Chapter ٣

ALLOGENEIC HEMATOPOIETIC STEM CELL DONATION: STANDARDIZED ASSESSMENT OF DONOR OUTCOME DATA. A WBMT CONSENSUS DOCUMENT

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Introduction

During recent decades, the number of allogeneic hematopoietic SCTs (HSCTs) has steadily increased by, up to, 10% annually on a global scale[1–3]. Furthermore, several new trends in transplantation have emerged: the introduction of reduced-intensity conditioning (RIC) regimens has led to an increase in the number of HSCT performed in older patients and those with comorbidities and G-CSF-mobilized PBSC have in part replaced BM as the main source of hematopoietic stem cells (HSC) in adult and pediatric patients.

These developments are accompanied by a parallel increase in the number of donors involved in transplantation and substantial changes in the donation process. The rapid expansion of the unrelated donor registries, with more than 19 million HLA typed unrelated donors worldwide, has allowed for an increase in unrelated HSCT activity, now surpassing the number of related donor transplants in some regions[1,3]. The median age of related donors has increased with the increasing age of the recipients, leading to potentially more donors with occult or manifest comorbidities at the time of donation. As a consequence of RIC, an increasing number of donors becomes involved in multiple donations of therapeutic cells. It is likely that this trend will continue for the next decade; it might even increase further with future progress in transplant regimens. Furthermore, if the use of stem cells for non-hematopoietic indications and/or organ repair is confirmed as a useful therapeutic tool, this may accelerate the demand for stem cell donations.

Since the beginning of HSCT, donor safety has been recognized by the community as an important issue[4–7]. Today, numerous donor outcome registries exist in different countries or in individual institutions but only the World Marrow Donor Association (WMDA) collects donor outcome data from unrelated donors on a global level. The serious events and adverse reactions (SEAR) and serious product events and adverse reactions (SPEAR) are collected centrally.

Very rare events may become apparent when the number of donations increases, but only if a large amount of the collected data can be analyzed. Such events may have detrimental effects on donation, if they become public without the benefit of coherent investigation and explanation by the scientific and transplant community.

Hence, the need for collection of donor data has been underlined by the recent release of the guiding principles on human cell, tissue and organ transplantation by the World Health Organization (WHO) in Resolution WHA63.22, endorsed in May 2010. Donor safety and follow-up are specifically expressed as principles with data collection and analysis as integral part of any therapy[8]. This need has not yet

Table 1: Differences between related and unrelated donor characteristics

	Unrelated donors[a]	**Related donors**
Age limit	Limited to adult donors 18-60 years	Unlimited 0-70 years
Number of donations allowed for same donor	Variable, but limited by registries PBSC: 1-2 BM: 1-2 Maximal: 1-4 donations, median 2 donations[48]	Unlimited, except for center-specific guidelines
Maximal dose of G-CSF per day	Usually 10-12µg/kg/d	Usually 10-12 µg/kg/d, doses up to 20 µg/kg/d possible
Maximum volume per donation (volume for apheresis or volume for BM collection)	Often limited depending on donor's body weight/blood volume	Unlimited
DLI	Number of donations variable from one to multiple (no limit)[48]	Unlimited, except for center-specific guidelines
New mobilizing agents	Used very conservatively, usually not recommended before first experiences have been collected in related donors	Used conservatively but may be used more liberally than in unrelated donors
Donor eligibility criteria	'Healthy donor'[21] most often very similar to the eligibility criteria for blood donors	Multiple co-morbidities might be accepted
Donor motivation	Altruistic/volunteer	Emotional relationship with the recipient or family. Mostly very willing, but some may donate because of familial obligation alone
Donor advocacy	Yes	Might be the same team as for the patient[49]

[a]*Limits might differ depending on individual donor registry's guidelines.*

been completely addressed yet by other regulatory bodies like FACT-JACIE (www.factwebsite.org, www.jacie.org).

Today, large registry studies in unrelated donors[9–11] form the basis for the current knowledge on the frequent side effects during BM and PBSC donation, which are

usually of mild or moderate severity. Smaller studies from related donors suggest that these frequent side effects occur with the same pattern in related donors[12–15].

