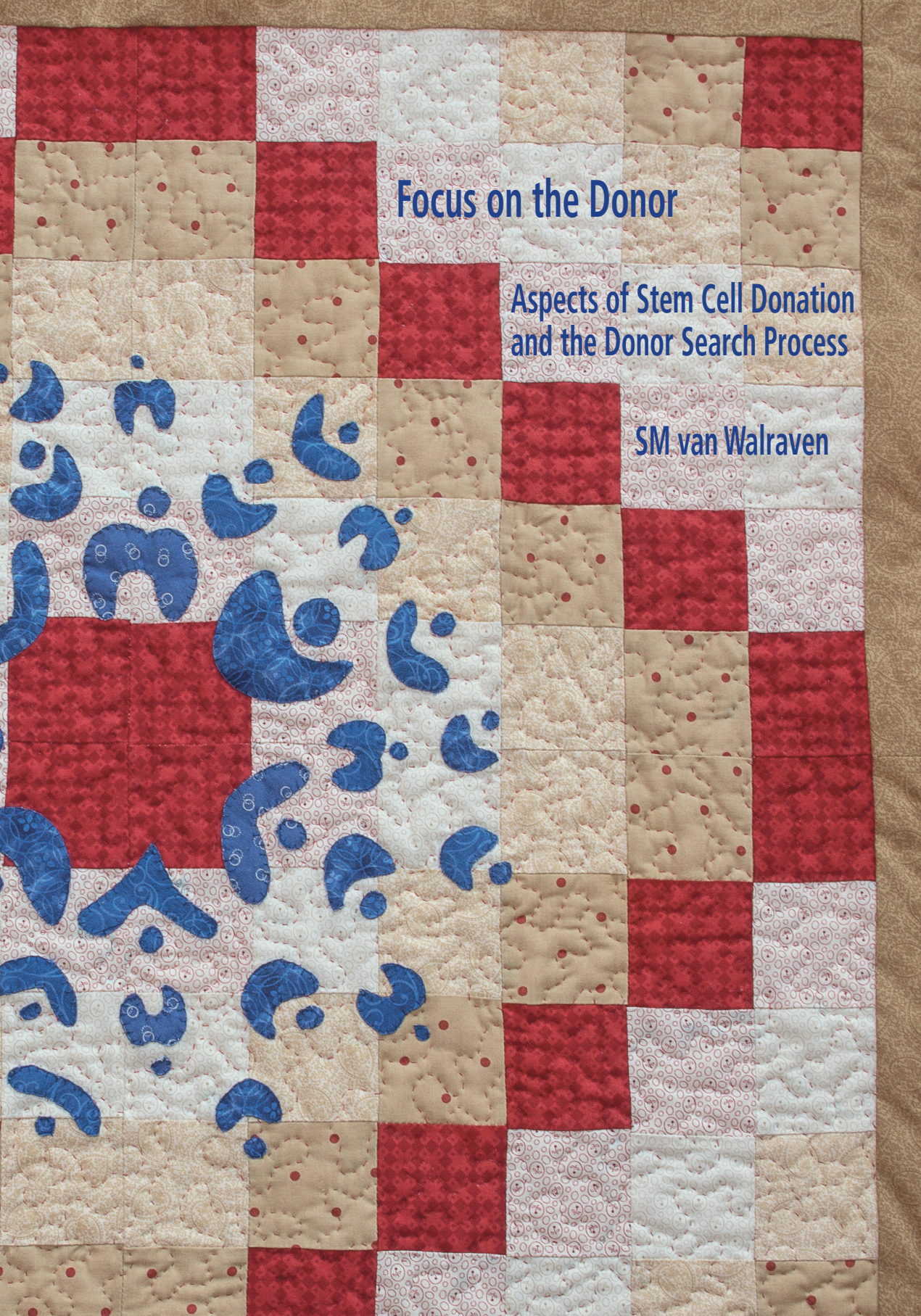

Focus on the Donor

Aspects of Stem Cell Donation and the Donor Search Process

SM van Walraven

STELLINGEN

1. The assumption that parents never refuse to donate is not a reason to use them as means to an end. (this thesis)
2. Not the size of the global donor inventory but the diversity and availability of donors are keys to success of hematopoietic stem cell transplantation. (this thesis)
3. Banking of high quality cord blood units is probably the best option to compensate for the lack of minority donors in the global inventory. (this thesis)
4. A global registry for any donor's serious events and adverse reactions is the only way to prove safety of stem cell donation. (this thesis)
5. Unrelated donor search is like top sport: the faster, the better. (this thesis)
6. Despite the fact that some humans can be legitimately sold such as soccer players, we disapprove of remuneration for the donation of tissues or organs.
7. Donor autonomy, in addition to donor safety, should be paramount. (Belinda R. Avalos, Biol Blood Marrow Transplant,2011;17:1739-1746)
8. Donor altruism as motivation to donate must not be confused with 'carte blanche'.
9. A donor registry is a means not a goal.
10. When you come away from quilting you are not in the same mood (Maggie, in Burt & Atkinson, Journal of Public Health Advance Access, 2011;1-6)

Focus on the donor: aspects of stem cell donation and the donor search process

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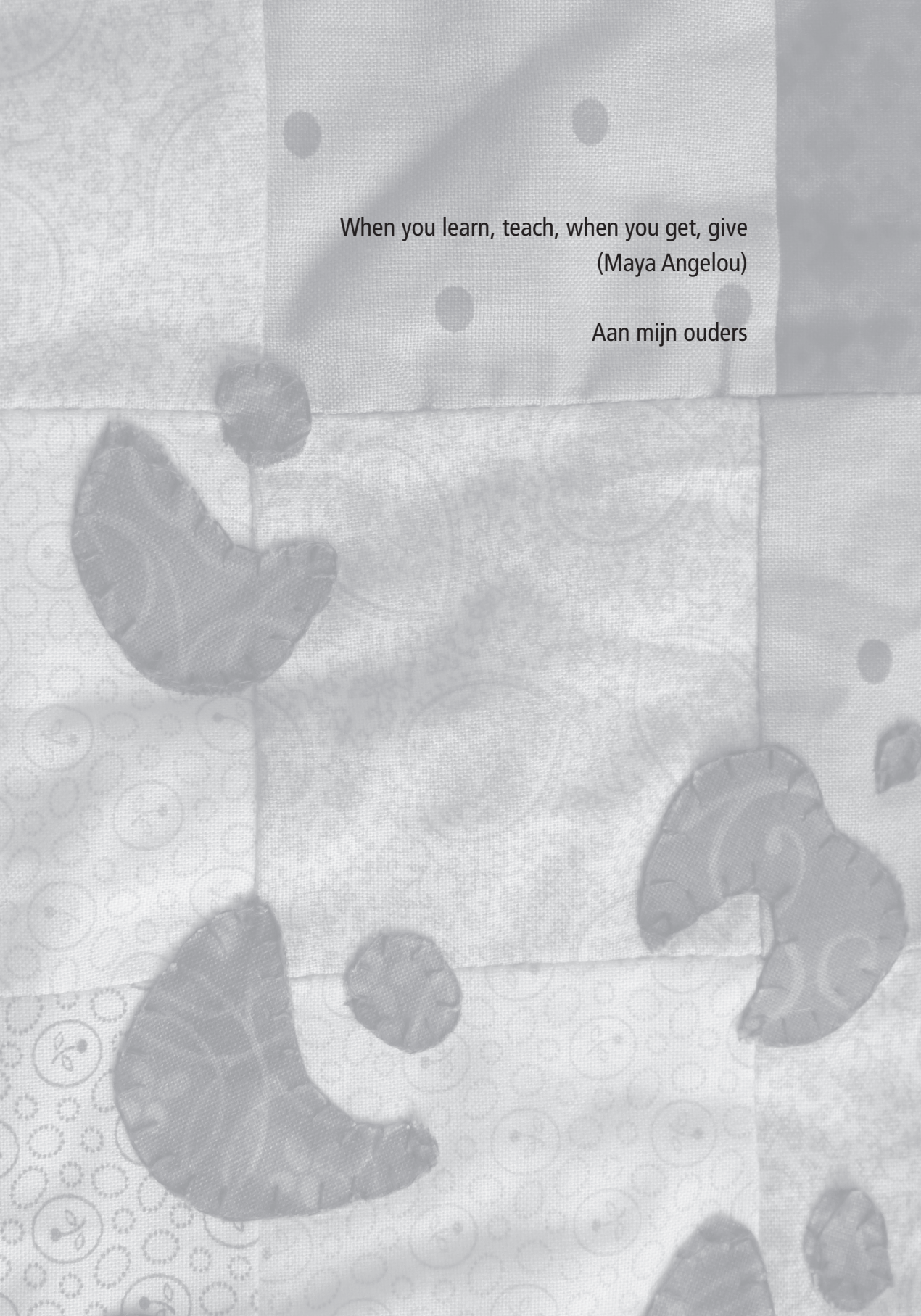
When you learn, teach, when you get, give
(Maya Angelou)

Aan mijn ouders



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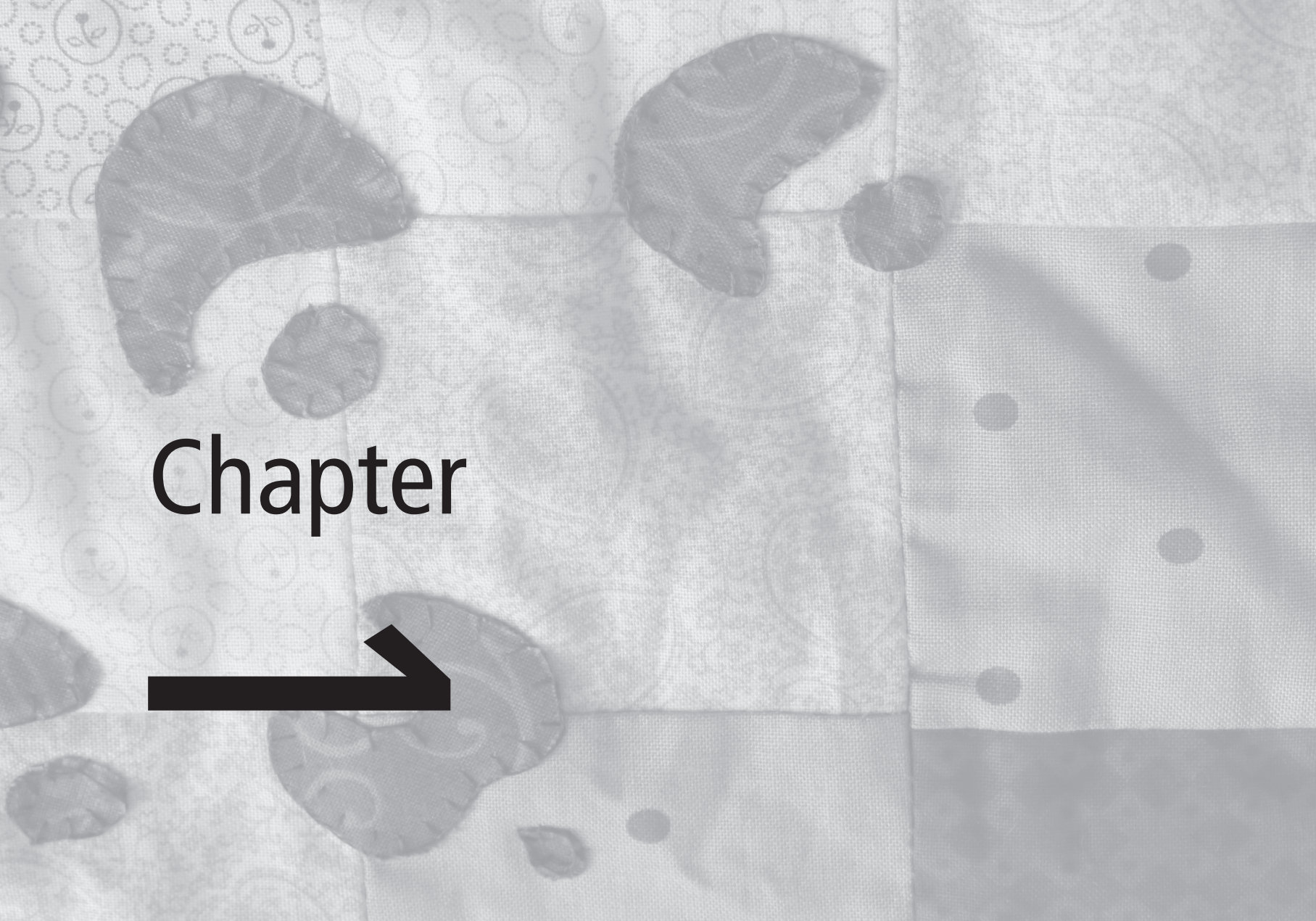
Chapter

