamphilon et al, 2008). The influence of G-CSF on future haematological events in previously healthy individuals is not easy to determine, especially in related donors where there may be a genetic predisposition to leukaemia (Nagler et al, 2004). Follow-up in most clinical trials would almost certainly have ceased by the time that such an event occurred. The background incidence in the general population is so low that many thousands of donors would need to be followed in order to identify an increase in risk due to the donation procedure. For AML, based on an annual incidence in the US of 5/100,000 (which translates into a cumulative incidence of 0.05% at 10 years), it has been estimated that even if the risk was increased 10-fold by G-CSF, it would be necessary to follow more than 2000 donors for a period of 10 years to identify the increase (Hasenclever & Sextro, 1996). Follow-up was limited to a maximum of 2 years (range 1 week to 2 years) in the 6 RCTs in our systematic review (Siddiq *et al* 2009).

(iv) Methodological quality

of the six RCTs included in the systematic review was difficult to assess and generally poor. Only one study reported adequate methods to generate the randomisation sequence and only four of the six trials included more than 80% of randomised donors in the outcome analysis. Moreover, all studies were sub-studies of larger recipient-based randomised trials. The assessment of the parent trials from which these donor studies originated was required to fully understand the methodological quality. Many aspects of trial design and sample size assessment were not, *a priori*, developed to evaluate outcomes from the perspective of the donor. The lack of consistency in reporting donor outcomes meant that the results of the systematic review were largely limited to a descriptive not quantitative analysis. This limitation may be rectified with RCTs designed from the onset to evaluate the outcome for donors.

Clinical Trials: What information is really required to adequately inform donors?

Based on the findings from the clinical trials we analysed, a number of issues emerged which require further primary research. A better understanding of all risks, including short term and longer term, as well as of low frequency events, is needed. Psychological consequences are poorly understood. More consistent comparisons of health-related quality of life and psychological indicators will be needed from a larger and more complete cohort of donors, without the concerns that the proportion of donors completing these assessments represents only a smaller fraction of a larger study sample and are not representative. Is it possible to design and complete more methodologically sound RCTs to answer these points and which are not sub-trials of larger trials evaluating recipient outcomes? This is problematic because most transplant physicians usually have a clear preference as to which stem cell source is most appropriate for any given patient. One large trial by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) in North America is currently recruiting (https://web.emmes.com/study/bmt/protocol/0201_protocol/0201_protocol.html). Although the primary aim of this study is to compare 2 year survival probabilities in patients, an important secondary outcome is comparison of donor return to baseline toxicities and quality of life. This trial, which has an accrual goal of 550 donor-recipient pairs, consents both the donor and recipient for participation and follow-up prior to randomization and includes longitudinal assessments, including quality of life. Enrollment is expected to be complete by mid-2009 with results available in mid-2011.

Alternative sources for donor outcomes data - Registries

Given the current limitations regarding information from the published literature concerning RCTs, alternative sources of data might be explored. Observational studies, especially if they include a large and representative sample of the donor population that is monitored for their health, quality of life and adverse effects, might provide valuable follow-up information. Several large HSCT outcomes registries exist but these are primarily concerned with monitoring recipient outcomes and most have not collected donor outcomes for all transplants in a systematic way, though some are starting such activities.

HSC donor registries are an essential source of donor follow-up data; most collect some level of donor outcome data and a few have large-scale donor follow-up programs. Whilst this is observational information collected from non-randomised donors, it still represents an important resource to capture the overall incidence of adverse occurrences, including rare events. Moreover, it is possible that this type of prospective data collection could be extended to related donors (Halter et al, 2009).

The WMDA requires that registries collect reports of adverse events that affect either donors or HSC products. Registries of volunteer unrelated donors are expected to conduct follow-up of individuals who donate HSC, including the reporting of severe adverse events and reactions (SEAR) according to WMDA Standards. Up to now the WMDA has had no direct role in the conduct of clinical trials, although the NMDP analyzes and publishes outcome data on specific groups of patients in which the HCT was carried out using grafts provided by them (McGlave et al, 2000, MacMillan et al, 2008). Until recently there has been little or no systematic collection of outcome data for related donors - most of the key data collected is solely concerned with volunteer unrelated donors (Halter et al, 2009: Pamphilon et al, 2008).

