Chapter 5

DONOR SAFETY: THE ROLE OF THE WMDA IN ENSURING THE SAFETY OF VOLUNTEER UNRELATED DONORS: CLINICAL AND ETHICAL CONSIDERATIONS

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Since the beginning of hematopoietic stem cell harvesting from volunteer unrelated donors, ensuring donor safety has been a necessary goal of all parties involved in the process. As donation of BM or PBSCs is not in the interest of the donor's own physical health, donor registries and transplantation centers must take into account both medical and ethical aspects involved in the donation procedure. One of the principal goals leading to the formation of the World Marrow Donor Association (WMDA) was to establish internationally acceptable standards for all aspects of unrelated donor care.

Introduction

The first World Marrow Donor Association (WMDA) recommendations and requirements for standardized practice in this regard were published in 1994[1]. This paper discusses the current WMDA guidelines for both medical and ethical aspects of donor safety. Where possible, each of the issues has been introduced using the appropriate WMDA Standard (version 1 November 2008). Explanatory remarks and key references about the Standards are provided. This document deals primarily with adult unrelated donors, and aspects specific to mothers donating cord blood units can be found in 'International exchange of cord blood units-the registry aspects' in this series.

Donor recruitment, including education, managing expectations and informed consent

WMDA Standards

- The willingness to become a donor must be the individual choice of each adult donor or each maternal donor of a cord blood unit, that is, donations must be voluntary. Donors must be willing to donate on behalf of any patient being treated in any part of the world.
- Donors must not be paid for their donation, but may be reimbursed for expenses incurred during the donation process, for example, time lost from work or travel to the collection center.
- Adult donors and maternal donors of cord blood units must be informed regarding their potential role in the donation of hematopoietic stem cells, the risks involved in the donation and the tests to be performed on the donor.
- Signed consent must be obtained initially at the time of recruitment.

Context[2,3]

Volunteerism is one of the basic principles of becoming an unrelated hematopoietic stem cell donor or donating cord blood units for public use. Education given at the time of recruitment should not only include appropriate information on the registration, counseling and the donation process, but also emphasize the voluntary nature of the donation and that the donor has the right to withdraw. Although the primary responsibility of the registry is in protecting the donor and ensuring their safety, the registry must ensure that the donor is aware of the serious, and potentially life-threatening, consequences to the recipient if the donor chooses to withdraw at any time, but particularly if this is after the recipient's pretransplant conditioning has commenced. Donors should also be informed that there is a reasonable possibility of

multiple or subsequent donation requests. In addition to verbal information, donors must be provided with appropriate written information before or at the time of recruitment and during the various stages of the search and donation process.

Confidentiality

WMDA Standards

- To ensure confidentiality, the identity of donors must be protected. Approaches to ensure donor confidentiality must be established. The registry must have a written policy listing the conditions under which donors and recipients might be informed of each other's identity. These policies must comply with governmental laws on disclosure.
- Donor and patient identity must remain confidential during the search process, so that only appropriate registry personnel can have access to these data.

Context[2,4]

The fundamental idea of anonymity or confidentiality during the search and donation process is to prevent, in every possible way, influencing or coercing the donor to undertake something that they either do not understand or do not wish to do. Violating the principle of confidentiality during the search process makes it practically impossible for the donor to make an unbiased decision. However, many registries do allow certain patient information to be given to the donor (for example, age, gender, disease of the recipient). Thirty-five percent of the registries allow direct donor-recipient meetings after a previously established time period. In the light of present therapies (for example, reduced intensity or non-myeloablative conditioning), where subsequent donations are more often requested from donors, each registry should carefully consider their policies, to ensure the donor has, at all times, the free and unbiased ability to choose whether to continue to donate or not.

Donor health assessment and eligibility

WMDA Standards

- Requirements for donor health affecting the eligibility of donors must be established.
- Characterization of adult volunteer donors or maternal donors of cord blood units for blood group markers, for the presence of infectious diseases and for any other markers considered important in transplantation must be performed.

- The medical history of donors selected for specific patients must include questions to identify persons at risk of disease transmissible through transplantation, according to WMDA recommendations.
- The adult volunteer donor must be medically examined to ascertain fitness to donate. This examination must be performed by a physician who is not a member of a team who has cared for the patient.