Sporadic case reports and a recent large survey among transplant teams demonstrate that the donation procedure can be associated with a small but real risk for serious adverse events and reactions (SAE/R)[16–19]. Current experience suggests that risks seem to be higher for related than for unrelated donors with the caveat of reporting bias and lack of an adequate amount of prospective follow-up data in the related donor setting[9–11,18]. These rare SAE/R that occur with estimates of about 1 in 3–5000 for serious and 1 in 10–20000 for lethal events are still incompletely understood[9–11,16–19]. Hence, there is urgent need for better understanding of short-term SAR and to identify donors at risk. Because of the rarity of the events, progress can only be achieved by large international collaborations that include both unrelated and related donors. Despite the fact, that related and unrelated donors might differ for many basic characteristics (Table 1), the quality of adverse reactions associated with stem cell donation is not expected to be different between related and unrelated donors forming the rationale for a uniform donor follow-up for all types of donors.

Generally, donor eligibility criteria for related donors are less strict with only a few definite criteria[20] and may vary significantly between different centers. In contrast, eligibility criteria for unrelated donors are summarized by WMDA recommendations[21] resulting in somewhat more homogenous donor selection criteria. Together with the unequal basic characteristics, this may lead to differences in the incidence and/or severity of adverse events in related vs unrelated donors but large data sets to support this hypothesis have first to be set up.

The question of long-term effects of donation is even less understood. Despite an intensive discussion on hematological malignancies in donors after exposure to growth factors a few years ago, data to assess reliably long-term SAE are still lacking[22–25]. The fact that these issues have already been raised almost 15 years ago[5] underlines the ongoing urgent need to standardize short- and long-term donor follow-up.

Methods

The recently founded Worldwide Network for Blood and Marrow Transplantation (WBMT; www.wbmt.org), recognized the need for global cooperation in the field of HSCT and defined donor issues as one of its prime tasks. In August 2009, a workshop of an international group of representatives involved in related or unrelated HSC donation developed a consensus for such a donor follow-up on a global level, taking into account that resources for new tasks are limited in most teams. These collected

data should form the basis to address donor risks in public discussions to safely maintain allogeneic HSCT as an important treatment for many patients in need. Hence, two main topics were identified that should be addressed with priority:

- Prospective data collection should include all SAE/SAR during the donation procedure from all types of donors in the same way, that is, unrelated and related donors.
- Prospective data collection on potential long-term complications should focus on a minimum data set, that is, incidence and type of malignancies and autoimmune disorders only, and include all donors as above.

Results

Currently available data and experience have been reviewed in detail to form the rationale for this consensus. It has been observed, that most immediate or short-term SAR, related to the donation procedure, occur either before (during mobilization, induction of anesthesia) or within the first 30 days after donation. Hence, this time period needs to be analyzed carefully for all donation procedures. It follows the convention for a 30-day post-intervention period, which is currently established for other surgical and medical interventions. Beyond this point, follow-up and data collection will focus on a few potential late events. While they have been selected based on the biologic action of mobilizing agents currently in use, both PBSC and BM donors will be followed on long term. The reason to also follow BM donors is twofold: Some of them may get EPO and/or G-CSF before or after collection of therapeutic cells and BM donors who did not get any mobilizing drug may represent the best available control group for evaluating late effects in donors. Long-term follow-up will be more time consuming for centers. Therefore, we propose an approach that should be achievable with a minimum of resources.

For more specific questions, clinical studies are needed with a separate funding and predefined donor populations and follow-up.

Immediate/short-term SAR associated with the donation procedure:

SAR, in the context of HSC donation, have been described for both BM and PBSC donation[4,26], including rare fatal events, mainly of cardiac or cardiovascular origin[17–19,27]. Currently, it is suggested that related donors could be more frequently affected, because of less strict donor eligibility criteria in this group. SAR may occur during mobilization, before cell collection, during the collection or shortly thereafter. Most cases have been reported as case reports or by retrospective studies, hence causality is frequently not conclusive and relative risks cannot be estimated. Some of these SAR, such as thrombotic and cardiovascular events or splenic rupture, might

be explained by the biological effects of G-CSF that have recently been reviewed in detail[26,28] or are associated with an inherent risk of the collection procedure used (anesthesia, central venous catheter related complications, anticoagulation during apheresis, human error). Preexisting comorbidities of the donors are likely to have contributed to other SAR (for example, precipitation of sickle cell crisis or inflammatory diseases).