GENERAL INTRODUCTION IN STEM CELL DONATION AND THE SEARCH FOR A STEM CELL DONOR

Tissue donation: giving rather than taking

The first attempt to use blood for transfusion purposes, with fatal results for both patient and donors involved, was described in the late 15th century, almost 50 years before the existence and working of the cardiovascular system became known[1]. The way this first donation/transfusion attempt was carried out – involving minor donors, remuneration, and lacking informed consent – is in contradiction with the modern philosophy of altruistic donation. In the 17th century in France, Denys performed transfusions using blood collected from sheep and calves with variable outcome. It would take until 1901 before Karl Landsteiner discovered the major ABO blood groups and until 1907 before transfusion of human blood became a reality. Sir Percy Oliver started a transfusion service in 1921 from his own home. The first official Blood Transfusion Service, consisting of a panel of 400 volunteers, was established over less than a century ago, in 1926 by the British Red Cross[2]. The first Dutch transfusion service was established 4 years later in Rotterdam following the model of Sir Percy Oliver. The use of blood and (other regenerative) tissues donated by related and unrelated volunteer donors has since then become indispensable for standard practice of health care. However, frequent transfusion reactions in these early days were a trigger for further investigation, which lead to an increasing knowledge about leukocyte antibodies and human leukocyte antigens (HLA)[3,4]. It was the start of a deeper understanding of the HLA system that would take another half century, and is still ongoing today. Although in the 1950's and 1960's attempts for transplantation of human bone marrow were undertaken, and after the first successful administration in 1964 of HLA compatible donor platelets[5], the importance of HLA in donor selection to treat thrombocytic patients became soon clear[6,7]. This knowledge was subsequently applied in the field of kidney transplantation, where retrospective studies showed that donations from HLA identical donors had far better clinical outcome than mismatched donors[8]. The first successful bone marrow (BM) transplantations from HLA identical sibling donors were undertaken in 1968 in both the United States of America (Seattle) and Europe (Leiden)[9,10], soon followed by studies where identical twins acted as donors[11,12]. Expanding knowledge of the HLA system has led to a

The first recorded attempt of a blood transfusion was described by the 15th-century chronicler Stefano Infessura. In 1492, Infessura noted that the blood of three boys was given to Pope Innocent VIII, who had fallen into a coma. Following orders from a physician, the blood was transferred to the pontiff through the mouth, as the concept of intravenous circulation had not yet been discovered. The three young blood donors, all ten years old, had undertaken this experiment after being promised a ducat each. Unfortunately, the Pope and all three boys died[1].

practice where not only phenotypically matched or partially mismatched family members can provide suitable stem cell transplants, but also volunteers are deemed appropriate for patients lacking an HLA identical sibling donor[13]. The use of donor derived stem cells for transplantation has now been commonly practiced for almost half a century, and is considered as a standard procedure for the treatment of defined haematological, immunological and metabolic disorders. Traditionally stem cells were harvested from BM through punctures in the sternum and posterior iliac crest[14]. Since 1994, recombinant human granulocyte colony stimulating factor (G-CSF) mobilized hematopoietic progenitor cells (HPC) collected from allogeneic healthy donors have been used as an alternative to BM harvesting[15]. In The Netherlands, G-CSF stimulated HPC collection has been performed in family donors since 1995. In 2004 the use of G-CSF in volunteer unrelated Dutch donors was approved by the ethical advisory panel of Sanquin, the Dutch national blood supply organisation, proving at that time most of the potential stem cell donors.

International collaboration for the provision of unrelated donor stem cells

Since only 30% of patients in need of hematopoietic stem cell transplantation (HSCT) have an HLA matched sibling donor, the obvious need for suitable alternative donors was soon recognized and addressed. In the late 1970s the first registries for unrelated donors were established. With the finding that stem cells from placental blood are able to sustain hematopoietic recovery, the first umbilical cord blood banks started inventories of cord blood units (CBU)[16]. International cooperation has resulted in the development of a continually increasing worldwide pool of unrelated donors and cord blood units, accessible through the participating registries of Bone Marrow Donors Worldwide[17]. One of the first attempts in electronic data interchange of donor and recipient information was the establishment of the European Donor Secretariat (EDS). The European Marrow Donor Information System (EMDIS), a European Union supported project to develop a protocol to exchange information between registries during the unrelated donor search, was initiated in 1992 and has since then replaced EDS. The evolution of the EMDIS protocol is a continuous effort with currently involvement of over 30 donor registries. With the development of EMDIS Cord the EMDIS community is intensifying the collaboration with cord blood banks, providing real time comprehensive CBU data to enhance the unrelated CBU search.

For the mainstream of patients, it is not only the number of available donors but the search time span that is the major influencing factor determining the chance of reaching transplantation[18-22]. A Dutch study reported almost one third of patients for whom a donor was identified never reach HSCT due to deterioration in the patients' health. This was most likely due to the length of the search process[23], usually defined as the time between diagnosis and transplantation, and not as the time to identify

an acceptable donor. For example, a prolonged time span between diagnosis and transplantation in patients of older age are found to reduce leukaemia free survival, and increase transplant related mortality[20]. The unrelated donor search is a dynamic process, sometimes complicated by unexpected factors. The deferral of a donor just prior to stem cell transplantation is most inconvenient and can consequently cause delay of the treatment process and in the worst case death of the patient. Anticipation of such situations, and identifying a back-up donor or cord blood unit in the initial donor search could save precious time and prevent distress. The expansion of the global donor inventory not only in quantity of donors but also in quantity of HLA phenotypes and quality of HLA typing, has increased the chance of finding an acceptable unrelated donor, although the advantage seems to be in particular for patients of north western European descent[23].

Donor care and safety: the importance of a standardized system

Despite overlapping aspects in the procedures of BM and PBSC collection, dynamics of care management for HPC family donors differ substantially from care for unrelated donors. The first reports of successful HSCT only indirectly mentioned the consequences of donation for the family donors involved. Despite the importance of their contribution, at that time donors seemed to be considered of minor interest and no attempts to document immediate effects or follow-up (FU) were reported. A possible explanation is that donors, as healthy volunteers, might be considered as non-patients by the medical staff, in contrast to the recipients who are the 'real patients'[24,25]. Over time, the importance of donor care management and donor insurance in case of unintended sequelae have become clear, although not initially for the family donors. Presently, still almost half of all stem cell transplantations worldwide are carried out with donors who are a relative of the recipient[26]. With the introduction of unrelated stem cells as a source for transplantation the first donor studies addressing the medical risks of stem cell donation were initiated[27-29].

Voluntary donation of haematopoietic progenitor cells requires as an imperative, that informed consent procedures be established for all stages of the donation process[30]. Informed consent is considered a fundamental principle, not primarily with the goal to explain medical terms and conditions in every detail, but to provide a donor with an overview of the risks or implications of the treatment for his personal health and well-being[31]. The decision to donate tissue or cells is to be made free of any coercion and in accordance with international legislation and regulations, but it also requires the implementation of a quality system to optimize and maintain a certain level of quality and safety for both the donor and the recipient[32,33]. The attitude towards a donor is important for a positive donation experience, and to prevent him/her of feeling unimportant or even neglected once the tissue is obtained[24,25]. Clinical practice and medical ethical considerations have dramatically improved over time.

However, findings from surveys in Europe and the United States indicate that the care for the family donor and in particular the informed consent procedure is still (more) often performed by medical staff members who are indirectly involved in the recipient's care rather than an independent physician, and as such introduce a potential conflict of interest[34,35].

Although research mainly focused on the unrelated donor, Confer & Stroncek[36] have suggested that the standard of acceptable risks for family donors should not be lower than that of unrelated donors, i.e. protecting the volunteer relative from undue risk is no less important than protecting the unrelated donor. The establishment of a (global) standardized system for family donor care comparable to unrelated volunteer donors is meant to protect and follow-up on donor's health, without limiting a donor's decision-making autonomy or freedom to choose. Consequently if there is an increased health risk for a family donor to donate, while a suitable unrelated donor is available, it can be discussed if, despite the unfavourable cost-benefit ratio, it is ethical to expose the family donor to donation. In daily practice however family donors, because of their relationship with the recipient, may be accepting a higher than medical deemed tolerable risk or even disregard their own health issues. A possible explanation for this behaviour is that for related donors the benefits are so much higher[37], that they are willing to accept higher potential risk. For example, age as donor exclusion criterion is strictly adhered to in the unrelated donor setting, in contrast to the family donors, where very young children and elderly donors are commonly used. In the Netherlands, the use of minor donors requires proxy consent by the parents or legal representatives and legal permission granted by an independent family judge of the local court, after a psychological assessment of the potential donor.

It is unclear whether, in case the suitability of a related donor is doubtful, the costs to perform an unrelated donor search and obtain products are a barrier in the decision making process to initiate the search for an unrelated donor. However, it was mentioned by Labopin et al. that initial HLA typing restricted to HSCT candidates after reaching first remission to reduce costs, introduces a potential delay in reaching transplantation[38].

Optimal care management for stem cell donors is now well described by regulatory authorities[39-41], but only recently explicitly addressing the needs for family donors. Regulation for unrelated donor care management started in 1994 with the international collaboration World Marrow Donor Association (WMDA). The WMDA is bringing together experts from all over the globe on all aspects of HPC donation, including clinical, legal, ethical and regulatory issues[42]. The WMDA standards are addressing all stages in the process of unrelated stem cell donation[41]. Changing international legal and regulatory requirements necessitates a continuous

process of revision and re-evaluation of the standards. Additional guidelines and recommendations for the safe and ethical use of stem cell donors are regularly published. The development of clinical protocols for additional treatment of relapse, viral reactivations, and immunotherapy, often require multiple donations of multiple stem cell products, demanding a prolonged donor commitment and the potential to affect the donor's health. This is once more a reason to address and review the role and follow-up of donors involved.

Follow-up

The need for and importance of long term follow-up of stem cell donors, related and unrelated, was first addressed with the introduction of G-CSF in healthy individuals[43]. The Ethics and Clinical Working Groups of the WMDA are committed to this area and have, utilising their experience and expertise, actively pursued major changes. Follow-up and reporting of adverse events in all donors, conform the WMDA Serious Events and Adverse Reactions registry, were addressed at workshops in Berne (2009), Leiden (2011) and Vienna (2013). The initiative is a joint effort of the WMDA and European Group for Blood and Marrow Transplantation (EBMT), acting as a subgroup of their Late Effects working party and attended by representatives from a number of international organizations and registries concerned with donor care. This resulted in the establishment of an EBMT Board Committee on Donor Follow-up in 2012; one of the goals of this committee is to set up a regular donor follow-up registry for all EBMT Transplant Centres (TCs) and review any new EBMT research protocols where stem cells of allogeneic donors are involved. In 2013 the EBMT introduced the possibility for systematically collecting adverse event and longer follow-up information for family donors as part of their regular data registry. Education of the EBMT TCs is planned to reach implementation of regular collection and registration of donor follow-up in the EBMT database, with the potential of data observation and analysis.

One of the obstacles in organizing related donor follow-up remains the financial aspect. In general, cost for HPC donation (including the treatment and care for the donor during the donation process) are paid for by the insurance company or health service providers of the recipient. In practice, since there is no further financial reimbursement from insurance companies, follow-up of the family donor ends after one year. This is in contrast to the follow-up of unrelated donors, who are advised and offered a regular follow-up until at least 10 years after donation[42]. The cost for unrelated donor (UD) follow-up is covered in the price of the product. To date, the financial cost of long term follow-up of family donors has not been explicitly addressed by pertinent legislative authorities and as such no regulations regarding this issue have been formulated, but initial coverage of FU in the donation costs seems to be the most effective way.

Regardless the major differences between family and volunteer donors, safeguarding of the donor should be a basic principle in any donor care management. Respect for a donors' health and safety, is the least that should be offered in exchange for their devotion, sacrifice or altruism. Without the availability and devotion of donors worldwide, the practice of HSCT would not have advanced and become as successful as it is today.

Extraordinary donations: parents and children as donors

It can be argued that family donors confronted with a very ill relative for whom they might be the only hope for survival, do not have a choice, and in fact relatives cannot be considered as voluntary donors[44-47]. The process of decision making has evolved over the years from paternalism (treatment decisions are solely made by the physician) to autonomy (the decision is made by the patient/donor or his representatives). However, current developments have lead to a situation of so called shared decision making: the decision as a result of collaborative approach between the physician (expertise) and the patient's and/or his representatives (perspectives)[48]. Society might expect parents to sacrifice everything for their child, but do not offer support in the decision making process, where it is often felt there is no choice[49]. External expectations (e.g. expressions by relatives or social desirability) might influence a free of bias decision and cause coercion. Similarly parents of minor donors may be unable to make a rational decision if they give proxy consent for one of their healthy children to act as a stem cell donor for their other seriously ill child. In this light, the earlier mentioned assumption that family donors are naturally motivated to donate, might be a fallacy, since they are, often in a state of shock with limited time, forced to make a choice[50]. Within the donor population, family donors, in particular parents and minors, form a special group, and as such they are more vulnerable than healthy individuals, as they can either be desperate to take all risks or feels in the social context of the family circle obliged to donate. It is therefore the ethical and moral duty of the medical professionals to protect family donors and help them make a fully informed conscious decision.

