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FAMILY DONOR CARE MANAGEMENT: PRINCIPLES AND RECOMMENDATIONS

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Abstract

The World Marrow Donor Association (WMDA) is an international organization fostering collaboration in clinical transplantation and promoting the interests of unrelated stem cell donors. The WMDA has developed standards for the recruitment, counseling, work-up and subsequent donations to protect the interests of donors. Although the care of family donors has been carefully considered and managed in transplant centers (TCs) internationally over numerous years (and increasingly TCs are facing accreditation programs, which address this issue) there is currently a lack of standardized guidelines for the management of family donors. The underlying principles of family donor care are in many ways identical to those concerning unrelated donors, although key ethical considerations differ. Although the WMDA is primarily involved in the field of unrelated donors, we believe that it is important to collaborate with those involved with family donors, to standardize the care. This document hopes to encourage increased collaboration between those caring for related and unrelated donors, and build on the extensive work, which has already been undertaken in this field to homogenize care. We recognize that there will be financial, regulatory and logistic differences in different countries and that the manner in which these principles are achieved may vary.

Introduction

The dynamics of care management for hematopoietic stem cell family donors differ substantially from unrelated donor care, although there are overlapping aspects to both procedures. A survey carried out by the European Group for Blood and Marrow Transplantation (EBMT) Nurses Group/Late Effects working party showed that at present there is a lack of recognized standardized guidelines for the management of family donors[1]. The World Marrow Donor Association (WMDA) was established to foster international collaboration to facilitate the exchange of high-quality hematopoietic stem cells for clinical transplantation world- wide and to promote the interests of donors[2] In former years, working groups of the WMDA have set up guidelines for the recruitment, counseling, work up and informed consent procedures, subsequent donations and transport of stem cell products to protect volunteer stem cell donors. Since the establishment of Bone Marrow Donors Worldwide (BMDW) in 1989 is worldwide, over 13 million volunteers have been registered as stem cell donors[3], of whom over 80,000 have actually donated stem cells for an unrelated recipient. A substantial proportion of SCTs are also carried out with stem cells from family donors (for example, family members of the patient). In many countries transplantation centers (TC) are obliged to conform to an accreditation program such as the Joint Accreditation Committee ISCT & EBMT (JACIE) or the Foundation for the Accreditation of Cellular Therapy. These factors have led to demands for new guidelines for the care management of family donors. JACIE requires written criteria for stem cell donation to protect the donors' safety. Related stem cell donation presents substantial ethical challenges, which differ from those associated with unrelated donation. Although the WMDA is primarily involved in the care of volunteer donors, the Ethics Working Group and the Clinical Working Group of the WMDA determined that care for family donors is of critical importance, and as such formed a subcommittee to establish recommendations for this particular group of donors. In this paper, the different steps in the donor care process will be explained, discussed and recommendations for family donor care will be given.

Donor recruitement

Traditionally, the health-care professional of the recipient was also responsible for the donor. Although there is no substantiating evidence, it would seem rational that from time to time divided loyalties and conflicts of interest could arise, more often to the disadvantage of the donor than the recipient. To avoid these potential problems and to assure maximal donor protection and integrity of the transplant program, it is important that the donor is assessed by a practitioner who is not directly involved in the recipient's care. The practitioner does not necessarily have to be geographically

dislocated and may even be in the same hospital. It is important that the practitioner has an understanding of donor rights and that they can advocate for the donor. In some TCs, this may be achieved by dedicated specialist personnel for donor care management, while in others, members of the transplant team may be identified and empowered to fulfill the donor advocate role.

As there is a need for information before consent, we recommend donor counseling before tissue typing. In this way any obvious reluctance to donate, or any medical problems precluding donation, can be identified, which will allow for deferral of unwilling or unable donors before establishing a full HLA match. As donors may be physically distant from the TC, an assessment and counseling may need to be carried out by telephone or email and it is important that good donor information, which can supplement such discussions, should be available. Whereas volunteer donors decide for themselves whether to join the register or not, family donors do in fact not have the anonymous choice whether to become a donor or not. They are directly approached with the request for HLA compatibility typing for their relative, often at the same time the recipient is identified as a candidate for transplantation. Even in the case of donor drives, volunteer donors always have the choice to join or not whereas relatives often feel coerced by the knowledge of a relative in need of SCT[4]. It is therefore important to give family donors a fair chance to decide whether or not to become a donor. A positive balance has to be found between risks for the donor/benefit for the recipient, but also benefit for the donor/risks for the patient, both physically and emotionally[5].