Context[5,6]

The WMDA has developed recommendations about the eligibility criteria and evaluation of donor health with a view to ensuring donor safety before, during and after the donation; and protecting the recipient from diseases transmissible by the graft. In order to avoid accepting ineligible donors onto the registry, the medical evaluation of the volunteer before or at recruitment is of critical importance. Once a donor is selected for a specific patient, a thorough medical history, examination and investigations are required. As the health status of the donor may change over time, it is reasonable to ask the donor relevant questions about their health at any time that they are contacted for a potential donation.

The eligibility criteria may differ depending on whether the registry is affiliated to a blood transfusion service or not. Registries recruiting only among blood donors may have stricter health criteria than those recruiting other members of the public. Because a blood donor is rarely unique and a specific blood transfusion rarely critical, it is possible to implement stricter risk management than would be appropriate for a hematopoietic stem cell donor, where an individual may be the only person available worldwide who can provide for a curative procedure.

Registries will ask questions to assess the donor's risk of having a transmissible disease (for example, infectious, autoimmune or genetic disorders). Many of these questions may be of a sensitive nature (for example, use of non- prescription drugs or sexual behavior). Testing for specific infectious disease markers (for example, hepatitis or HIV) is mandatory to protect the recipient. Donors must thus be informed that in the event of a positive result they will be counseled as to the impact and implications of the findings and any consequences that there might be to his/her health. In some, but not all, cases the donor may be medically deferred.

Donors may elect to donate stem cells either by BM harvest or G-CSF-mobilized PBSC collection. The donor should be fully informed about the pros and cons of each method. Although the final choice of route of donation rests with the donor, in practice many donors will agree to whichever product is requested by the transplant center (TC), if a preference is stated. In certain circumstances, the donor may only be permitted to donate by a single route (for example, donors with a history of

serious back pain may not be permitted to donate BM). Such restrictions must be communicated to the TC. Conversely, in some cases the TC will only accept a certain product; for example, certain treatment protocols require either BM or PBSC. In such cases, the TC may need to search for a different donor. It should be borne in mind that in the future additional mobilizing agents and routes of donation could emerge.

The legal and regulatory requirements for donor health assessment in individual countries may well be additional to the WMDA recommendations.

Registry responsibility for liability and death (benefits) insurance

WMDA Standards

- Fully informed and legally valid written consent must be obtained from all adult volunteer donors at the time of workup.
- The registry must assume responsibility and establish procedures for all donor medical expenses including the precollection physical examination, the collection proce- dure and all post-collection medical expenses that are directly related to the donation. No donor should assume financial liability for any portion of the follow- up testing and/or stem cell harvest/procurement process. The registry is responsible for all reasonable expenses incurred by the donor.
- The registry should offer disability and death benefits to all stem cell donors. These benefits might be provided through insurance coverage.

Context[7,8]

Fully informed consent is a central principle of self- determination, however any medical intervention carries a certain level of risk. It is critical to reduce the risk to the lowest possible level for the individual undergoing the procedure, as well as for the persons and institution performing the procedure. A donor should not be asked to consent to donate stem cells without adequate insurance or other recognized recompense arrangements in place.

Minimum criteria for accessing a donor

WMDA Standards

- The registry must make their policy for the minimum criteria needed to allow a specific donor to be available for a specific patient available to the public.

- This policy might include a minimum level of HLA match, guidelines for patient-specific criteria such as specific diseases or disease stages for which transplanta- tion is not considered appropriate, the optimal amount of marrow aspirated based on the weight of the donor, or requirements for TC credentials.

Context[8-11]

When a stem cell donation is planned from an unrelated donor, the patient and the TC enter into an agreement with the donor and the donor registry with expectations on each side. It is important for the WMDA to provide some level of reassurance that registries protect their donors' expectations by ensuring that the donation is not futile. Each registry must establish the minimal information required from the TC (and must make these criteria known), such as patient demographics (weight, age), indication for transplant (including the type and stage of the disease), confirmatory HLA typing, TC credentials (for example, accreditation status) and likelihood of a request for a subsequent donation. For more detailed information regarding TC accreditation processes, please refer to the 'Standards, regulations, and accreditation for registries involved in the worldwide exchange of hematopoietic stem cell donors and products' in this issue*.