BM donation by young children for the benefit of their sibling in need of stem cell transplantation has been practiced for over 40 years. BM donation in early childhood is rare, and as such, literature on immediate effects and long-term outcome is scant. It is perhaps characteristic for the time, but when asked in 1998, the 37 year old woman, who was the first child donor in Europe (in 1968) to recall her experiences, she only remembered 'that is was cold, I was sitting in a big bed and wanted to go home' (personal communication, Symposium on the Occasion of 10 Year Europdonor).

Although BM donation in childhood is legally accepted, guidelines for paediatric donor care have been lacking for a long period[51]. The publication of the Committee

on Bioethics of the American Academy of Pediatrics (AAP) is the first step towards the development of guidelines for the clinical practice and management of pediatric donors. The AAP also emphasized the importance of research in both child donors and their recipients as well as the collection of long term follow-up data to gain insight in the effects of the use of hematopoietic growth factors in healthy children from countries where this is allowed[52]. Published studies concerning child HPC donors are restricted to investigations of immediate and sometimes long term side-effects of the use of hematopoietic growth factors[53-58] and psychosocial effects in a limited number of children[59,60].

Parents can act as a source of stem cells for a selected group of children in need of stem cell transplantation who lack an HLA compatible donor. This form of transplant has recently become more widely used, although the transplant related mortality rate is higher than in transplantations with HLA identical donors[61-63]. New technological developments have led to more encouraging clinical results in haploidentical transplantation[64]. Experiences of parents fulfilling a dual role as caregiver and stem cell donor, and their long term follow-up, are however scarcely reported. As, for every HPC donor, a reasonable balance between donor commitment and risks, and patient's needs is required[65].

Donor Remuneration

The voluntary nature of blood donation was one of the main principles for Sir Percy Oliver, when he started the blood transfusion service in the United Kingdom. Subsequently also donation of stem cells or tissue for the well being of an unknown person, are considered acts of altruistic behaviour[27-29,45,66,67], and thus performed voluntarily, without expectation of receiving any type of reward. With the founding of the WMDA the unpaid nature of donation, was included as a cardinal principle[68]. Currently donors of HPC do not receive any reimbursement beyond other than out of pocket expenses. This policy is stated in Transplantation Acts and subscribed by the World Health Organisation. The A lawsuit filed against the National Organ Transplantation Act in 2009 in the USA, challenging prohibition against remuneration of volunteer HPC donors, has re-opened the public debate[69]. Advocates and opponents of donor remuneration, not only in the United States, but internationally in the professional field of transplantation, have watched this case closely. The decision of the Ninth Circuit Court of Appeals in December 2011, that peripheral blood stem cells, but not bone marrow donors, may be paid for the donation, has surprised the HSC transplant community. It is the opinion of the WMDA that any change to the current laws around donor remuneration would have serious repercussions for both patient and donor health. In addition, the international exchange of products, which is absolutely critical in stem cell transplant where a 'unique' product is required, would be gravely threatened.

Conclusion

Allogeneic HSCT has become the standard of care for many otherwise incurable diseases. In this process, the availability and suitability of related and unrelated volunteer donors are indispensable factors and need to be treated as such. Possible improvements in HSCT are continually being investigated in an attempt to cure post transplant recurrence of cancer or refractory infections. The development of new treatment strategies, such as immunotherapy, often imply additional or subsequent donation requests from donors. As a result, not only a prolonged donor commitment is required but also the necessity to adjust long term donor care.

Outline of the thesis

Over the past decades various aspects in the dynamic field of family and unrelated donor selection and stem cell donation have not yet been settled. Stem cell sources have been expanded from bone marrow to the use of mobilized hematopoietic progenitor cells and stem cells harvested from umbilical cord blood. The immediate effects and long term follow-up of unrelated donors, in particular those exposed to growth factors have been structurally undertaken, as demanded by international regulation. However, for family donors long term follow-up studies are mainly performed in retrospect, and cohorts are often small. The lack of well-documented pre-donation conditions for donors demonstrates the need for stricter guidelines for care management of family donors. In this thesis various aspects of stem cell donation underscoring the need for change are described, and include the following studies:

- A qualitative study on the experience of parents who have donated stem cells to their child
- A long term follow-up study in children, who have donated bone marrow under the age of 13 years
- The immediate side effects and long term follow-up of the first Dutch cohort of family donors treated with G-CSF
- Donor availability between 2001 and 2012 for Northwest European (NWE) and non-NWE patients

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Part I

Donor Care Management


Chapter
২

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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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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Part II

Safety of Donation


Chapter
4

CLINICAL OUTCOMES AFTER PERIPHERAL BLOOD STEM CELL DONATION BY RELATED DONORS: A DUTCH SINGLE CENTER COHORT STUDY

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Background

Relatives donating peripheral blood stem cells (PBSCs) may be accepted for donation on less strict criteria than unrelated donors. We evaluated the occurrence of adverse events during procedure and follow-up, with a special focus on donors who would have been deferred as unrelated donors.

Study design and methods

All 268 related PBSC donors at our center (1996-2006) were included. Data were retrospectively collected from medical reports and standard follow-up. Health questionnaires were sent from 2007. Medical outcomes of donors, deferrable or eligible according to international criteria for unrelated donation, were compared.

Results

Forty donors (15%) would have been deferred for unrelated donation. Short-term adverse events occurred in 2% of procedures. Questionnaires were returned by 162 (60%) donors on average 7.5 years after donation, bringing total person-years of follow-up to 1278 (177 in deferrable donors). Nine malignancies and 14 cardiovascular events were reported. The incidence rate of cardiovascular events in eligible donors was 6.5 (95% confidence interval [CI], 2.5-12.3) per 1000 person-years compared to 44.9 (95% CI, 17.4-85.2) in deferrable donors; incidence rates of malignancies were 4.6 (1.4-9.6) and 24.0 (6.0-53.9) per 1000 person-years, respectively, in eligible and deferrable donors. All incidence rates were within the range of age- and sex-matched general population. No autoimmune disorders were reported.

Conclusion

In both the eligible and the deferrable related donors treated with granulocyte-colony- stimulating factor there are few short-term and long- term problems. The occurrence of post-PBSC cardiovascular events and malignant disease in related donors appears to be within the range of the general population.

Introduction

Recombinant human granulocyte-colony-stimulating factor (G-CSF) is increasingly used to mobilize peripheral blood stem cells (PBSCs) from healthy donors for allogeneic hematopoietic transplantation. In the Netherlands, PBSC collection has been performed in related donors since 1995. Counseling, collection, and formal follow-up evaluations of unrelated donors conducted since 2004 are performed in accordance with national policies that conform to the World Marrow Donor Association standards[1]. Although related donors are screened by independent physicians not involved in care of the patient, many of these donors are accepted for PBSC donation despite the presence of conditions for which they would be deferred if they were unrelated donors.

There is ample information about the short-term effects of the PBSC procedure in related and unrelated donors, indicating an acceptable safety profile in comparison to marrow donation under general anesthetic[2,3]. Nevertheless, some serious and potentially life-threatening complications have been described in allogeneic PBSC donation procedures, including splenic rupture[4,5], anaphylaxis, vasculitis, and acute lung injury[6]. Myocardial infarctions[7], thromboembolic events, sub-arachnoid hemorrhage, and cardiac arrests have been reported in at least 13 cases either during G-CSF mobilization or within 30 days after PBSC harvest[8,9]. Careful donor selection and observation might mitigate but not completely abolish these risks.

Potential long-term complications are, however, less well known. There are some reports suggesting that administration of G-CSF may enhance malignant transformation in patients[10-12]. Some have reported the occurrence of hematologic and solid malignancies in healthy donors after donation of G-CSF-mobilized PBSCs. Furthermore, there are concerns about the potential development or exacerbation of autoimmune or systemic inflammatory diseases[3,8].

These considerations regarding possible long-term effects have stimulated investigators to report on long-term follow-up of PBSC donors[13-15]. However, long-term data concerning this topic in related donors are relatively scarce. Leitner and colleagues[16] observed a cohort of 171 related donors; de la Rubia and coworkers[17] described findings from a voluntary national registry of donation and follow-up of predominantly related donors; Halter and colleagues[8] reported international survey data from the European Group for Blood and Marrow Transplantation concerning both related and unrelated donors. None of these investigators found an increased incidence of malignancies; all authors mentioned the higher age of related donors as a relevant issue and called for systematic long-term follow-up.

Here we report follow-up data concerning a Dutch cohort of related donors. Because of the apparent difference in acceptance of related donors in comparison to unrelated donors, we also separately analyzed the data on the individuals who would not have been accepted under international screening criteria for unrelated donors.

Materials and methods

Study population and PBSC procedure:

The study cohort consisted of all related donors who underwent G-CSF mobilization and PBSC harvesting at Leiden University Medical Center from May 1996 to May 2006; the recipients were all patients at the hospital's transplantation unit. The study was performed as part of a larger study that also comprised a prospectively enrolled group of donors and for which ethical approval was obtained from the hospital medical ethics committee.

Donor consent and medical clearance were performed by an independent physician. Subject to careful medical assessment, related donors could be accepted without upper age or body weight restrictions and sometimes in the presence of conditions which would constitute contraindications for unrelated stem cell donation. A short description of the procedures and reference criteria is given in Appendix S1, available as supporting information in the online version of this article.

Donors received 10 μg/kg G-CSF (filgrastim, Amgen, Inc., Thousand Oaks, CA) once daily. The white blood cell (WBC) count was checked on the fourth morning for dose adjustment (halving) to take place if there was an increase above 70 x 10^9/L. The fifth dose was administered at the end of the fourth day. PBSC apheresis (COBE Spectra, CaridianBCT, Lakewood, CO) was conducted on the fifth and, if necessary, sixth or subsequent day after an additional dose of G-CSF. If required, calcium was supplemented. Standard procedures allowed reinfusion of autologous platelets (PLTs) prepared from the stem cell product if there was a postapheresis PLT count below 50 x 10^9/L or if it was below 80 x 10^8/L and a second day of apheresis was needed. After completion of the procedure, follow-up visits were scheduled at both 1 month and 1 year after collection.

Data collection:

We extracted data from medical records and hospital information systems concerning predonation examination, donation, and follow-up visits. Furthermore, we evaluated findings of medical screening and noted cases of acceptance where the donor

would have been deferred under the criteria for unrelated donors. Mobilization and apheresis procedural data were extracted, including data on deviation from standard G-CSF schedule, use of a central venous catheter (CVC), the number of apheresis sessions, PBSC harvest, and reinfusion of autologous PLTs prepared from the stem cell product. We retrieved information on requested target stem cell dose and yield, as well as on second requests for hematopoietic stem cells and donor lymphocyte collections (donor lymphocyte infusion). Finally, we recorded serious adverse events (SAEs) during follow-up.

In November 2007 we sent all donors a standardized health questionnaire by post. It comprised 14 yes or no questions about medical diagnosis and treatment indicative of health problems since the donation; free-text explanation was to be added if there were any "yes" responses. If the information given was not clear, one of the investigators (JWO) contacted the donor by telephone or e-mail for clarification. When necessary medical details were requested from treating physicians with written consent from the donor. If the questionnaire was not returned, several attempts were made to check the address and find the donor. In January 2011 we accessed the hospital patient database to ascertain whether the recipient was alive or retrieve the date of death.

Definitions:

Donor eligibility status was retrospectively assessed according to the Assessment Tool at Workup from the National Marrow Donor Program (NMDP, 2009 version, Minneapolis, MN)[18], which was applied alongside general blood donation criteria. Broadly, unrelated donors must have no history of cardiovascular, diabetes, systemic autoimmune, eye, or thyroid disease; donation is permitted up to age 60 years and a body mass index (BMI) of 40 kg/m^2. Donors who would not have been eligible as unrelated donors are referred to as "deferrable donors".

All events requiring unscheduled medical examination or treatment from the start of mobilization until the 1-month follow-up were taken into consideration and categorized as procedure-related SAEs.

Follow-up period is defined as the period starting 1 month after start of G-CSF to the latest contact with the donor. Contacts from 30 up to 100 days were considered as early follow-up and contacts from 100 to 730 days as late follow-up.

The study outcomes were as follows:

1. Any malignancy (basal cell carcinoma excluded).

2. Cardiovascular disease (CVD) after the procedure: a combined outcome of medically diagnosed fatal or nonfatal myocardial infarction, newly diagnosed coronary disease treated by medication or ischemic vascular disease, cardiac intervention or vascular intervention, cerebrovascular event, medically diagnosed transient ischemic attack for which treatment was instituted, or venous thromboembolism.
3. (Systemic) autoimmune disease of any type.

