Allogeneic Hematopoietic Stem Cell Donation—Current Status with Regard to Safety

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) represents the first choice of treatment or an important therapeutic option for numerous diseases. Several stem cell sources, such as bone marrow, mobilized peripheral blood stem cells, and umbilical cord blood, are suitable for HSCT in clinical practice. However, this procedure is strongly related to availability of a histocompatible donor. In order to increase the probability of finding a histocompatible donor, national and international registries have been developed. Voluntary donation of bone marrow or peripheral blood stem cells for HSCT, both in the related or unrelated setting, is a well-established procedure with an invaluable ethical significance. Even if both procedures are safe, they are not risk free; therefore, the greatest attention has to be paid to the donor and to the donation process through a careful monitoring protocol for donor safety.

Keywords

Allogeneic hematopoietic stem cell transplant, bone marrow donation, peripheral blood stem cell donation, side effects, adverse events

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Allogeneic hematopoietic stem cell transplant (HSCT) has evolved from an experimental therapy to an elective treatment for many hematological and non-hematological diseases. HSCT is strongly related to the availability of a histocompatible donor—around 25 % among family members. The establishment of national registries of hematopoietic stem cell donors and cord blood units joined worldwide enables finding a suitable donor in patients without a human leukocyte antigen (HLA)-matched sibling.

Today, more than 18 million hematopoietic stem cell donors and cord blood units from 65 registries and 47 cord blood banks are available to provide life-saving stem cells to patients.[1] The last European blood and bone marrow transplant (EBMT) survey reported 26,859 first transplants, of which 40 % were allogeneic, performed in 615 centres during 2008.[2] In Italy during 2009, the Gruppo Italiano trapianto di midollo osseo (GITMO) registered 1,474 allogeneic transplants.[3] Over the past decade, a major shift has occurred from bone marrow (BM) to cytokine-mobilised peripheral blood stem cell (PBSC) collection as the main procedure for obtaining allogeneic hematopoietic stem cells.[4] Hematopoietic stem cells are present in bone marrow and represent the 0.1 % of circulating cells in the peripheral blood. This percentage may increase to 5 % after mobilization.

Influence of Stem Cell Source on Transplant Outcome

There are phenotypic and biologic differences between BM and PBSC. Due to a higher number of CD34+ cells, a shorter time to engraftment both in nucleated cells and in platelets is observed with PBSC,[5] however, the higher number of T-lymphocytes infused with PBSC appears to increase the incidence of chronic graft-versus-host disease (GVHD).[6]

Considering the impact of stem cell source on transplant outcome, many trials have been performed without consistent results. In 2005, a meta-analysis of 1,111 myeloablative HLA-sibling transplants was performed by the 'Stem Cell Trialists'.[7] This analysis showed that there are no significant differences in overall survival (OS) nor in non-relapse mortality (NRM) between patients receiving BM or PBSC; a sub-analysis of phase of disease showed a better five-year OS in advanced patients receiving a peripheral stem cell transplant (39 % versus 29 %; $p<0.01$). Of note, the increased incidence of chronic GVHD in peripheral stem cell transplant strongly influences patient quality of life; therefore, a decisional model has been proposed, suggesting that allogeneic peripheral stem cell transplant represents the treatment of choice in terms of OS and quality of life, with an advantage of seven months over bone marrow cells. BM gives better results only in low-risk patients.[8] Moreover, BM remains the primary source in non-malignant disease.

BM or peripheral stem cell donation is a demanding procedure that requires a considerable commitment on the part of the donating individual. Due to the invaluable ethical worth of donation, great attention and care must also be paid in the donation process to donor eligibility for stem cell collection.[9]

Reporting of Serious Events/Adverse Effects

Even though serious adverse events are rare, the World Marrow Donor Association (WMDA) created a serious events/adverse effects registry (SEAR) reporting system in which >80 % of donor registries worldwide participate. The SEAR database gives good insights into the occurrence of serious events and adverse effects regarding stem cell donation by unrelated donors. Any event concerning the donor that results in death or is life-threatening, requires in-patient hospitalization, considerably prolongs existing hospitalization, or results in persistent or significant disability/incapacity must be reported.