Registries should review their policies regularly, as the field can advance rapidly in some of these areas. In addition, registries should have internal structures to address individual requests, which either appear to fall outside or are not addressed by their policy. The policy is not intended to be 'absolute' and it is expected that registries will have a medical director, medical advisory group or committee to act as an arbitrator of the decision- making process.

Subsequent donations

WMDA Standards

- Adult volunteer donors must be fully informed in advance of the original donation regarding the possibility of and possible procedures involved with a subsequent donation of hematopoietic stem cells or blood products intended for therapeutic use for the same patient and the risks involved in the second donation.
- The registry must have a written policy regarding the process to be followed upon a request by a TC for a subsequent donation.

*) In 2010 Bone Marrow Transplantation published in a Special Section a series of White Papers by the World Marrow Donor Association (WMDA). The reference for the mentioned paper is by Hurley et al, Bone Marrow Transplantation, 2010;45:819-824

Context[12,13]

Unrelated donor stem cell transplant activity is increasing and in 5-10% of cases a subsequent donation of stem cells or donor lymphocytes may be requested. It is acceptable practice for any TC to request a subsequent donation and it is recommended that donors should be counseled about this possibility before their first donation. In most PBSC-mobilized donations, the yield of CD34+ cells far exceeds the cell dose that TCs regard as optimal and sufficient for transplantation; hence, many registries will routinely allow 'excess' cells from the original donation to be stored in case of future need, in order to decrease the likelihood of a donor needing to give a subsequent donation. In this case, the consenting procedure must include this option. Some registries may have a requirement that the donor be informed if the excess cells are used. Registries must have policies that cover such topics as: the number of subsequent donation requests which will be accepted, the time period between donations (or before a donor is allowed to donate to a different patient), the route of donation (for example, number of G-CSF-mobilized PBSC collections allowed) and the possibility of donating to a different recipient.

Second donations of stem cells have not been shown to be associated with an increased risk of donor complications, but the yield of CD34+ cells may be lower in some donors. However, because there is a paucity of data regarding the outcome of multiple donations, the WMDA is not able at this time to recommend evidence-based stipulations and therefore broad guidance only can be given. The policies within individual registries may differ, and indeed there is a broad diversity in practice between registries. It is recommended that all registries have a structure to process and consider individual requests that fall outside of their policy (for example, medical director or review board). It is important to document such requests and the subsequent decisions.

Donors as research subjects

WMDA Standards

- Consent must be obtained if donor blood or other biological material or information is stored and/or used for the purpose of an ethically approved research project.
- Cells or DNA from donor and recipient should be preserved for research purposes by the registry if approved by national legislation in the countries of the patient and donor.

Context

The current practice of transplantation often includes treatment in the context of a clinical trial or components of the procedure that are intended to address research questions. This has led to the discussion about whether it is appropriate in all settings to ask volunteer donors to donate stem cells and whether they are research subjects if they become involved in such protocols. In the majority of transplant protocols involving a research question for the patient, the donor is not regarded as a research subject. However, it is important to avoid conflicts of interest between donor centers and TCs, thus a document addressing this issue, and outlining when the donor is or is not considered a research subject, has recently been produced by the WMDA. Furthermore, it is quite possible that in the near future, donor registries will receive requests for donors to donate stem cells or other tissues for applications other than hematopoietic disorders.

Donor follow-up

WMDA Standards

- The registry must have policies and procedures for the short-term follow-up and care of adult volunteer donors for conditions related to the hematopoietic stem cell donation. Short term is defined as within the first year following donation.
- The registry must have policies for the long-term follow-up and care of adult volunteer donors for conditions related to the hematopoietic stem cell donation. Long term is defined as the time period following the first year after donation and extending for at least 4 years.

Context[14–20]

Volunteer unrelated donors have been donating hemato- poietic stem cells since the late 1980s. In the early years, stem cells were harvested, usually under general anesthesia, from BM through punctures in the iliac crest. Complications of this procedure are rare, and follow-up was usually only short term (with the inference that 'short-term follow- up' is meant to ensure that the donor recovers in a reasonable time period from the actual donation). With the advent of administering hematopoietic growth factors (G-CSF) to volunteer unrelated donors and the harvesting of PBSC through apheresis, further discussions about the need for long-term follow-up ('late effects') were set in motion. Definitions of short-term and long-term follow-up have been a topic of discussion at recent international meetings. The number, frequency and method of donor contact following harvest differ among registries and the type of stem cell source donated.