Statistical analyses:

Data for all donors are presented, with comment on completeness of information. Means, medians, and interquartile ranges (IQRs) were calculated as descriptive statistics. For each donor, the number of follow-up years was determined from the time of donation to the latest contact date. Annual disease-specific incidence rates were calculated as the number of events per 1000 person-years of follow-up, including all follow-up years until occurrence of the first event or until the latest contact date with donors without events. Confidence intervals (CIs) are given for the 95% level of statistical significance.

To compare incidence rates in our study group with those in the general population, age- and sex-specific incidence rates of CVD and for cancer within the Dutch general population were retrieved from the national statistics database (http://statline.cbs.nl/statweb/?LA=en) and from the national cancer registry (http://www.iknl.nl/). Using the number of follow-up years for male and female donors in each age band we calculated the numbers of cardiovascular events and malignancies which would be expected in the study population if they had the same rate as in the general population. The standardized morbidity ratio (SMR) was determined, the ratio of observed events to the number expected. (A SMR less than 1 means that there were fewer events in the study cohort than expected.) The SMR and 95% CI were calculated for the whole cohort and also separately for the deferrable versus eligible groups.

Results

Population characteristics:

The 268 related donors had a median age of 43 years (range, 14-70 years) at donation; the demographic charac- teristics of the cohort are shown in Table 1. Forty donors would have been deferred according to NMDP criteria; the reasons are summarized in Table 2. Apart from age over 60 years, BMI over 40 kg/m^2, and hypertension (>160/95 mmHg), medical contraindications were present in 10 donors: Factor V Leiden and/

or previous deep venous thrombosis (n=2), coronary atherosclerosis and medication or revascularization (n=2; stable), aortic valve stenosis (stable), Parkinson's disease, past treatment for breast cancer (more than 5 years previously), diabetes mellitus Type 1 or 2 (n=2), or low concentration monoclonal (M) protein.

Table 1: Donor characteristics and medical history*

Donor characteristics	All donors (n=268)	Deferrable (n=40)
Female	115 (43)	18 (45)
Age at donation (years)	42.8 (34.6-51.2)	60.4 (46.9-63.5)
BMI† (kg/m^2)	24 (22-28)	27 (24-30)

** Data are reported as number (%) or median (IQR)*
† BMI known for 242 donors

Table 2: Deferral reasons of 40 deferrable donors*

Deferral reasons	Number
BMI (> 40 kg/m2)	2
Hypertension (> 160/95 mmHg)	13
Other medical conditions	10
Age > 60 years	21

** More than one reason may apply*

All procedural data were complete for 262 donors. Data on both target and yield of CD34+ cells were available for 234 donors. A collection of PBSCs that was deemed adequate was achieved in all but three donors (1.1%; one female and two male donors deferrable for age over 60 years).

The collection was completed in one session in 176 donors (66%): 76% for male and 52% for female donors. Most of the remaining donors underwent 2 days of apheresis; more than two sessions were needed in five (three males). A CVC was used in 22 of 268 (8%, 16 females). Four females out of these 22 donors were deferrable (two for hypertension, one for age >60 years, and one for both BMI > 40 kg/m^2 and hypertension).

Follow-up visits are recorded for 230 donors (86%): 207 (77%) for early follow-up within 100 days and 156 (58%) for late follow-up approximately 1 year after collection, some because of subsequent donations. There was no correlation between this follow-up attendance and survival of the recipient in the first 6 months after transplantation. A total of 122 donors made subsequent donations: 113 donated

lymphocytes (donor lymphocyte infusion) on one or more occasions, seven donors underwent a second PBSC collection, one donor donated granulocytes, and one donor donated marrow because of inadequate PBSC yield. The interval for subsequent donations was on average 329 days (IQR, 170-398 days; median, 248 days).

Procedure-related and short-term events:

G-CSF led to changes in hematologic variables as expected. Eighty donors (30%) received autologous PLTs (60 donors once and 20 donors twice or more) separated from the PBSC product. No transfusion reactions to PLTs or serious biochemical changes were recorded. All of the mild elevations of LDH and bilirubin normalized within 6 weeks of harvest.

Table 3: Procedure-related SAEs

SAEs	Sex (M/F), age (years)	Deferral reason (if present)
Excessive tiredness, one night hospitalization after PBSC	M, 32	Hypertension
Chest pain; no explanation	F, 34	
Inpatient opiate pain control; G-CSF stopped on Day 3 with WBC count of 59.7 x 10^9/L	M, 39	
Inguinal venous thrombosis after CVC	F, 45	
Persistent pain symptoms at injection site	F, 24	
Potentially serious dose incidents		
Received incorrect G-CSF dose; no excessive increase in WBC count	F, 36	Previous DVT
No dose reduction on Day 3 (WBC count was 80 x 10^9/L); precollection WBC count of 107 x 10^9/L	F, 55	Previous DVT

DVT = deep vein thrombosis

Table 3 shows the SAEs, one of which was related to the use of a CVC. In all, five donors (2%) required unscheduled medical attention and/or hospitalization during the period of G-CSF administration or harvest or during the direct follow-up period. We found no correlation between donor's eligibility status and the occurrence of short-term procedure-related SAEs. The table also details two potentially serious dosing incidents. A total of eight donors (3%) reported excessive tiredness in relation to the procedure, which lasted for longer than 1 week, persisting until 6 weeks post-donation in three cases.

Follow-up:

Figure 1 summarizes the response to the follow-up questionnaire. Of the 268 donors, 162 returned questionnaires giving a response rate of 60%. Responders were more likely to be female and older; there was no difference in proportion of responding donors according to death or survival of the recipient.

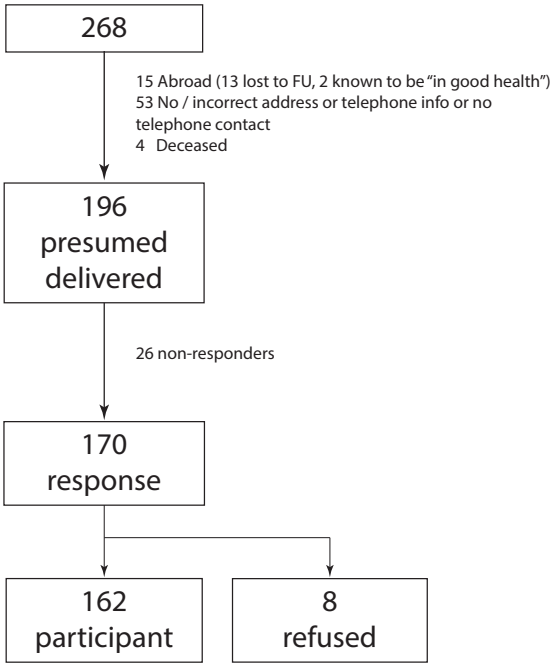

Figure 1: Responses to the follow-up (FU) health questionnaire

The total number of donor follow-up years was 1278. The median follow-up was 4.5 years (range, 0-13.6 years; IQR, 0.6-8.4 years). No autoimmune disorders had been diagnosed during the follow-up period. Table 4 shows the reported long-term morbidity and follow-up outcomes together with the eligibility status of the donors. Fourteen (new) cardiovascular events had occurred and nine malignancies were diagnosed (excluding two donors who had been treated for basal cell carcinoma). In all, four donors are known to have died: one of a cardiovascular event and two from lung cancer while a fourth donor is known to have died but the cause is unknown. Four donors had a new diagnosis of Type 2 diabetes and two, previously controlled on diet alone, had started taking oral antidiabetic agents; one of these six donors was in the deferrable group (for age >60 years). A donor who had suffered from persistent pain at the G-CSF injection site continued to be affected by fibromyalgia-like symptoms over 5 years after donation. The donor who had a femoral venous

thrombosis still suffered from functional impairment in the leg and inability to work despite adequate anticoagulant treatment and resolution of the thrombus.

Table 4: Follow-up findings in donors

Sex (M/F), age (years) at donation	Interval (year)	Problem during follow-up	Deferral reason (if present)
F, 45 and 24		Persistent symptoms after procedure	
Cardiovascular total n = 14; interval median, 3.5 years (range, 6 weeks-10.5 years)			
F, 70	5.8	Pacemaker implantation	Age
M, 37	3.2	Dissecting aneurysm*	
M, 42	4.9	TIA	
M, 44	2.4	Myocardial infarction	Hypertension
M, 45	6.8	Myocardial infarction	Hypertension
M, 47	0.6	DVT	
M, 50	3.8	Peripheral vascular disease	Other
M, 52	3.7	Myocardial infarction	
M, 54	1.4	Angina pectoris diagnosed	
M, 55	4.9	Myocardial infarction	Hypertension
M, 57	1.5	Coronary revascularization	
M, 58	0.5	Vascular dementia	
M, 60	10.5	Cardioversion for atrial fibrillation	Age
M, 62	0.2	Myocardial infarction	Hypertension
Malignancies total n = 9; interval median, 4.2 years (range, 3.0-10.1 years)			
F, 16	4.1	Hodgkin's lymphoma	
F, 46	4.2	Breast cancer	
F, 51	7.6	Bowel cancer	
F, 52	7.5	Lung cancer*	
F, 55	8.6	Breast carcinoma in situ	
F, 70	3.9	Breast cancer	Age
M, 44	10.1	Glioblastoma	Hypertension
M, 60	3.1	Rectal cancer	Age
M, 66	3.0	Lung cancer*	Age

** Deceased; in addition a female donor in the eligible group, aged 56 at donation, is known to have died but the date and cause are unknown*
DVT = deep vein thrombosis; TIA = transient ischemic attack

Table 5 shows the incidence rates of cardiovascular events and of malignancies in the study cohort and age- and sex-adjusted rates in the general population. The incidence rate of cardiovascular events in deferrable donors was 44.9 per 1000 person-years (95% CI, 17.4-85.2 per 1000 person-years) in comparison to 6.5 per 1000 person-years (95% CI, 2.5-12.3 per 1000 person-years) in eligible donors. The rates of cardiovascular events and malignancy in deferrable donors were in the range of the expected rates on the basis of age- and sex-specific rates in the general population; that of cardiovascular events in eligible donors was 0.6 times that of the general population (95% CI, 0.2-1.1).

Table 5: Incidence rates (IRs) of cardiovascular events and malignancies in study cohort and comparison to general population rates

				Comparison with Dutch general population	
Study population	**Events**	**Person-years at risk**	**Incidence rate* (95% CI)**	**Expected IR†**	**SMR (95% CI)**
CVD					
Eligible	7	1080	6.5 (2.5-12.3)	11.5†	0.6 (0.2-1.1)
Deferrable	7	156	44.9 (17.4-85.2)	33.3†	1.3 (0.5-2.6)
Malignancy					
Eligible	5	1086	4.6 (1.4-9.6)	3.9‡	1.2 (0.4-2.5)
Deferrable	4	167	24.0 (6.0-53.9)	10.2‡	2.4 (0.6-5.3)

** Per 1000 person-years*

† Expected rate per 1000 person-years on the basis of age- and sex-specific population figures: "Hospital admission for disease of heart orcirculation"

‡ Expected rate per 1000 person-years: incident cancer diagnoses

Discussion

In this cohort of related donors, 15% would have not been accepted according to international criteria for unrelated PBSC donation. The likelihood of procedure-related SAEs was similar in these deferrable donors compared to donors who would have qualified as unrelated volunteer donors. The overall incidence of 2% short-term procedure-related SAEs associated with mobilization and PBSC harvest is consistent with figures previously reported in larger series. For instance the Center for International Blood and Marrow Transplant Research and European Group for Blood and Marrow Transplantation reported 15 (1.1%) donation-related adverse events among 1337 allogeneic, mostly related PBSC donors, of which five were catheter-related[19].

The use of autologous PLT transfusions was imple- mented in our institution to comply with the guidelines, which do not allow stem cell apheresis if the preapheresis count is below 80 x 10^9/L and which require daily monitoring until recovery of PLT counts if the postapheresis count is below 50 x 10^9/L. The procedure and its effect for the donor as well as for the stem cell product have been validated in our center. No adverse transfusion effects were observed.

In our long-term follow-up, the incidence rate of cardiovascular events in deferrable donors was 45 events per 1000 person-years (95% CI, 17-85 events per 1000 person- years) in comparison to 6.5 per 1000 person-years in eligible donors. Rates of malignancy as well as cardiovascular events in both deferrable and eligible donors were in the range of age- and sex-adjusted population rates. The point estimate of the SMR for malignancy in the deferrable group was 2.4; however, the 95% CI is very wide and our data cannot exclude an increased incidence up to 5.3-fold.