The WMDA has developed recommendations about the eligibility criteria and evaluation of donor health with a view to ensuring donor safety during the entire donation process.[10]

Family and Voluntary Unrelated Donation

Although unrelated donors benefit from standardised care guidelines established by national and international donor registries and associated organizations,[10,11] no specific guidelines are available for related donors.[12] Another important factor that distinguishes related from unrelated donors is the relationship between donor and recipient.[13] This relationship may push the donor to hide some important medical information in order to be considered eligible for the donation. Moreover, with the introduction of reduced-intensity conditioning, a higher number of older patients are candidates for HSCT. This implies that in the related setting, where no limits of age are established for donation, donors may be older. For these reasons, a related donation may be considered a less safe procedure. An EBMT analysis performed on 51,024 first HSCTs (related and unrelated) between 1993 and 2005 reported five donor fatal events, all in the related setting.[14]

Bone Marrow Donation

BM donation consists of hematopoietic stem cell aspiration from both hips (posterior superior iliac crests) under general (GA) or regional anesthesia (RA). The donor is hospitalized for at least one night[15,16] and one or two red blood cell autodonations are also necessary before the procedure. The main consequences for the donor are pain and bruising at the site of aspiration and anemia.[17] The donor may require pain killers for a short time after the procedure and some time off work. The fatal and serious adverse events reported are fortunately rare.

Type of Anesthesia

BM harvest may be performed under GA or RA. Although both methods are generally considered to be safe and are commonly used, there are only a few reports that compare their safety and efficacy among stem cell donors.[18–20] In a recent retrospective study of 281 BM donations (207 GA, 74 RA), no significant difference was noted regarding numbers of adverse events during and after the procedure. This observation strongly suggests that there is no 'anesthesia of choice' and that the choice depends on the donor or the anesthetist's preference.[21]

Stem Cell Mobilization

The collection of hematopoietic stem cells mobilized with recombinant human granulocyte colony-stimulating factor (rhG-CSF) from the bone marrow into the bloodstream of healthy donors has now become a routine procedure. It consists of the subcutaneous administration of rhG-CSF at the dose of 10 µg/kg for four to five days, followed by the harvest of circulating stem cells by the process of leukapheresis. Short-term events related to PBSC donation are due either to cytokine administration (local reaction, pain, fevers), central line placement or leukapheresis (bleeding, hypocalcemia). The most frequent serious complications are related to pulmonary congestion, splenic rupture and vascular thrombosis.[22]

Moreover, when a growth factor is administered in a healthy donor, the highest attention has to be paid to possible late effects and in particular to malignancies.[23] Several studies have been performed with the aim of evaluating the long-term incidence of leukaemia in stem cell donors after G-CSF administration. In particular, Bennett et al.[24] have described two cases of acute myeloid leukaemia in related donors after mobilisation with rhG-CSF. More information on this topic is available from registry studies: in a National Marrow Donor Program (NMDP) analysis performed on 2,408 unrelated PBSC donors from 1999 to 2004, with a median follow-up of 44 months, the incidence of cancer in the donor cohort did not significantly differ from that of the control population. In particular, no case of myelodysplasia or myeloid leukaemia was observed in donors receiving rhG-CSF.[25] In another study from the German Bone Marrow Donor Centre (DKMS) on 3,928 unrelated PBSC donations, malignancies occurred in 12 donors; only the incidence of Hodgkin's lymphoma (two cases) differed significantly from that observed in an age-adjusted population.[26]

Larger prospective studies are needed to evaluate the real incidence of hematological diseases in healthy donors.

Use of Biosimilars in Peripheral Blood Stem Cell Mobilization

The increasing use of stem cell mobilization and collection from healthy donors for use in allografting opens the opportunity for the use of biosimilars. The EBMT, considering the limited experience with G-CSF biosimilars, stresses that the use of biosimilars for stem cells mobilization in healthy donors represents an ethical dilemma because they receive no therapeutic benefit from the use of these drugs.[3] Therefore, the EBMT recommends evaluation of safety and efficacy data before using them in volunteer donors. Considering the detrimental effect that unexpected toxicity might have in normal individuals donating their PBSC, sufficient experience with the biosimilar product and adequate follow-up should be required. Safety data can only be obtained by performing an adequate number of stem cell mobilization procedures and conducting long-term follow-up in patients undergoing autologous stem cell transplantation.[27] According to the East Midlands G-CSF Guideline (National Health Service [NHS]) the same advice should also be considered for autologous stem cell mobilization.[28] In this setting, a preliminary report on patients affected by multiple myeloma and lymphoproliferative diseases comparing standard G-CSF versus biosimilar (ratiograstim) showed similar results in terms of days for collection and CD34+ yield.[29] The WMDA has adopted the same policy as the EBMT and states that any new product for mobilization should not be used until safety data are available.[11] For the Austrian Society of Hematology and Oncology (ASHO) the use of biosimilars cannot be recommended without concerns, including filgrastim for stem cell mobilization in healthy persons, filgrastim for non-therapy-related

neutropenias, therapeutic use of filgrastim for neutropenic fever, or biosimilars for pediatric diseases.[30,31]