Late SAE/SAR associated with the donation procedure:

Late SAE/SAR are defined as SAE/SAR possibly related to the donation procedure with onset more than 30 days after completion of the donation. Chromosomal changes and changes in microarrays have been described after G-CSF stimulation raising concern on an increased long-term risk for hematological neoplasms[29,30]. These concerns have not been substantiated so far[31]. Chromosomal changes seem to be transient and do not affect CD34+ stem cells. Observational data from unrelated donor registries do not show an increased risk for secondary malignancies[32], but the number of donors followed is still limited, given the large number needed to detect an even considerable increased risk for hemato-oncological neoplasms[33,34]. Further- more, epidemiologic studies are required for comparison of neoplastic events observed in healthy stem cell donors and representative control populations. It is important to realize that G-CSF, PEG-G-CSF and CXCR-4 antagonists recruit different cell populations according to global gene and mRNA expression levels[34–36]. Finally, it is possible that biosimilars of G-CSF and EPO will also be applied in healthy donors although recent statements from the European Group for Blood and Marrow Transplantation (EBMT) and WMDA do not recommend it outside of the context of well set up safety studies. This emphasizes the need to include all current mobilizing agents as well as any new agents that will be introduced into clinical practice in the future in a prospective follow-up.

In related donors, an increased risk for hematological malignancies might be expected owing to the same genetic background as the patient and the known association between HLA and malignancies[37].

The degree of risk increase is difficult to estimate from available data. Epidemiological studies in families of patients with hematological neoplasms suggest that the risk to develop any malignancy is at least twice that of a normal population[38]. Some of these donor characteristics may also apply to unrelated donors. So far it is not known how many volunteers joined the unrelated donor registries because of close relationships with a patient (that is, being a relative or having had close contact during many years, which could also include a common exposure to carcinogenic agents) and it is obvious that motivation patterns might

differ between different countries depending on different recruitment strategies of individual registries. Another issue that complicates the interpretation of long-term donor follow-up data is the effect of medical clearance before donation: Donors may be healthier than a non-donating age- and gender-adjusted control group as they have passed the medical clearance on confirmatory typing and work-up level. Furthermore, very little is known about the 'lifestyle' or socioeconomic status of individuals who register as potential stem cell donors compared with the general population. Thus every comparison of donor malignancies with age- and gender-adjusted incidence ratios of the general population has to consider this potential bias. Currently, a prospective study is under way at the German Bone Marrow Donor Center (DKMS) that addresses this question by analyzing the incidence of potential late SAE in donors who donated compared with registered donors who were not asked yet to donate but underwent the same health checks simultaneously (AH Schmidt, DKMS, personal communication).

Short-term application of G-CSF changes lymphocyte subset populations and might lead to long-term immunological effects. New onset autoimmune disorders have been reported rarely[39,40], but a causal relationship with previous G-CSF exposure has not been confirmed.

Recommendations for a minimal donor follow-up:

Practical aspects for donor outcome follow-up are addressed below (Tables 2 and 3).

Definition of donation procedure: The donation procedure is defined as a procedure with the intent to collect an adequate number of therapeutic cells, that is, HSC, MSC, lymphocytes, natural killer cells or other cells. The donation procedure starts with the first injection of a mobilizing agent, the start of anesthesia or the start of apheresis (in cases of non-stimulated leukapheresis, for example, for DLI) and usually ends with one or multiple collections. However, the accomplishment of a collection is not required. Even if the preparative actions (that is, start of injections, apheresis or anesthesia) are stopped prematurely (because of donor or recipient reasons) the activity fulfils the definition of a donation procedure and the donor shall be registered and followed-up.