Unrelated donors are provided with independent donor advocacy, confidentiality and protection by the stem cell donor registry. It is an important requirement that unrelated donors always have a specified independent donor advocate to discuss any doubts they have regarding the donation procedure, and that they can make a decision to proceed, or not, without coercion. Independent donor assessment is equally necessary for family donors and involvement of an independent committee or independent counseling (psychologist, donor's advocate) should be considered. The role of this person is to perceive any coercion during the information/predonation process and to assist the donor to overcome any barriers to donation. This person should have knowledge of the risks and side effects of any type of stem cell donation and transplantation outcome to fulfill this role. Despite this it has to be accepted that by its nature, the possibility of familial pressures/guilt in the family context will never be completely eliminated. The requirement for an independent donor advocate has been recognized by some countries/TCs and has been introduced by some centers. The optimal donor advocate will have a primary role distinct from the transplant team. Alternatively, this could be a member of the transplant team who is identified as undertaking this role, is trained in donor rights and who is not involved in the

care of that donor's recipient (that is, will advocate for the donor in an unbiased manner). TCs must have policies for dealing with situations wherein a conflict of interest between the family donor and others may arise. These should include an independent advocate acting in the interests of the family donor. It is recognized that, for smaller TCs with limited finances and limited suitable expertise, appointing a donor advocate may be challenging. In these situations, adequate procedures to document and address potential conflicts of interest are even more important.

Children acting as donors require further consideration. Laws and regulations governing minors acting as a donor for a sick sibling, differ from country to country. Indeed, in some countries a court of law now has to make the final decision to permit a pediatric stem cell donation[6] Furthermore, children need a special approach. Guidelines for child donor counseling and clearance need to be separately established. For children who cannot consent, the need for advocacy to protect their interests is essential, especially as a parent who is signing consent may have conflicting feelings because of their need to be involved in decisions concerning the welfare of both the patient and the donor.

Rarely, adult donors with severe developmental or psychological problems rendering them mentally incapable of informed consent are considered as stem cell donors for a relative. These can be either donors who have always been mentally challenged (for example, Down's syndrome) or donors who are suffering from a psychiatric illness. It is advised to first establish whether the aspirant donor could endure the donation procedure (both physically and mentally), before performing HLA testing[7,8]. Again, some countries have decided to enforce the rule of the law courts to decide on suitability for donation in case of mentally incapable donors who cannot decide for themselves.

Informed consent procedures

Volunteer donors give their (written) informed consent when they sign up for the registry. Whenever an unrelated donor registry receives a request for confirmatory typing or high-resolution typing, they ask the donor yet again for informed consent, according to the WMDA recommendations[9]. Before asking for informed consent, family donors should be informed carefully regarding risks and benefits of and alternatives to the donation procedure. Although TCs usually have a preference for the source of stem cells for transplantation, volunteer donors are given the choice whether to donate BM or stimulated PBSCs. At present, it is unclear to what extent family donors have the opportunity to choose between forms of donation. Ideally, we recommend that the information procedure should be the same for both family and

unrelated donors. Long- and short-term risks of G-CSF administration and of donation should be clearly presented and understood by family donors. The TC should ask for written informed consent for the donation procedure, including physical examination and infectious disease marker testing, administration of G-CSF and apheresis, or BM harvesting under general or local anesthesia. Family donors should also be asked for written permission for storage and discard of either their DNA or cells for future testing or research as well as exchange of donor characteristics with third parties (for example, EBMT/CIBMTR/APBMT databases) for research purposes. For minors or mentally incapable adults, a proxy consent procedure is in most cases inevitable. Depending on the local laws and regulations, confirmation by court might be part of the procedure. Although this group of donors could not comprehend the effect of the donation procedure, they do have the right to receive information, appropriate to their age/mental capability. Procedures should be in place to assess the donor's capacity to consent, compliant with local regulatory frameworks. According to the European Union directive on safety of tissues and cells, all of the above is mandatory[10].

Donor eligibility

The average age of family donors is different from that of unrelated donors. Elderly donors especially are more likely than age restricted unrelated donors to have co-morbidities that may complicate or prevent donation. Systems should be in place to assess potential donors before HLA typing. These should include written information on the implications of giving blood for HLA typing, outlining the problems of withdrawing after a match has been established. They should include an assessment of general health and willingness to donate (possibly by telephone, using a health questionnaire[11]) before HLA typing. In this way, obstacles to donation, both psychological and medical, can be identified and addressed before matching, thus avoiding finding a fully matched donor who has subsequently to be deferred.