Bone Marrow Versus Peripheral Blood as a Stem Cell Source—Side Effects and Adverse Events

Some randomized controlled trials have been conducted comparing HLA-identical sibling allogeneic donation of BM and PBSC.[16,32–36] A recent meta-analysis of the Cochrane Central Register of Controlled Trials[37] has been performed with the aim of analyzing donor safety. The six trials, with 765 related donors (388 BM, 377 PBSC), provided a range of data on the adverse effects associated with hematopoietic stem cell donation as well as comparative findings on the tolerability and safety of the two donation methods. Both physical and psychologic side effects were reported. Both BM and PBSC donors experienced similar psychologic morbidity, and both had fatigue and reduced energy after the procedure. BM donors experienced more pain at the donation site, greater incidence of hemorrhage, anemia and hypotension, greater tendency to have more days of restricted activity and were more likely to require hospitalization after donation. Even though these data showed a greater number of adverse events in the BM group (56 %) compared with the PBSC group (44 %), there is no clear evidence of which collection method is safer for the donor. The main limits of this study were due to limited reports of donor experiences, short follow-up and inappropriate and heterogeneous psychologic morbidity assessment among the trials.[38]

The previously reported EBMT analysis[14] of 51,024 first HSCT related and unrelated (27,770 BM and 23,254 PBSC) contained five donor-fatal events (one BM versus four PBSC), and 37 serious adverse events (12 BM versus 25 PBSC; $p<0.05$). The most frequent adverse events in BM donation were cardiac and related to the anesthesia, while in PBSC donation they were pulmonary embolism and deep venous thrombosis.

In an NMDP survey,[39] BM donors most often reported pain at the collection site (82 % back or hip pain) and anesthesia-related pain sites. In contrast, PBSC donors most often reported bone pain (97 %) at various sites during filgrastim administration. Fatigue was the second most reported symptom by both BM and PBSC donors (59 and 70 %, respectively). PBSC donors reported a median time to recovery of one week compared with a median time to recovery of three weeks for BM donors. Both BM and PB donors experienced transient changes in their white blood cell, platelet and haemoglobin counts during the donation process, with most counts returning to baseline values by one month after donation and beyond. Serious adverse events were uncommon, but these events occurred more often among BM donors than PBSC donors: 1.34 % in BM donors versus 0.6 % in PBSC donors.

Moreover, from October 2009 to May 2010, the WMDA reported seven serious and adverse events in BM donors and 36 in PBSC donors. In the former group, one persistent back pain, one disc prolapse, one grade III heart block while anesthetised, one wound infection, one broken aspirate needle retained and three cancers (testicular, breast and Ph-positive acute lymphoblastic leukaemia [Ph+ ALL]) were reported. In the peripheral stem cell donation group, the more frequent reported adverse events were cancers (10 patients), of which only two were hematological (one plasmocytoma and one chronic myeloid leukaemia [CML]), splenic complication (four patients), allergic reaction (two patients), chest pain (two patients), electrocardiogram (ECG) changes (two patients), etc.[40] The occurrence of malignancies has not to be directly correlated with the donation and as reported by others, does not significantly differ from that of the control population.[25]

Conclusion

The high ethical value of donation and its central role in HSCT implies that the highest attention must be paid in donor selection and donating process. Particular attention must be paid to donor evaluation with the intent to protect the volunteer from the risk of damaging his or her health and to offer the recipient the best quality of treatment. Both types of donation (BM and PBSC) are safe; they have different side effects and all donors should be informed about the procedures and their possible specific adverse effects. There is still a need for a more accurate reporting system and to perform a longer donor follow-up to evaluate the safest type of donation. Moreover, particular attention must be paid in the recruitment of related donors to their potential older age and to hidden morbidity. ■

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