A theoretical concern has always been that use of G-CSF might favor the development of malignancy which would only become apparent after several years' latency. The overall number of malignancies in our study was relatively high compared to other studies. Halter and coworkers[8] reported the survey of both related and unrelated donors by the European Group for Blood and Marrow Transplantation, which included almost 100,000 person-years of follow-up of more than 23,000 PBSC donors. A total of 12 hematologic malignancies occurred. While the rate of hematologic malignancy was higher in PBSC donors (1.2 vs 0.4 in 27,770 former marrow donors) this is probably explained by the higher age of related PBSC donors. Pulsipher and coworkers[15] reported on follow-up findings ranging from 2 days to 99 months, with a median of 49 months, on 2408 unrelated donors (9% older than 50 years at donation) for recipients within the NMDP program; there were 21 nonhematologic malignancies excluding basal cell carcinoma and one case of chronic lymphocytic leukemia. Concerning solid malignancies in former PBSC donors, Hölig and coworkers[14] reported on 3928 unrelated donors in whom a total of eight nonhematologic and four hematologic malignancies occurred. All investigators made comparisons with data for the general population and found no indication of any increase. Our cohort was approximately 9 years older than the donors reported on by Hölig and coworkers who had a median age of 34 years; in our group only two malignancies occurred in donors aged below 40 at the time of donation. Although our data give no reason for concern that there might be a relevant increase in rate of malignancy, our cohort is small with a limited follow-up. More person-years of follow-up would be needed to reject the possibility even of an implausibly high 10-fold increase in rate of malignancies[20].

The occurrence of autoimmune disease has less frequently been evaluated[16,21]. So far, no investigators have found any indication of an increase of autoimmune conditions. Even if we consider a worsening of existent Type 2 diabetes mellitus as a possible effect of G-CSF, the six cases of new or worsened Type 2 diabetes in our cohort are not in excess of what would be expected.

Our study benefits from the fact that it describes results from a single center using uniform standard procedures; however, the relatively small group of donors remains a limitation. Its retrospective design, in particular the impossibility to trace a large number of donors, is a further limitation. This leads to missing data and a risk of ascertainment bias. The SMR is calculated using age- and sex-specific population rates and the numbers of follow-up years in females and males in each 5-year age band. Hence the result is fully adjusted for the fact that responders tended to be female and older. However, any conclusions are based on the assumption that responders and nonresponders do not differ in their rate of the studied outcomes. In the observational setting the validity of this assumption cannot be tested. The difficulty of follow-up of related donors beyond a year after G-CSF exposure is encountered by other investigators[16,22,23]. In the Netherlands, the standard schedule ends after the 1-year attendance because the recipient's health insurance only reimburses such follow-up to 1 year after donation. In our study this lack of routine follow-up was addressed by postal health questionnaires. However, nearly one-fifth of donors could not be traced and the overall response of 60% is suboptimal.

A strength of the study is that it additionally captured data on CVD in the years after participation in the PBSC procedure. The incidence of late vascular events beyond 4 weeks has to our knowledge never been systematically recorded. The comparison with population data gives no indication of any excess morbidity. However, donors should normally constitute a lower-risk population, which is reflected in the incidence of CVD in the eligible group.

Importantly, the incidence rate of approximately 45 per 1000 person-years in the deferrable donors suggests that the safety margins in this group are smaller. Vascular disease is an important reason for deferring donors in view of the short-term risk of thrombotic complications. The survey by Halter and coworkers[8] describes clustering of cardiovascular events in the first weeks after the proce- dure. This was not seen in our study population although three cardiovascular events occurred in the 7 months after the procedure.

Raised and/or drug-controlled blood pressure and age were the most frequent reasons for which the related donors would not have been eligible for unrelated

donation. Candidate-related donors, most of them being siblings of cancer patients, tend to be older than unrelated donors and age in itself brings increased risks of CVD. In our center the donor assessment is performed by a physician who is not involved with the treatment of the patient. While this prevents any conflict of loyalties and minimizes risk, it is not a strict policy to rigidly defer all donors with one or more characteristics, including age, that would have led to deferral of an unrelated donor. Our data are consistent with other observations and show that if screening is performed as for unrelated donation, a population at lower (cardiovascular) risk will be selected. We also found that related donors who do not meet acceptance criteria for unrelated donors have a higher incidence of cardiovascular events, indicating smaller safety margins. Therefore, these criteria – including age – should in our opinion also be taken into consideration in the assessment of related donors. If a family member presents factors that would lead to deferral for unrelated donation because of potential higher risk of the procedure, it should not be assumed these risks may be accepted even if the donor is willing to proceed for the sake of a family member.

Overall our results show acceptable risks of the use of G-CSF in these related donors concerning most important side effects. The long-term occurrence of CVD and of malignancy for both eligible and deferrable donors falls within the range reported for the population. However, the small size of the study means that the CIs are wide. There is insufficient information to conclude that there are no relevant long-term increases of cardiovascular or malignant disease. Late medical events will not be systematically captured unless active follow-up extends beyond the first year, not only for unrelated but also for related donors. We therefore strongly support efforts by the international transplantation community to ensure long-term follow-up for unrelated donors and related donors as well[22,23].

In conclusion, this study gives no indication of long-term increased risks of CVD or of malignancies in related donors who have undergone G-CSF mobilization and PBSC apheresis, but cannot exclude this either because of the small size of the cohort.

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Conflict of interest

The authors declare no conflicts of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Related donor selection procedures at Leiden University Medical Center, 1996-2006.

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.

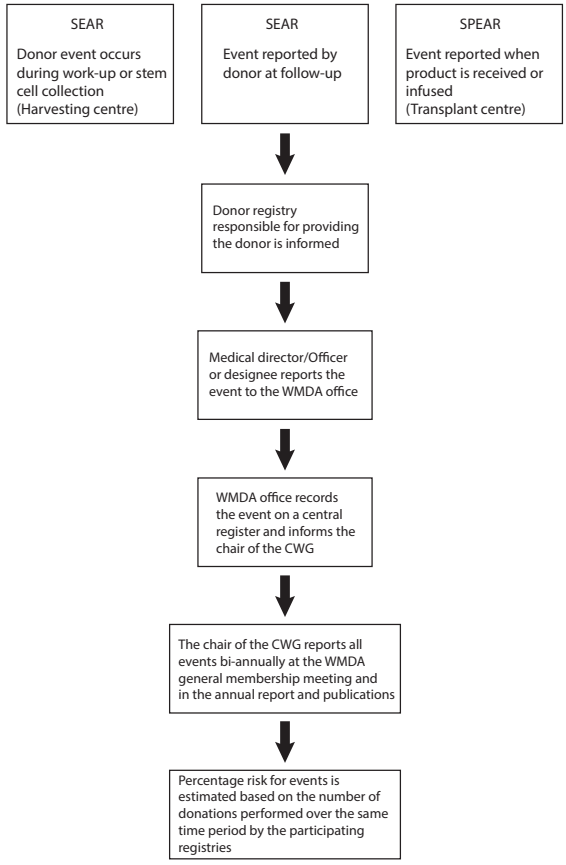

Figure 1: Mechanism for reporting serious adverse events to the WMDA (SEAR and SPEAR)

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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Part III

Special Considerations in Donations During Childhood and Parenthood

Chapter

MANAGING A DUAL ROLE – EXPERIENCES AND COPING STRATEGIES OF PARENTS DONATING HAPLOIDENTICAL G-CSF MOBILIZED PERIPHERAL BLOOD STEM CELLS TO THEIR CHILDREN

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Abstract

Hematopoietic stem cell transplantation is an effective therapy for life-threatening hematological diseases. Parents may be asked to donate hematopoietic stem cells for their child when no compatible related or unrelated donor is available.

Objective: Parents donating G-CSF mobilized peripheral blood stem cells simultaneously and uniquely fulfill the dual role of donor and caregiver for their ill child. The experiences of both sibling and unrelated stem cell donors have been extensively reported but not those of parental donors.

Methods: We therefore undertook a study specifically to investigate the experiences and coping strategies of parental stem cell donors. In-depth qualitative interviews were conducted with 13 parental donors, which were subsequently transcribed and subjected to thematic analysis. In addition, parental coping was assessed utilizing the Utrecht Coping List.

Results: Qualitative analyses revealed four main thematic categories describing the way parental stem cell donation was experienced, namely 'Hope and Fear', 'Need for Information', 'Do Anything for your Child' and 'Transplant Outcome' In addition parents noted similar difficulties which were unrelated to their specific role as a donor, for example they felt socially isolated.

Conclusions: Individual information for the parents needs to address not only the transplantation procedure but particularly those aspects related to the donation process. We feel there is a need for a protocol specifically designed to support and coach parental donors.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a proven treatment for selected children suffering from malignant and non-malignant life- threatening diseases[1]. Since the first bone marrow transplantations were performed, several methods of HSCT have evolved. At present, hematopoietic stem cells are obtained from bone marrow, peripheral blood or umbilical cord blood of a healthy donor. Donors are matched for human leukocyte antigen (HLA) type, and may be family members or unrelated volunteers[2]. The source of hematopoietic stem cells depends on the patient's disease and the availability of a donor.

The most important factor affecting the outcome of HSCT is the degree of the HLA match between donor and recipient[1,3]. A sibling with the same inherited HLA is considered the best donor, but is found in only 30% of all patients requiring HSCT[4]. For patients without a family donor, an unrelated donor might be optional. Currently, the HLA characteristics of 14.6 million donors are registered in Bone Marrow Donors Worldwide (www.bmdw.org). Despite this, a significant number of children requiring urgent HSCT will be left without an HLA matched donor. For these children, haploidentical HSCT is a feasible alternative. Haploidentical HSCT is a procedure utilizing stem cells from a donor who is one full HLA haplotype mismatched with the patient. In a pediatric setting, stem cells are commonly obtained from a parent, undergoing G-CSF administration to mobilize peripheral blood stem cells, which are then collected by a leukaepheresis procedure. Although technical advances have improved outcome[1], haploidentical transplantation has a higher risk for transplant-related complications and mortality[5-7]. A delay in immune recovery leads to vulnerability to viral reactivations post transplant[8]. Despite these potential disadvantages, haploidentical transplantation is, in specific cases, the only chance for cure for patients without an acceptable fully matched donor.

Parents requested to donate stem cells for their own child may feel that they have no alternative but to agree. This perception of limited options raises questions about the degree to which parents may feel pressured or even compelled to donate. Taylor[9] concluded that a parent has to fulfill dual roles, the role of parent and caregiver of a seriously ill child and that of stem cell donor. Conflict of interest in the decision-making process seems to be implied, but parents' perception of donating stem cells can be equally considered as an extension of parental care.

Although an individual child's chance of a cure with HSCT may be considered poor, parents tend to believe that their child will survive[10]. Despite this optimism, Oppenheim *et al.*[11] found that the main source of parents' distress was the fear of the child's death, whether imminent or at a later stage. Experiences of stem cell donors, both related and unrelated, have been extensively investigated[12-16]. Although levels of parental distress prior to HSCT have been shown to be temporary and unrelated

to the type of transplant[17-19], the distress in haploidentical parent donors has not been specifically studied. This seems an area of particular concern as these donors are likely to be more vulnerable, given the fact that their child is seriously ill and they have a vested interest in protecting and caring for their child.

Table 1: Demographic characteristics of parents (donors) and children (recipients)

	Study participant	**Study non-participant**
Parent characteristics		
Age at donation in years (median; range)		
Mothers	38.4 (33.6–47.7)	40.4 (34.3–42.7)
Fathers	38.2 (28.9–44.5)	38 (32.8–56.1)
Gender		
Female	6	3
Male	7	5
Marital status		
At donation		
Married	13	6
Separated	0	2
At follow-up		
Married	12	6
Separated	1	2
Ethnicity		
Dutch	10	4
Non-Dutch	3	3
Time from donation to study in yrs (median; range)	2.7 (0.4–5.0)	3.6 (0.3–5.8)
Child characteristics		
Age at transplant in years (median; range)	8.7 (1.1–13.8)	8.9 (4.6–15.8)
Girls	7.1	7.4
Boys	8.8	10.0
Gender		
Female	3	1
Male	8	6

	Study participant	Study non-participant
Diagnosis		
Malignant	9	4
Non-Malignant	2	3
Survival		
Alive	5	2
Death	6	5

Parents are in the position of fulfilling both caregiver and donor roles. As parental perceptions have not been investigated in this context, the central goal of this investigation was to investigate experiences of parents who had donated G-CSF mobilized peripheral blood stem cells to their child.

Participants and methods

Twenty-three haploidentical transplantations were performed in 18 children between 1997 and 2002 in the pediatric transplant unit of the Leiden University Medical Centre. The majority of children were referred for HSCT from other academic pediatric units, located throughout the Netherlands. Three children received transplants from both their father and mother, and one father donated twice. A total of 21 parents donated stem cells to their child. Of these, five parents were excluded for various reasons, i.e. living abroad (n=2), not able to understand and communicate in Dutch (n=1) or suffering known severe psychiatric disease (n=2). Sixteen parents were invited to participate, of whom 13 (82%) consented. At the time of the interview, six children had died either from infection (n = 1), graft failure (n=2) or relapse (n=3). Bereavement was not an exclusion criterion. Characteristics of donors and children are summarized in Table 1. The protocol was approved by the institutional Medical Ethics Committee.