The possibility of long-term effects from G-CSF (in family donors) was raised by two publications in 2004 and 2006. The WMDA addressed these concerns as a priority and a consensus statement regarding the safety of G-CSF was released. This was widely publicized through the WMDA website, international meeting sessions and peer-review publications. The WMDA guidance indicated that insufficient evidence of long-term effects to donors exists, and therefore halting the donation of G-CSF-mobilized PBSC from volunteer donors was not recommended. Ongoing basic research and clinical studies are being performed to further investigate any impact of G-CSF on the long-term health of donors.

Although serious adverse events (SAEs) (short and long- term) are currently collected within WMDA, there is no such registry system for family donors. During a donor outcome workshop in Berne (2009) (in collaboration with the European Society for Blood and Marrow Transplantation, EBMT) a minimal data set of follow-up information to be collected from all donors (family & unrelated) worldwide was agreed. A document describing the data set and providing recommendations for implementation is in preparation.

Patient follow-up

WMDA Standards

- The registry should collect data on the status of the patient post transplant.

Context[21]

A WMDA survey on patient follow-up practices has shown that registries collect data on transplant outcome for several reasons. Some registries collect data to inform the donor on the outcome of the transplant, if he/she so wishes. In this case, registry staff should be trained to counsel donors, in the event that the transplant has not succeeded. Other registries prefer not to inform the donor, and collect data for their own quality assurance system. A number of registries are collecting data for research and statistical analysis purposes. The frequency and duration of patient follow-up requests also differs among registries. With the yearly increase of transplantation activity, the number of follow-up requests is also growing. Collaboration with international organizations, such as the Center for International Blood and Marrow Transplant Research (CIBMTR)/EBMT/Asia Pacific Blood and Marrow Transplantation (APBMT) to exchange donor-recipient details, could reduce the workload for the TCs.

Adverse events following donation

WMDA Standards

- Donor health issues post-donation potentially affecting the health of a patient having received a hematopoietic stem cell donation from that donor must be reported to the TC.
- Adverse events affecting donors undergoing harvest of hematopoietic stem cells and occurring long term as a consequence of the donation must be defined, identified, documented, investigated and corrective action taken.
- SAEs occurring at the registry or at its associated entities must be brought to the attention of the WMDA in a timely manner.

Context[22–25]

Each registry has a responsibility to provide the best advice and to protect the health of the donor, as well as ensuring the integrity of the stem cell product (that is, the safety of the patient). To assist registries in this effort, the WMDA developed a voluntary system of reporting SAEs in 2001 (Figure 1). All registries who are members of the WMDA are encouraged to participate in the scheme. For a registry to achieve WMDA accreditation, participation is requested.

It is the responsibility of the chief medical officer (CMO), or equivalent, of each registry to report SAEs in a timely manner to the office of the WMDA. The office maintains the central database and informs the chair of the Clinical Working Group (CWG). It is the responsibility of the CWG chair to collate the SAEs and to report these back to the general membership at the annual meetings. The SAEs are also published in the WMDA annual report. Currently reports remain anonymous.

Two registers are in place:

- SEAR – Serious Events And Adverse Effects Registry. SAE reporting in the donor follows clinical trial definitions (that is, any event in the donor that leads to: life-threatening disease, death, in-patient hospitalization or considerable prolongation of existing hospitalization, persistent or significant disability/ incapacity and the association of the event with the donation are graded as definite, probable, possible and unlikely). Examples of such events are events related to anesthetic, cardiac, infective or hemostatic complications, mechanical injury and (late) malignancies.
- SPEAR – Serious Product Events and Adverse Effects Registry. This system highlights risks to the patient related to the product. Examples include impairment of the quality of the graft (for example, clots, damage to the bag,

loss of part of product), wrong product infused, severe infusion reactions, serious transportation problems, unpredicted transmissible infection risk (for example, Hepatitis B), unpredicted transmissible non-infection (for example, malignancy) risk. Damage to stem cells due to unsafe transportation is also an important consideration, and WMDA recommendations for couriers and transport arrangements are in place and should be followed.