The idea that a substantial health risk to a donor is justified because the donor is donating to a relative is questionable and certainly controversial. Therefore, it is recommended that a local set of Donor Evaluation Guidelines, similar to those operated by an unrelated stem cell donor or blood donor panel, is adopted to inform decisions on specific medical conditions, for example, cardiovascular disease. When donors do not meet eligibility criteria, a procedure must be in place to assess and document decisions. However, divulging pertinent confidential medical information to family members must be at the discretion of the potential donor. According to JACIE, all results (normal and pathologic) have to be explained to a donor and in case of pathologic results the donor has to be informed regarding the consequences, further diagnostic tests or treatments. The donor medical examination should be carried out

by a physician who is not involved in the recipient's direct medical care, but who is familiar with the possible risks and side effects of a BM harvest or an apheresis procedure. This is particularly important in those cases in which family donors place pressure on themselves and the medical team to be declared as medically suitable when there is doubt. When increased donor risks are identified, procedures should be in place to assess these against predicted benefits for the recipient. It is not reasonable to expose family donors to increased health risks wherein the recipient's outcome is likely to be poor.

Guidelines for donor physical examination and eligibility should include:

- Clinical assessment of general health.
- Assessment of donor's potential risk factors for blood-borne viral infections (such as HIV, Hepatitis B and Hepatitis C) and prion disease (as is mandatory according to the European Union directive and JACIE).
- Referral for specialist clinical assessment of donors with co-morbidities.
- Assessment of risks for pediatric donors.
- As far as possible an assurance that the donor understands the implications of donation. Donors should know that they have the right to refuse donation at any time, but the implications to the recipient should be explained to them.

Adverse events registry

Over the past years, case reports concerning both family and unrelated donors have been published for serious adverse events. The WMDA Clinical Working Group registers severe events and adverse reactions concerning unrelated donors in the severe events and adverse reactions registry. Family donors are probably more at risk of developing adverse reactions[12]. A number of countries have established long-term follow-up arrangements for family donors, either as a legal requirement or as research protocols. The establishment of an international registry of adverse events for all donors can be envisaged. A subcommittee of the WMDA and the EBMT Late Effects Working Party has been established to specifically address this issue (as well as barriers to its success, for example, financial). Only structured registration will give more insight into adverse effects of donation, including both short- and long-term effects of G-CSF administration in family donors. In addition, current adverse event reporting through the severe events and adverse reactions registry only captures data on severe adverse events and reactions of unrelated donors. It is recommended that in addition to these data, the suggested international registry should, at least for an appointed time period, also capture data from any potentially donation-related

adverse events (from family as well as unrelated donors), whether severe or not, as this is the only way to identify the actual occurrence of risks and side effects for both family and unrelated stem cell donors.

Follow-up

The necessity for long-term follow-up in healthy individuals to determine any harm (for example, malignancies) from administration of growth factors has been under discussion since the first (family) donors were treated with G-CSF[13].The need for continued donor safety monitoring might be of even more significance in the family donor, because they are on average older than unrelated donors and therefore more frequently experience adverse events[12]. As studies have shown cytogenetic variances in lymphocytes after the administration of growth factors[14,15] more research is needed to determine whether cytogenetic analysis should be implemented in structured donor follow-up. Currently, a study involving donors in the United Kingdom is addressing this issue. Moreover, follow-up of family donors of patients who have died requires special consideration of the emotional and psychological needs of the family.

Some registries advise follow-up of unrelated donors for at least 10 years after G-CSF administration and potentially for life[16]; however, there is currently no scientific evidence to suggest the optimal length of follow-up. The maximum follow-up for family donors is often short (up to 1 year). It is hoped the data from countries where long-term follow-up of family donors are being pursued will help to inform us of any benefits to extending this time period. More research in this area is to be encouraged. The decision as to who is responsible for the costs incurred by this long-term donor follow-up is likely to vary between countries and perhaps between different centers within one country. Whatever the local situation this issue must be resolved for each transplant program at either local or even national level. The WMDA has developed short questionnaires for donor follow-up that can easily be accessed and implemented[17].