Data registries: It is proposed that recording of donor outcome data should become a part of the already well-established registries of member societies of WBMT (that is, Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), Asia Pacific Blood and Marrow Transplantation Group (APBMT), Center for International Blood and Marrow Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), Eastern Mediterranean Blood and Marrow Transplantation

Table 2: Minimal data set to be reported after the end of the donation procedure

Time interval covered: start of donation procedure until day 30 after completion of the procedure Time of report: between day 30 and day 100 after the donation procedure
Donor data
Donor ID[a]
Age at donation
Sex
Relationship to the recipient (twin / sibling / other family member / unrelated donor)
Collection data
Start date of the procedure
Was the product collection completed? (yes / no)
Number of collections / subsequent donations
Were hematopoietic growth factors used (for example, G-CSF)? (yes / no)[b]
Were cell binding inhibitors used (for example, plerixafor)? (yes / no)[b]
Was EPO used? (yes / no)[b]
Were othe drugs usedfor mobilization? (yes / no)
Product
BM (including collections of MSC)
PBSC
Both (BM and PBSC)
Unstimulated leukapheresis (for example, DLI)
Others
Complications in temporal association with the donation procedure
Report only serious adverse reactions (SAE/R) with International Classification of Diseases (ICD)10 coding (a list with a selection of the anticipated most frequent events is available in Supplementary Information[c]). Report every SAE/R occurring within the interval between start of the donation procedure and day 30 after end of the donation procedure

[a] There is no global unique donor identifier yet. Each center/registry defines the unique donor ID by its own identifier (in the future, the ongoing WBMT activity towards a unique transplant center and patient identifier may also include a unique donor identifier).

[b] Mobilizing agents may be used before either PBSC or BM collection and should be reported in any circumstances. Neither generic names nor information on dosage will be collected in this data set.

[c] Supplementary Information accompanies the paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)

Group (EMBMT), World Marrow Donor Association (WMDA)). Identical data sets will allow combining data for analysis from registries of different societies of WBMT. Societies and national registries are encouraged to reach agreements on how to organize data collection so that double reporting will be avoided.

Data collection: Data from the donation procedure and from long- term follow-up will be collected. Questions have been designed to be as simple and as few as possible, and are based on WHO toxicity criteria and International Classification of Diseases (ICD) code where appropriate, as these items are already implemented in routine use in many countries, well established and standardized.

For reporting, the current ICD-10 code should be used. The most recent version for coding including the possibility for online search can be accessed at www.who.int/classifications/icd/en/.

Table 3: Minimal data set to be reported for long-term follow-up

Time interval covered: up to 10 years after completion of the last donation process Time of report: minimal reporting after 1 year, 5 years, and 10 years but annual or biannual reporting is recommended
Donor survival status
Date of last follow-up or death
Donor alive? (yes / no)
If no, cause of death: ICD code
Malignancy
Hematologic malignancy? (yes / no / unknown)
If yes, certainty of the diagnosis: confirmed / unconfirmed by medical data
ICD code
Non-hematologic malignancy? (yes / no / unknown)
If yes, certainty of the diagnosis: confirmed / unconfirmed by medical data
ICD code
Autoimmune disease
Autoimmune disease? (yes / no / unknown) (a list with a selection of the anticipated most frequent events is available in the Supplementary Information)
If yes, certainty of the diagnosis: confirmed / unconfirmed by medical data
ICD code

Time of data reporting for procedure-related data including donor and collection procedure characteristics (Table 2): These data should be reported between day 30 and day 100 after the procedure is completed. The time interval covered is the period from the beginning of the donation procedure until day 30 after the completion of the procedure. It is important to note that more rapid initial reporting for SAR might be required by authorities or individual societies. Every new attempt to collect cells is regarded as a separate donation procedure with the focus on the donation procedure, not the type of cells collected, that is, a BM donor undergoing a donation procedure for BM-derived HSC or MSC should be registered and followed irrespective of the collected cell type. Many cells might be collected without a mobilization procedure. For example DLI donation may occur several times, either by whole blood donation or after repeated apheresis. Other examples may be natural killer cell or DC donations. Whatever the cell type is, the donation will be characterized as unstimulated leukapher- esis donation. The time schedule for follow-up is always determined by the last donation procedure. Contrary to voluntary unrelated donors, an upper limit for the frequency and the total number of therapeutic cell donations is frequently missing in related donors. Prolonged persistent lymphopenia has been described in donors after repeated collections[41], but information on the long-term follow-up are very scarce.