Several large unrelated donor registries now collect donor outcome data in a systematic manner. The NMDP has recently published reports of donor follow-up (Miller et al, 2008, Pulsipher et al, 2009) showing, for example, that in 2408 PBSC donors evaluated, bone pain due to G-CSF occurred in roughly 80% and myalgia, headache and fatigue in about 70%; female donors had more bone pain as well as higher rates of adverse events and grade II-IV and III-IV CALGB (Cancer and Leukemia Group B) toxicities. In all, 0.6% experienced serious or unexpected toxicities but all recovered completely (Pulspiher et al, 2009). The NMDP is also undertaking a prospective outcome study of related donors, termed the RDSafe study (DC Confer, Chief Medical Officer, National Marrow Donor Program, Minneapolis, MN, USA. Personal Communication, 2009). The Spanish Donor Registry has now reported data on 320 PBSC donors followed for >2 years. Bone pain and headache were the most frequently recorded side effects; no donor has developed a haematological malignancy (de la Rubia et al, 2008). The Swiss Blood Stem Cells Donor Registry now routinely collects outcome data for both related and unrelated donors as required by Swiss legislation (G Nicoloso, Chief Medical Officer, Swiss Blood Stem Cells, Bern, Switzerland. Personal Communication, 2009).

In order for registries to produce meaningful data that is of value in clinical practice and research, data should be collected in a more comprehensive and transparent manner with minimal exclusions. Well conducted registry evaluations might be expected to provide outcome results that are more generalizable to a wider population, and they should evaluate outcomes in 'real life', rather than in the context of an experimental study design with many carefully controlled variables. The recent publication on the use of registries for evaluating patient outcomes by the Agency for Healthcare Research and Quality (Gliklich & Dreyer, 2007) discusses the quality domains that may be relevant to assessing the rigour and

reliability of data from registries. These components include planning, design, data elements and governance. As examples, the process for identifying and reporting outcome events should be clearly described, specific eligibility inclusion and exclusion criteria stated, and the follow-up time required to detect events of interest should be specified. Operational definitions of all outcomes and adverse events are required, and methods should be in place to ensure the integrity of the data by training data collectors using standard techniques and by making an analysis plan readily available.

Conclusions

It is the responsibility of those who care for both related and unrelated donors of HSC to ensure that their safety is paramount. They should be provided with nationally or internationally agreed, well-structured information to help them to decide whether donation is feasible and which modality of donation they prefer, if a choice is available to them. We have addressed how this information might be obtained and considered two main sources: RCTs, which, as we have reported in our systematic review (Siddiq *et al* 2009), are confined at the present time to related donors only and the use of HSC registry data confined predominantly to unrelated donors. Whilst clinically it may be acceptable to compare outcomes between related and unrelated donors, it is important to examine whether comparing the data sets is methodologically appropriate. Principally whether the patterns of outcomes observed in the registry data are reflected in the RCTs and the extent to which confounding factors influence the registry data. Exploration of both these issues will be beneficial to all future work in this field.

It will be essential in future to ensure that all donors, including children <16 years receive appropriate follow-up. A minimum of 10 years has recently been suggested by the WMDA for unrelated donors (H Greinix, Medical University of Vienna, Vienna, Austria, Personal Communication, 2009). The correct comparator groups should be included, e.g. BM versus PBSC donation. Data should then be compared with ageand sex-matched normal (non-donor) populations to evaluate whether adverse outcomes are a result of the donation experience or an expected outcome within the normal population group. In the future, data collected prospectively from transplant registries coupled with well-designed prospective clinical trials will help to provide the advice that will ensure optimum governance of HSC donation.

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Number of Donors

Trial

184

Bredeson et al, (2004)

329

64

Fortanier et al, (2003)

Favre et al, (2003)

Heldal et al, (2002)

	Trial Methodol	ogy	
tem cell source BM/PB (n)	Number of Donors in parent study	% included in donor experience trial	% donors included in outcome analysis
16/86	228	79% BA 83% BB	34 - 58%
166/163	350	%†6	>80%
31/33	111	%LS	<i>i</i>
30/31	61	100%	>80%
30/29	Not stated		>80%

BM, bone marrow; PB, peripheral blood

* A minimum number of 80% was only available for the early outcome analysis points in these 2 trials. At later outcome assessment points, the number available for analysis was considerably reduced.

>80%

42% BM 37% PB

175

38/31

69

61 59

> Kennedy et al, (2003) Rowley et al, (2001)