- Short-term follow-up is defined as follow-up until 1 month after donation. The costs may be covered by the patient's insurance company where relevant. The follow-up is likely to consist of a health questionnaire and may include a check on blood cell count.
- Long-term follow-up is defined as follow-up until 5 or 10 years after donation and is internationally recommended to safeguard donor safety[15,18] For unrelated donors, the registries are responsible for carrying out this follow-up program. The responsibility for long-term follow-up of family donors may fall to the TCs, but the financial and logistic arrangements, which will be associated with this must be carefully considered. This is the only credible way to determine the

risks of donation in this population. The follow-up is likely to consist of a short health questionnaire (self-reporting) or, when possible, by comparisons and evaluations of the donor registry with the national cancer incidence registry or death registry. Ideally, the follow-up from unrelated and family donors should be standardized and a minimal data set of information to be collected should be agreed universally. However, the financial and logistic implications of this may differ between different groups, and in different countries, and this must be taken into account.

Multiple and subsequent donations

New developments in the treatment of hematological diseases might involve the infusion of more than one donor-derived cell product. Donors should be informed beforehand whether the recipient is involved in a program that might demand an additional donation such as donor lymphocytes. In addition, a subsequent donation might be necessary when the transplantation was not successful or in case of relapse of the original disease. For unrelated donors, registries have strict rules and regulations for second or third donations and how often they allow a donor to be administered hematopoietic growth factors. It is recommended to have a similar system for family donors. This may include a review of the subsequent donation request before assessment of the donor, by a medical advisor or advisory group (preferably more than one physician within a TC) to assess the risk/benefit ratio to both the donor and recipient. In other words, there should be good clinical evidence to support performing an additional donor cell harvest and infusion.

Donors as research subjects

Current protocols are often research based and may involve the donors or donor-derived products. Besides provision of appropriate study-family information, donors should be given the option to discuss their participation with an independent person[19]. For example, the harvest of additional mesenchymal stromal cells from BM or natural killer cells from additional aphaeresis can be part of new research protocols, demanding subsequent donation procedures. Development of protocols to support the treatment of severe infections in neutropenic patients with donor-derived granulocytes after stimulation with G-CSF and dexamethasone is yet another example of cellular product donation. These (frequently family) donors should also be offered a similar long-term follow-up program. In a situation, when the donor is a research subject, institutional review board approval has to be obtained as is the case when recipients are involved in research.

The involvement of child donors in research protocols (for example, as a healthy control) should be carefully considered and requires expert ethical/medico-legal consultation. Again, a good balance between risk for the donor/benefit for the patient and vice versa has to be priority.

Conclusion and recommendations

A number of challenges face us today. Stem cell donor care is well described according to the European Union directive for safety of tissues and cells; however, the daily practice for family donor care management differs substantially from the treatment of unrelated donors. Although the WMDA has concentrated its efforts on volunteer unrelated donors, one could argue that similar recommendations and standards should be considered for the protection of family donors. This is not a direct activity of the WMDA and may be considered by other transplant organizations. The Ethics and Clinical Working Group of the WMDA, however, feel they have a responsibility to offer its experience and expertize in this area. Similarly, the follow-up and reporting of adverse events in all donors has been addressed at a recent workshop in Berne. This was initiated through a subgroup of the Late Effects Working Party of the EBMT and attended by representatives from a number of international organizations and registries concerned with donor care. Owing to dissimilar circumstances (the donor is either a relative or a stranger) it may be challenging to comply with all these recommendations. It is, however, essential to establish protocols for family donor care and recognize the donor as an autonomous identity. This will help to observe the positive balance between a donor's commitment and a patient's needs. The following is recommended:

- Counseling, including written information covering all aspects of family BM/PBSC donation should be available for each family member before HLA testing. This should cover the option for the donor to choose not to donate.
- As a family donor who is physically or emotionally unable or hesitant to donate may feel pressure from family members, TCs should establish procedures to ensure that donors are appropriately counseled regarding their right to refuse typing or donation. The practitioner (for example, independent advocate, physician) counseling the donor should have a documented donor advocacy role and should not be involved in the recipient's care. The donor must retain the right to divulge or not divulge the content of these discussions to interested parties including the patient or family members.
- Systems should be in place to evaluate clinical risk to the donor against defined criteria and to document decisions made.

- Systems should be in place both for adverse event reporting and for long-term follow-up of related as well as unrelated donors.

Conflict of interest

The authors declare no conflict of interest.

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