Practice of data reporting may be essentially the same as for patient data. Precise rules might be defined by the individual member societies of WBMT or legal authorities from individual countries.

Definition and reporting of SAR: Common adverse events are well known and will not be collected in this dataset (modifications of the current proposal might become necessary in the future for selected donor groups if new mobilizing agents become regularly used in healthy donors). Reports shall include adverse events defined by WHO toxicity grades 3 and 4[42] or SAR using essentially the same definition as WMDA: (1) death, (2) life-threatening events, (3) events requiring in-patient hospitalization or prolongation of existing hospitalization owing to WHO grade 3 or 4 toxicity and (4) events that result in significant disability/ incapacity[43].

In many countries, these events are also required to be reported to the regulatory authorities. It is evident that a causal relationship with the donation procedure will often be difficult to establish; therefore, all events occurring in temporal relationship to the donation procedure and fulfilling either of these definitions shall be reported.

Long-term outcome data – time of data reporting and items: Until otherwise required by national regulatory authorities minimal follow-up should be reported

after 1, 5 and 10 years but annual or biannual follow-up reports are encouraged.

Reporting will be limited to three items: survival, onset of malignancies and onset of autoimmune diseases. These are simple questions that can be asked by written or electronic mail, by internet-based survey or by phone.

In the case of a positive reply, the level of evidence should be indicated, that is if the diagnosis was confirmed by medical data (that is, a diagnostic procedure as a pathology report, serological confirmation in certain autoimmune diseases, diagnostic criteria, for example, American Rheumatism Association (ARA) criteria fulfilled in rheumatoid arthritis and so on). The exact diagnosis should again be coded according to the ICD.

Use of newsletters, short message services, new media and social network facilities may help to maintain contact with donors, decrease numbers of donors lost to follow-up and ensure adequate data capturing. Many initiatives are already in place in different countries. Hence, one aim will be to connect and combine the already ongoing efforts. Analysis of donor outcome data may follow the same rules as, for example, analysis for late effects in transplant recipients.

Conclusions

Thanks to ongoing progress in transplant techniques and supportive care, allogeneic HSCT can be offered as a curative treatment to a steadily increasing number of patients. Securing the willingness of donors to donate in the future is crucial for further development of treatments with allogeneic therapeutic cells. It is obvious that this willingness will heavily depend on the safety of current and future donation procedures. Many issues on donor safety have been addressed in the recent years by different groups. Side effects during HSC donation are frequent but only transient in the overwhelming majority of related and unrelated donors. However, serious adverse events do occur rarely in the context of BM and PBSC donation. A causal relationship is not always evident and the true incidence of these events remains unknown because of different definitions and observation intervals for SAE/R. Most data on donor safety are from unrelated donors who represent a positive selection among healthy individuals. Data on related donors are scarce[12–15,44–47] and only a few prospective trials or registration studies are underway (RDSafe study in the US (cf.: www.cibmtr.org), registries for related donors in Japan, Spain, Poland, Nordic donor registry and Switzerland). Certain donor populations may represent special risk groups, like children, elderly donors, haploidentical donors (when higher doses of mobilizing agents and/or larger volumes for cell collection by apheresis might be used in these donors), donors with multiple donations for HSC and/or other

therapeutic cells and need to be studied in more detail.

Theoretical concerns about long-term effects after donation have not been verified yet. However, reliable data based on prospective registration and follow-up of all kinds of donors are still lacking. Current data sets are too small, follow-up is too short and numbers of donors lost to follow-up remain a problem, approaching 50% even in well-conducted registry studies[11] and thus impair the robustness of the conclusions drawn.

Data collection and analysis of donor outcome have to become an integral part of HSCT, to define incidence and risk factors for SAE/R in short and long term to protect donors' health. The aim of a global standardized data collection is to allow us to define risks by large international combined registries.

Donor safety must be included in overall HSCT risk assessment. These issues also need to become part of accreditation standards. Reimbursement for donor outcome data registration must become part of the transplant coverage by insurance companies or national healthcare systems. Joint efforts led by WBMT in collaboration with its member societies are needed to achieve this goal. Additional private funding might become valuable, depend- ing on national properties.

Conflict of interest

The authors declare that they have no conflict of interest.

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