For the purpose of this study, a phenomenological approach is appropriate. In-depth qualitative interviews were conducted with study participants with the goal of examining their 'lived experiences' in the context of the donation process[20]. All interviews were conducted by the lead research investigator (SMvW), the majority in participants' homes, and audio-recorded, using a minidisk recorder. Participants were able to stop the recording at any time. Three parents paused the recording due to emotional reactions to the topics being discussed. All interviews opened with an invitation for parents to describe their donation-related experiences.

> *"Mr, Mrs, you have donated stem cells to your child ..... which placed you in a special position, you had a dual role: the role of a parent and the role of a donor. Could you please tell me what it was like for you to*

be a parent of a child with a life threatening disease and the donor for that child at the same time? From the moment you were confronted with being a donor, would you describe your experience, and share as many of your thoughts, perceptions and feelings as you can recall"

The parents were allowed to freely describe their experiences in their own words. Probes were used to elicit additional information and examples when necessary. The interviewer focused particularly on instances of how the experience of donating stem cells to their child had influenced parents' physical, emotional, cognitive and social functioning before, during and after the donation process. The length of the interviews varied per participant, but was never longer than 120 min (mean interview duration 45:28 min, range 28:20–115:54 min). Appointments for follow-up by telephone approximately 2 weeks later were made immediately after the interview. Field notes were made during the research process to obtain information on appointments, cancellations. Immediately after each interview, the researcher wrote a short impression with observational details concerning environment, weather, reception, interview setting and participant during the interview. These specific details are relevant and serve as a record of the researcher's own construction of meaning[21]. Each session ended with debriefing and parents were asked how they felt about the interview in order to minimize the risk of related emotional stress. In the follow-up call this was repeated. Without exception, all parents were positive about their participation in the study.

Interviews were transcribed and analyzed using standard qualitative analytic techniques[21], the central goal of which was to discover thematic elements that emerged as part of the parent interviews. Although we had some ideas about themes that might emerge, a grounded approach to the data analysis was used – i.e. themes were allowed to emerge as part of the analysis rather than being predetermined. The process of qualitative coding focused on identifying statements or phrases that seemed particularly essential or revealing about the phenomenon or experience being described. In this way, how parents expressed their feelings and the use of language were taken into consideration and subsequently utilized in the interpretation of the findings[20,21]. From the initial raw data we documented tentative themes, which were later refined and categorized by re-analysis of the data. Finally, four main categories were determined. To improve the validity of this analysis, themes identified during the qualitative analysis were discussed and confirmed, clarified, or revised with parents by telephone. Six interviews were categorized by senior transplant nurses, instructed in the method, and given the opportunity to listen to (parts) of the interviews. Results were compared and any intra observer differences were discussed and resolved by consensus, i.e. investigator triangulation[22]. In an attempt to quantify the qualitative findings gathered via the in-depth interviews, participating parents were asked to complete the UCL[23], which identifies the primary coping strategy of

individuals confronting a problem. This self-report questionnaire consists of 47 items on a 4 point Likert-scale. The items comprise seven subscales assessing different types of coping strategies: (1) Active problem focusing: view the situation from different angles and approach problems in a purposeful and confident manner. (2) Palliative reaction pattern: look for diversion and occupy oneself with other things (like smoking or drinking) so as not to have to think about the problem. (3) Avoidance behavior: let the case run its course. (4) Social support seeking: share feelings and seek comfort from others. (5) Passive reaction pattern: show hopelessness by immersing in the problem or the situation (6) Expression of emotions: show annoyance or anger or work off the tension. (7) Reassuring thoughts: console oneself with the thought that things will get better[24]. To allow for a structured analysis, the UCL strategies were traced back to the reduced classification of Lazarus and Folkman[25] as described by Heck *et al.*[26] (Table 2).The specific categories developed from the interviews were analyzed and logically assigned to the UCL coping strategies. To assess the internal consistency of the UCL the Cronbach's coefficient alpha was calculated for all seven subscales. Descriptive analysis was used to compare the results of fathers and mothers, as well as parents of surviving and deceased children.

Table 2: Comparison between the theory of Lazarus and Folkman and the scales of the UCL (Heck et al., 1989) in correlation to the categories found in the study

Lazarus and Folkman	Utrecht coping list	Categories in this study
Emotionally directed coping	Expression of emotions	Hope and Fear; Need for Information
	Passive reaction pattern Rejection	Transplant Outcome
Problem directed coping	Active approach	Needs for Information
	Seeking social support	Do Anything for Your Child
	Palliative reaction pattern	Need for Information
Evaluation	Reassuring thoughts	Transplant Outcome

Results

Analysis of the interviews revealed four main categories (investigator triangulation less than 2% adjustment):

- Hope and Fear
- Need for Information
- Do Anything for Your Child
- Transplant Outcome

Each category contained themes that were related to a specific time period in the total process of HSCT. These periods were (1) Facing haploidentical transplantation: parents are informed that no HLA compatible donor was available and confronted with the donation of haploidentical stem cells; (2) Decision making: parents have to decide to continue with HSCT and become their child's donor; (3) Donation process: parents are assessed as donor and given medication for the procedure; (4) Reflection: parents reflect on the transplantation period and outcome. The attempt to relate these categories to coping strategies as determined by Lazarus and Folkman and the UCL are summarized in Table 2.

Feelings of Hope and Fear were found throughout the transplantation process. The feelings hope for cure, and fear of losing one's child was often experienced simultaneously, leading to turmoil and confusion. Parents reported that on hearing that no HLA compatible donor was available, they experienced feelings of despair, frustration, powerlessness and sorrow:

> *"When we first heard that we could not find a compatible donor this was a very disappointing situation. We did not know how to go on"*

However, the use of reassuring thoughts as a way of coping with the extreme stressful situation was also evident. Parents expressed hope gained from the new developments in transplantation techniques and the offered opportunity:

> *"This was a surprise for us... We were told that only a donor with compatible bone marrow was acceptable. When we were told about this opportunity, we were very happy, and faced it very positively"*

This was despite the emotional stress of their role as a donor:

> *"... at that moment, you are so emotional,y.yes, so overwhelmed that you can do something for our child... everything else they tell you goes in one ear and out the other"*

The 'Need for Information' in relation to all aspects and periods of transplant procedure and donation varied, but was reported by all parents. This concerned not only the treatment for their child, but also about the donor procedure:

> *"The information session is more about the patient. They talk to the parents about their child. There should also be a specific session for the donor"*

Parents were uniformly dissatisfied with the donor information, e.g. they were unprepared for the bone marrow puncture undertaken during the physical examination:

"I had this talk with the physician and some blood samples were drawn. 'You will also have a bone marrow puncture'. What? 'Didn't you know?' No, I was really upset and frightened. Nobody told me about it before; the nurses didn't tell me anything'. 'It would have been better if they had put the side effects and long term effects in a folder. What can you expect, what is going to happen, how often you get the injections etcetera? (...) I still do not know what the long term effects of the growth factors are, what it can cause to my bones for instance"

The lack of familiarity with the hospital environment, staff and the isolation procedures compounded the difficulties. Parents used the Internet to supplement the information, which is a way of problem directed coping. Parents spoke of the uncertainty and lack of information about the future. The experimental character of the treatment meant the medical staff were not always able to resolve these issues for the parents.

"What I can remember, every time, we talked about that period and they said: it could have been different. If you hadn't done it, he might have also died. And then what? So..., yes such things, they told us such things, mostly. Yes, what I said before, when we left after such a meeting, we felt: why did we go there," .....

Parents would 'Do anything for their child' but often had feelings of powerlessness or having no choice. The decision-making process was mentioned by all participants. All parents were unanimous about their decision to donate although they all felt that they simply had no choice.

"..... In fact, we had no choice, it was made very clear. Without transplantation he would certainly die"

Two parents mentioned the importance of taking the opinion of their child (7 and 8 years old) into consideration during the decision-making process.

"I think that it is very important, that we, as parents, despite how nayve our children seem to be, do not underestimate them. Children who have suffered so much, have heard so much, have seen and felt and experienced so much, they are able to make that decision for themselves"

"It was clear for him. He wanted to go there, he wanted to be cured. We talked it over with him, I was afraid he was not able to comprehend everything, but it was clear for him. And I think he made the right choice"

One parent felt guilty for making the decision on behalf of his child who was

not capable of doing so. The last category, 'Transplant Outcome' is more or less a reflection by the parents concerning the whole process.

> *"I realize now that the whole period in Leiden, was complicated, but also gave us a lot of hope"*

Some parents expressed feelings of helplessness, but equally did not blame any individual for the outcome.

> *"I cannot blame anyone. This is what Life has caused me"*

All parents mentioned that maintaining contact with other people was important to overcome these feelings. Most of them were able to receive practical support from family members, although some found it difficult to discuss their situation with close family. Almost half of the parents reported it was important to have contact with a 'partner in misfortune', i.e. someone with a similar experience. Many emphasized the necessity to send newsletters to keep family, friends, school and colleagues updated about the progress of their child, in order to minimize their social isolation. This approach is also an example of seeking social support.

If children had died due to non-engraftment, rejection or post transplant infection some parents felt that they had fallen short of being a good donor. They felt the transplant outcome reflected on them personally and diminished their self esteem.

> *"I had these periods in the hospital, if only I could reverse, turn back the time. In particular the first time, when my cells were rejected"*

Fathers were less likely to place importance on their career and job prospects whereas mothers became more critical of other parents concerns such as minor illnesses and school achievements. They considered such things to be of less importance having confronted a life-threatening illness or even death of their child.

> *"You have learned to put things into perspective, you are aware the relativity of things. In early times I would get really wound up about things (...) The death of my son was my greatest lesson for life. How it went and also the way I face religion and after life, it has really changed me"*

Mothers were more likely than fathers to actively try to reduce stress by seeking social support and contact.

Parents whose child had died had, as might be expected, a more negative reaction to life events. They were more likely to seek reassuring thoughts to maintain the balance in their lives..

> *"You can't do anything about it. That's the way it goes. Parents didn't choose for it, neither has the child, to become ill'. 'I kept a diary, this period, and I can advice it to every parent. It really helped me to assimilate this period. There are also pictures in it, it brings back the memories"*

Parents universally reported that participating in the interviews was a positive experience. Several expressed relief and gratitude for the opportunity to tell their story. None of the parents expressed the need of additional psychosocial care as a result of the in-depth interview.

Discussion

Haploidentical G-CSF mobilized peripheral blood stem cell transplantation from a parent offers a new option and the hope for cure. The experiences of these parents have not been previously investigated. The use of an interviewer independent of the transplantation unit may have allowed parents more opportunity to discuss their feelings. Although this retrospective information may not be a genuine reflection of past experiences, is does however reflect the current view of parents regarding their dual role[25].

We were able to establish four distinct categories that encompassed the experiences of parental donors. The first of these, 'Hope and Fear', have been reported in previous publications in relation to being a stem cell donor[9,16,26] or being the parent of a stem cell recipient[17,27,28]. It is therefore not surprising that this category is of similar importance to parental donors, representing both roles. From a linguistic point of view, hope and fear are opposites; in practice they seem more often to coexist in these parents. The impact of being told that there was no suitable bone marrow donor made them confront the possibility of their child's death. It subsequently seemed incomprehensible to many that they would be considered an alternative donor. In our experience, parents oscillate between these contrary feelings attempting to find an emotional balance. Emotionally directed coping as described by Lazarus and Folkman, comparable to the expression of emotions (UCL), is reflected in this category. Parents acting as donors become in their own eyes the hope for cure. Vossen pointed out the fear, uncertainty and mental suffering of parents and patients[29]. He stated that taking care for these patients is not in the least routine, and demands an integrated approach to the delivery of good quality care.

Consenting to HSCT as a life-saving treatment for one's child places an overwhelming burden of responsibility on parents[9]. Aversa stated that virtually every patient has a donor[5], but parental donation is not usually discussed during the initial information session. A parent as donor is not the first choice. The reported lacks of sufficient information often lead to uncertainty and sometimes feelings of guilt.

The perception of the information provided may have been distorted because of emotional difficulties. Breaking bad news (i.e. no donor was identifiable) seemed to make parents numb and less receptive. We were not able to determine to what extent these recollections were altered by time, nor were we able to document what information had been given to the parents. However as this was uniformly reported it would seem likely that the extent of information given was either inadequate and/or poorly communicated. Parents' 'Need for Information' under comparable circumstances has been reported[16,30]. Fisher[30] reviewed eight studies on the needs of parents of chronically ill children. She found that the majority of parents were dissatisfied with the information they received. Similarly, this has been reported in parents of children diagnosed with acute leukemia[31]. Dermatis and Lesko[27] found that the strongest predictor of parental level of distress was the quality of the physician/parent communication. This category highlights both passive and active reaction patterns of emotional an problem directed coping strategies. In light of our findings we feel that this issue is of paramount importance which needs to be addressed by all centers undertaking haploidentical transplantation. As a result of this study we have optimized the information, using a standardized checklist and introducing the option of haploidentical transplant in an early stage of the consultation.