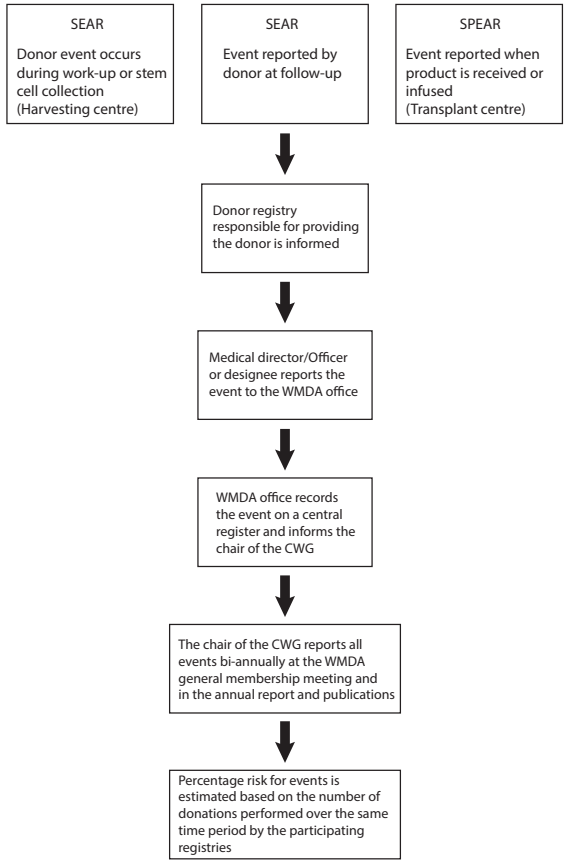

Figure 1: Mechanism for reporting serious adverse events to the WMDA (SEAR and SPEAR)

The WMDA is considering making reporting a mandatory requirement for all registries. In addition, consideration is being given to entering these events on an existing central register (for example, the ProMISe system of EBMT), although the legal and regulatory requirements in each country will have to be followed. A key consideration is ensuring that SAEs that occur in unrelated donors are communicated to physicians involved in the care of related donors. This is achieved through

collaboration with other societies, for example, EBMT, APBMT and CIBMTR. An unresolved issue exists around how to communicate information about the donor, which the TC may uncover, for example, a donor-derived malignancy or cytogenetic abnormality. Although many registries will inform the donor, currently there is no WMDA standard addressing this issue.

Collaborations

The Clinical and Ethics Working Groups have active collaboration with the following:

- European Group for Blood and Marrow Transplantation (EBMT)
- The donor subgroup of the Late Effect Working Party References (LEWP) of the EBMT
- Center for International Blood and Marrow Transplant Research (CIBMTR)
- Asia Pacific Blood and Marrow Transplantation (APBMT)
- Worldwide Group for Blood and Marrow Transplantation (WBMT)

Conclusions and future directions

One of the missions of the WMDA is to promote the interests of donors. This has been achieved by establishing a set of standards against which donor registries can be assessed. In addition to the standards, numerous publications of recommendations and guidelines for the safe and ethical use of volunteer unrelated donors have been published. These are continually being re-evaluated and revised in order to remain compliant with changing international legal and regulatory requirements. The WMDA works closely with other organizations in the field to attempt to standardize the recommendations. The interested reader is referred to the WMDA website for more information on the harmonization of international legal and regulatory requirements.

The WMDA addresses issues around donor safety that arise (for example, concerns around the long-term safety of G-CSF) and produces consensus statements based on the best available evidence and expertise. New standards are being developed which encompass these recommendations.

Today, the HSC field faces a number of challenges. As 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 need to be considered by other transplant organizations. The WMDA, however, has a responsibility to offer its experience and expertise in this area, and the Ethics Working Group and Clinical Working Group have recently produced a document addressing this issue. Likewise

the follow-up and reporting of adverse events in all donors has been addressed at a recent workshop in Bern. This was initiated through a subgroup of the LEWP of the EBMT and attended by representatives from a number of international organizations and registries concerned with donor care, inclusive of the WMDA.

Conflict of interest

The authors declare no conflict of interest.

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