The third identified category, 'Do Anything for your Child', is a proactive approach and can be considered as a way of problem-oriented coping. Although the chances for a successful outcome were not always hopeful, all parents took the offered opportunity, hoping they could thus save their child's life. This decision was not always easily made. Due to circumstances, some parents hardly had time to consider the procedure. Decision making as part of the consenting process for both the experimental treatment of their child and being a donor themselves suggests a possible conflict of interest. High levels of distress may limit the ability of decision making. Caregivers need to realize that parents are the ones who must live with their decision for the rest of their lives[32]. The urgency of transplant often reduced the opportunities for parents to balance the risks versus benefits. Although no parent was reluctant to donate, some admitted being fearful of the procedure. Knibbe[33] found in parents, who were asked to act a living liver donor for their child, that donation was 'not a matter of choice', due to the intimate relation with their child. This has also been reported by sibling donors[34]. Having a choice implies more than one option and for parents facing donation, not-donating means the certainty of losing their child, which is not an acceptable choice. In this respect, Atkins and Patenaude[26] and Christopher[16] both highlight donor's fears, emphasizing the importance of discussing the impact of a potential negative outcome on the donor's life. The perceived extension of parental duty must be considered. The willingness of parents to Do anything for their child should not be equated as a license to do anything with the parents. Counseling parents who are prospective donors may require specific

advocacy, as is the norm for unrelated HSCT donors[35,36].

The sense of isolation common to many parents whose child is undergoing HSCT was a major theme for all participants. The geographical dislocation from their home, away from family, resulted in isolation. Their unique situation as donor may have contributed to their loneliness. Many parents found it difficult to relate to others who had not donated stem cells. This study was not able to distinguish the extent to which this problem was related to the experience of parents acting as donors. Writing newsletters may have helped them to work through their emotions and in some way shielded them from direct confrontation with well-meaning enquiries. As a result family, friends, school and colleagues remain updated about the situation. This approach is both exemplar for palliative reactive pattern (emotion directed coping) and seeking social support (problem oriented coping). Again, like hope and fear, this illustrates the dichotomy of feelings.

Eight parents (including the two couples) were bereaved. Coping with this loss was seen as an inhuman burden and some parents had continued feelings of guilt and/or anger. Irrespective of Transplant outcome the parents' lives were altered. Severe depression as experienced by a survivor's father has been described by van Dongen-Melman[25], as maintaining the problem and feelings of loss. Losing a child can be experienced as a loss of oneself. This has been succinctly described in Louise Kaplan's book 'No Voice Is Ever Wholly Lost'[37], by a father:

> *"..., if losing a child is losing a piece of your own self, you can still get yourself back, maybe not all of yourself, but just enough to bring back the spirit of your child. Your child cannot live again. Some part of you will never live again. But you can still speak with the spirit of your child that was the spirit of you"*

Coping strategies can be problem directed (active approach, seeking social support or a palliative reaction), emotion directed (express emotions, palliative reaction pattern, rejection) or reappraisal (reassuring thoughts)[38,39]. Each of these ways of coping is meant to finally reduce the experienced stress. The transplant requires various coping abilities. Wochna[10] has found that helping family donors to cope during the search is an appropriate method to reduce stress. Rodrigue *et al.*[28] advises counseling and appropriate education to minimize parental stress. Frequently, the initial information session is the first time parents and transplant center staff meet and makes difficult the initiation of strategies aimed at assisting parents develop ways to cope with the dual role.

Conclusions and recommendations

The phenomenon of the dual role of parent and stem cell donor was not strongly

evident in the qualitative interviews, but parents' experiences were similar to both roles as described in the current literature. As the transplantation was the only chance for cure, parents considered the role of being a donor one of relatively minor importance. Their decision to consent to the procedure concurred with their feelings of having no other choice. Parents regularly experience simultaneously feelings of hope and fear which, although linguistically opposites, may be experienced simultaneously. Parents' efforts to balance these feelings is often the cause of confusion and additional stress. All coping mechanisms were evident in the conducted interviews. Parents were found to adhere to different coping strategies in different circumstances. These results show that parents' coping strategies need to be continually evaluated. Staff members of the transplant unit need to be aware of and respond to these changes accordingly, in order to be able to give appropriate support. Individual information for the parents needs to address not only the transplantation procedure but particularly those aspects related to the donation process. Based upon the findings of this study, we now routinely inform parents on a more frequent basis, with both spoken and written information, regarding not only the transplant but also their role in the donation procedure. We recommended that all units undertaking parental haploidentical stem cell transplantation should aim to develop specific guidelines and follow-up program for future parental stem cell donors. To this extent the World Marrow Donor Association is active in developing recommendations which may assist in the development of such guidelines[33]. Future studies should be conducted ideally in a multi-center setting to accrue sufficient numbers of parents and be designed to prospectively follow-up parents' experiences before, during and following donation. A donor subcommittee of the Late Effects Working Party of the European group for Blood and Marrow Transplantation is preparing such a study that will focus on both long-term follow-up of physical and psychosocial consequences of haploidentical G-CSF mobilized peripheral stem cell donation.

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Chapter

IMMEDIATE AND LONG TERM SOMATIC EFFECTS AND HEALTH RELATED QUALITY OF LIFE OF BONE MARROW DONATION DURING EARLY CHILDHOOD. A SINGLE CENTRE REPORT IN 210 PEDIATRIC DONORS

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Abstract

The first successful European pediatric allogeneic bone marrow (BM) transplantation was performed in Leiden, the Netherlands, in 1968, with a 7-year old female sibling donor. Since then, more than 300 young children have donated BM in our unit. We first retrospectively studied a cohort of 210 donors, younger than 13 years at donation, to survey procedures of donor eligibility and reports on immediate effects of BM donation. We then performed a long-term follow-up (FU) and health related quality of life (HRQoL) study. Despite the occurrence of previous medical conditions, no child was declared unfit to donate. We found that iron deficiency anemia or low iron stores in BM did not result in treatment or extended FU. Harvest volumes exceeded 15 ml/kg in 65% of donors, with more than half requiring allogeneic blood transfusions. Donors had no structured FU after their first post donation control. In this study 25% of donors reported at least one somatic complaint at long term FU. Finally long-term HRQoL revealed high scores in most sub domains (representing a higher QoL), compared to norm groups. These results indicate the need for development of (inter) national guidelines for pediatric stem cell donor care management.

Background

In the Leiden University Medical Centre (LUMC), in 1968, the first pediatric stem cell donor donated bone marrow (BM) for the benefit of her baby brother. Since then in over 40 years, more than 300 children have donated BM. Pediatric stem cell donation poses an ethical dilemma in that it exposes a healthy child to a potentially harmful medical procedure that has no direct clinical benefit. This is counterpoised by the positive emotional impact of being able to help a seriously ill sibling[1]. BM donation in early childhood is rare, and as such, literature on immediate effects and long-term outcome is scant. Although no cumulative registry data is available, statistics provided by the CIBMTR show that in the year 2006 over 4000 patients under the age of 20 years underwent allogeneic transplant transplantation[2,3]. Approximately a third of these received a graft from a related donor. We would estimate this to equate to approximately 3000 pediatric donors recruited annually worldwide. BM donation by minors is, according to international legislation, restricted to siblings[4]. In contrast, living solid organ donation is in Europe not permitted under the age of 18[4,5], although in the Netherlands, every person over the age of 12 years is allowed to carry a donor codicil. The use of first cousins, although practiced, falls outside EU regulations. While in our institution the minimum age for donation is six months, harvests elsewhere from younger children have been described[6]. Even though BM donation is a generally accepted and legally permitted, young children are considered incapable of giving informed consent[7]. Informed consent procedures for children involved in BM donation have only lately been specifically addressed[5,8]. In most cases, however, parents or legal representative of the prospective donors will give proxy consent for BM harvest[1], leaving the donor no other choice but to donate[9]. The recognition that a legal representative is required to protect the interest of the young donor (under the law), has only recently been adopted[10], albeit not universally. Legal representation for the benefit of family donors has been suggested, although smaller centers might be less able to implement this policy[11-13]. The lack of formalized (long-term) follow-up (FU) programs for (pediatric) donors is making it even harder to study the outcomes and impact on health and health related quality of life (HRQoL) in large cohorts. With the introduction of the use of hematopoietic growth factors in healthy individuals, the call for FU programs has resulted in a recommended system for unrelated stem cell donors, carried out by donor registries[14]. Individual institutions are required to develop a (pediatric) donor care program at their own initiative.

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 (FACT). These factors have led to demands for new guidelines for the care management of family donors. The current JACIE Standards (version 4) require written criteria for stem cell donation to protect the donors' safety, although there is no requirement for structured donor

follow-up at the present time[15]. In the 5th version, which will become actual in 2012, the section for donor selection, evaluation and management is extended, demanding TC's to develop a policy, including minor donors. So far, studies into donor experience and side effects have been undertaken in adult sibling donors where it was found that the physical side effects were outweighed by the reinforcement of donors' self esteem, and increased meaning and worth of life[16]. A Cochrane literature review focused on bone marrow versus peripheral blood stem cell donation in adult donors[17]. Since adverse events and complications in adult donors may differ from those in children, although the findings are of interest, they are not directly comparable. For child donors, literature on the immediate physical effects of donating stem cells is scant[6,18,19] or limited to the use of hematopoietic growth factors in children[20-25]. Furthermore research has concentrated more on the psychosocial effects in pediatric donors[9,26-28]. To date, no significant long-term FU studies in pediatric donors have been performed. We aimed to describe the characteristics of a large retrospective cohort of pediatric donors and further to analyze the immediate and long-term physical effects, medical outcome and HRQoL associated with the donation of BM in early childhood.

Donors & methods

Group I consisted of a retrospective analysis of recorded medical and/or computerized laboratory data. All donors aged less than 13 years at the time of donation, who donated BM from 1968-2002 (n=210), were eligible for this cross sectional study. Blood counts were expected to be performed during initial physical examination (PE), pre and post harvest. Datasets were obtained for medical history and examination, BM harvest volumes, immediate consequences of donation and erythrocyte transfusion history. Donor medical fitness and the immediate effects of the donation process were investigated. Bone marrow was harvested from the posterior iliac crests under general anesthesia. Red cells were salvaged from the graft and given back to the donor (institutional policy). According to our institutional guidelines, a target cell dose of 1-2 x 10^8/kg recipient body weight (BW) infused was aimed for successful engraftment. In cases where major ABO incompatibility was documented between donor and recipient, a minimum of 500 ml BM harvest was deemed necessary for processing. All available BM aspirates (n=145), routinely obtained at the time of harvest, were retrospectively analyzed to document hematological findings. A review of the original reports (produced by two independent observers) was undertaken by a trained pediatric hemato-morphologist, and representative archived material was evaluated to confirm the original findings. Furthermore the volume of BM harvested in relation to red cell transfusion requirements was investigated.

Group II consisted of a prospective cohort of childhood donors who were invited to complete a self reported questionnaire regarding general health and quality of life.

The inclusion criteria were at least 12 years of age at initiation of the study, resident in the Netherlands and fluency in the Dutch language. The invitation to participate consisted of a letter of explanation (consisting the background and objectives of the study) for donors and/or parents (in case the participant was younger than 18 years) and a request for informed consent. Surviving recipients and non-donor/non-patient siblings were invited to act as controls. The rationale to invite the survivors was to investigate whether their quality of life would impact the donors' responses

A self reporting health consumption questionnaire and validated questionnaires to assess HRQoL included Medical Outcomes Study Short Form-36, the General Health Questionnaire, and The Pediatric Quality of Life Inventory™ Version 4.0, depending on the age of the participant. Donors > 18 years (n=61) received the GHQ-12 and SF-36 questionnaires. The Medical Outcomes Study Short Form-36 (SF-36) is a widely used generic health status measure that is available as a validated tool in the Dutch language[29,30]. The SF-36 health survey is composed of 36 questions and standardized response choices. The instrument examines eight specific domains: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and general mental health (MH), scoring each on a scale of 0-100% (worst to best). Higher scores indicate a higher level of functioning or wellbeing.

The General Health Questionnaire (GHQ-12) has been extensively used as a short screening instrument for mental illness in general health care, and is available in the Dutch language. The instrument is found to be remarkably robust after widespread testing[31]. The instrument measures changes in normal psychological functioning. Items are rated on the standard 0-0-1-1 scale and summed to a total score.

The Pediatric Quality of Life Inventory™ Version 4.0 (PedsQL) is a modular instrument for measuring HRQOL in children and adolescents ages 2-18 years. The instrument consisting of four core scales (physical, emotional, social and school) was found to be valid and reliable[32]. All of the above, except for the physical functioning scale are summarized in the psychosocial health summery score. A five-point Likert scale is utilized and scores are linearly transformed to a 0-100 scale. The PedsQL™ 4.0 is applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions.

Where available, results were compared to Dutch norm groups (as provided with validated instruments) or information from the Dutch Central Bureau of Statistics (CBS)[33].

This study was approved by the Scientific Committee of the Willem Alexander Children's Hospital and the Committee for Medical Ethics of the LUMC in the Netherlands.

Statistical analysis

Descriptive analysis (e.g. histograms with normality curve, box plots), reported as percentages, mean values and standard deviations, was performed to examine whether the study groups were normally distributed. Analysis was performed using SPSS and MS Excel, to examine associations between the study groups. In addition patterns of association among variables were estimated based on variables' level of measurement. These included visual representation and statistical measures of association/difference (e.g. Chi-square, Fischer's exact test, paired T-test and analysis of variance (ANOVA)) to address the level of specificity. Differences and correlations were regarded as statistically significant if $p<0.05$.

Results

Group I - general

For 13 from the 210 eligible donors, no data was available, resulting in 197 donors (94%) eligible for further analysis. Two children included in the study were extended family donors (i.e. non-sibling relatives). They were cousins of the recipients and were HLA matched due to the presence of a frequently occurring haplotype in non consanguineous families. Donor characteristics of this group are summarized in Table 1.

Donor eligibility

All donors were evaluated as medically fit to donate by a qualified pediatrician, who until the early 1990's was a member of the pediatric transplant team, also involved in the care of the recipient. Thirteen donors in group I (7%) had a previous medical history; seven children had persistent problems at the time of physical examination (PE) prior to donation (Table 2), which warranted additional considerations. None were deemed unfit to donate. Only one child underwent physical evaluation prior to HLA typing.

Peri donation events

Of the seven donors with persistent problems at time of donation, four had documented severe adverse events during or immediately after harvest. Donor 027 was moderately difficult to intubate (Cormack and Lehane gr II: vocal cords

only partly visible) in light of an enlarged epiglottis, which was not documented at screening. Donor 071, a child with severe cardiac abnormalities, developed significant tachycardia during anesthetic, which responded to medical intervention.

Table 1: Demographic characteristics of donors

	All donors (n=210)	**Follow-up donors (n=79)**	
Donor characteristics	*at donation*	*at donation*	*at study*
Age in yrs. (median; range)			
Male	6.4 (0.6-12.0)	6.4 (0.6-11.1)	22.2 (12.8-39.4)
Female	7.7 (0.6-12.3)	7.1 (0.8-12.3)	23.9 (14.2-47.8)
Gender			
Male	113 (53%)	36 (45%)	
Female	97 (47%)	44 (55%)	
Recipient outcome			
1 year after donation	75% alive		78% alive
At time of study	60% alive		61% alive
Donor is (%)			
Twin sibling	4.3	3.6	
Younger sister	21.0	25.3	
Younger brother	24.3	22.7	
Older sister	23.3	30.8	
Older brother	26.2	16.4	
Younger cousin	0.9	1.2	
Ethnicity (%)			
Caucasian	80	87	
Recipient diagnosis			
Malignancy	139 (66%)	57 (72%)	
Immune deficiency	15 (7%)	3 (4%)	
BM failure	36 (17%)	13 (16%)	
Hemoglobinopathy	12 (6%)	4 (5%)	
Other	8 (4%)	2 (3%)	
Birth order (%) FU donors			recipients
Oldest child		33	36
Middle child		29	25
Youngest child		30	39
Only child (after bereavement)		8	n.a.

Table 2: Characteristics of donors with a pre-donation medical history

Gender (UPN)	Medical history	Age at donation	Harvest characteristics	Follow-up (self reported)
M (012)	Fontan procedure for hypoplastic heart; congenital asplenia*	8.4 yr	686 ml	Rulide prophylaxes; BMI 18
F (091)	Spastic tetraparesis due to perinatal asphyxia; suspicion for neurofibromatosis	7.7 yr	152 ml; Respiratory problems, one night ICU	Non responder
F	Blalock shunt for congenital transposition great arteries*	0.6 yr	No documentation	Non responder, recipient died
F (071)	Congenital heart condition, not other specified*	4.4 yr	681 ml; Tachycardia (Hb 6.4g/dl)	Stent placement; BMI 17
M	Premature born (34 weeks)	0.7 yr	131 ml	Non responder
M	Premature born (34 weeks)	8.9 yr	514 ml	Non responder, recipient died
F	Premature born (34 weeks); repeated febrile convulsions; pyelonephritis	6.5 yr	378 ml	Non responder
F	Premature born (36 weeks)	8.2 yr	748 ml; 2nd dx after 4 weeks for other sib	Non responder, 1st recipient died
F	Premature born (31 weeks); hypothyroidism*	1.7 yr	199 ml	Atopy; GE problems n.o.s.
M (027)	Non syndromal developmental delay*	7.8 yr	696 ml; Intubation gr II	Non responder, recipient died
M (081)	Failure to thrive*	0.7 yr	125 ml; Hypoxic, 50 ml FFP	Healthy
M	Heart murmur; testicular atrophy (suspicion adrogenital syndrom)	3.7 yr	396 ml	Non responder, recipient died
M	At 7 weeks: sleep apnea (6 months monitored)	5.6 yr	488 ml	Non responder

** indicates that the medical condition warranted consideration at time of donor physical examination. UPN of donors refer to the text*

Donor 091, a child with a severe tetraplegic handicap had post extubation breathing difficulties, leading to an overnight observation in the pediatric intensive care ward. Finally donor 081, a child of 7 months old with failure to thrive, weighing 8.3 kg, having undergone a harvest of 15 ml/kg bodyweight developed hemodynamic instability requiring volume replacement therapy with plasma. In spite of these operative complications, only one donor received donor FU.

Twelve of 210 (5.7%) donors donated sequentially: two donated to different recipients, the remainder donated for the same recipient due to either poor engraftment, rejection of the graft or relapse of the original disease. Median time between donations was 6.8 months (range 1-170 months). One child, who donated twice in four weeks for two recipients, was not re-assessed, but had laboratory results prior to the second donation; the other donors who donated more than once were all re-assessed for their second donation.

Three donors were diagnosed with minor infections pre-donation (sinusitis, otitis media) and treated with antibiotics; no FU was recorded.

Laboratory results

Laboratory results were available for 147/197 (74%) of donors. Both pre- and immediate post-harvest (within 24 hours) full blood counts were documented for 126 donors; nineteen donors had only pre harvest values documented. Older donors had a lower Hemoglobin (Hb) level pre donation than younger donors, possibly due to the harvest of an autologous unit. Despite transfusions, Hb levels after donation compared to pre donation, were reduced in 89% (n=113/147), with a median loss of 2.5 g/dl (SD 0,46; range 0.3-5.2; median Hb 10.5 g/dl; p=0.0001). In 28 donors a post donation Hb level lower than 9.7 g/dl (median 8.9 g/dl; range 6.6-9.5) was documented (p=0.0001). No medical intervention or laboratory FU was documented. These results are summarized in Table 3.

Table 3: Median Hb,Ht development at different stages of the donation process and harvest characteristics

	Physical examiniation Mean Hb/Ht levels		**Post donation (< 24 ht)**		**Hb loss**	**Paired T-test**	**95% CI**	**Median volume harvested**	
Age (yr)	**Hb Ht**	**N**	**Hb Ht**	**N**	**g/dl**	**P-value**		**ml/ kg BW (range)**	**Total volume (range)**
0-3	12.4 0.37	46	10.0 0.31	35	2.4	p<0.0001 p<0.0001	1.202-1.847 0.0487-0.0794	17 (7-47)	204 (115-799)
4-7	12.7 0.37	55	10.5 0.31	49	2.3	p<0.0001 p<0.0001	0.980-1.540 0.0415-0.0674	18 (6-44)	402 (128-794)
8-12	13.2 0.38	49	10.6 0.32	42	2.6	p<0.0001 p<0.0001	1.124-1.701 0.0505-0.0786	18 (9-31)	529 (299-1189)

Bone marrow analysis

BM reports from 145 donors were available. Seventy percent (n=106) bone marrow aspirates were representative for histological examination. Iron stores were determined by supra vital staining with potassium ferricyanide (Perls). Absence (n=16) or reduced (n=54) iron stores were evident, mostly in children with normal Hb levels. Age distribution analysis revealed that infants and pre pubertal children were more likely to have reduced BM iron stores. No further investigation into the iron status of the donors post harvest were undertaken and/or documented. Low iron stores of donors were not related to the transplant indication of the siblings (i.e. B-thalassemia, SAA). Four donors had decreased or absent megakaryocytes, but had normal peripheral platelet counts and morphology. Other documented abnormalities included white cell aberrations in 6%, mainly undiagnosed hypereosinophilia, lymphocytosis and five cases of mild leucopenia, none of which were actively pursued.

Harvest characteristics

Harvest volume data was available for 109 of all donations, including three second donations. Harvest volumes ranged between 6-47 ml/kg donor body weight (BW) (corrected for age, mean 18 ml[34], or 8-62% (mean 24%) of the estimated total circulating whole blood volume. In 65% (n=66) of donations the volume harvested exceeded 15 ml/kg donor BW, with 34 of these children donating more than 20 ml/kg. Donors with an older recipient (n=49) were more likely to donate a larger volume. In donors with a younger recipient (n=47), 21 donated more than 15 ml/kg, with six donating more than 20 ml/kg (see Figure 1). Transfusion data were available for 160 donors. Overall 94 donors (52.5%) received a blood transfusion, of which 74 were allogeneic. In children whose harvested volume exceeded 15 ml/kg donor BW, 71% (47/66) required blood transfusion (40 allogeneic, and 7 autologous stored units), compared to only 35% (14/40) donors when the volume was restricted to 15 ml/kg or less donor BW ($p<0.0005$). In total 25 children older than 10 yrs received their autologous red cells, harvested at the time of initial physical examination.

In 77 cases complete data regarding cell yield infused and total volume harvested were available. A poor cell yield in the graft (defined as $<1.0 \times 10^8$ per kg/recipient BW infused) was documented in only 10 cases, in all of whom greater than 15 ml/kg donor BW was harvested. None of these patients had documented graft failure, with eight long term survivors and two children having died from a relapse of their leukemia. A cell yield of $\geq 3.0 \times 10^8$ per kg/recipient BW was seen in 34 harvests; twenty of these donors donated more than 15 ml/kg donor BW. A major blood group incompatibility between donor and recipient requiring red cell depletion was evident in 18 couples, only six of whom were in the group of large volume harvests.

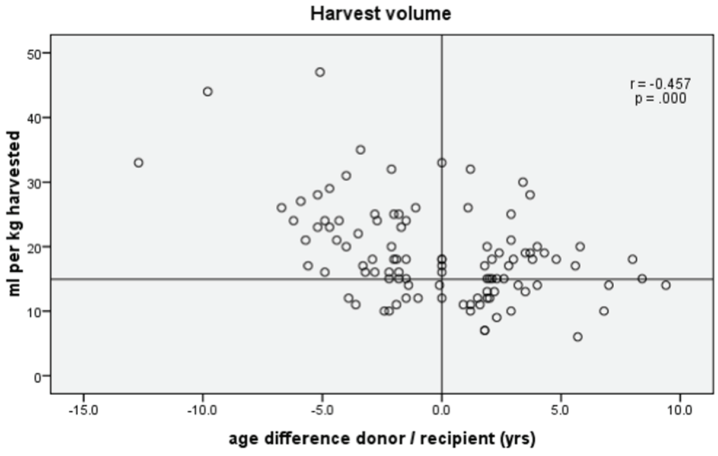

Figure 1: Harvest volumes often exceed 15 ml/kg (range 6-47 ml (mean 18 ml) donor BW, particularly in donors with an older recipient.

Short-term FU

Only 24 donors had documented FU information, within 100 days post donation, including hematological control. Only one donor (m, aged 7.9 yrs; Hb 9.0 g/dl, 1 week post donation) had a second FU 8 months after donation, due to persistent epistaxis. His Hb was 10.6 g/dl and platelet count 263 × 10^9/L at that time. With regards to the amount of donors that underwent large volume harvest and received allogeneic blood transfusions, no further FU with respect to the development of neither red cell antibodies nor transmissible diseases was performed. Reasons for not undertaking further evaluation for the remaining donors were not recorded.

Six donors had iron deficiency anemia pre-harvest, retrospectively diagnosed by characteristic red cell morphology in the presence of a hypochromic microcytic anemia in the absence of hemoglobinopathy. Intervention with iron suppletion was not documented. Full medical details were available for five of these donors. Four boys and one girl, aged between 3.1–11.4 years, who subsequently donated between 12 to 25 ml/kg body weight BM. Only three donors had their Hb levels controlled at six weeks FU, and in two donors persistent anemia was documented in the laboratory report. No data on long-term sequelae was available.

Self reported health questionnaire (group II); Long term FU

One hundred and ninety of the 197 group I donors were at least 12 years of age at the initiation of the study, and were thus eligible to participate. Seventeen of these were

referrals from abroad, with no known present address. The remaining 173 donors were invited by mail, to participate in a long-term FU study. Twenty-eight invitations were undeliverable, leaving 145 questionnaires that were presumed as received (Figure 2). Seventy-nine of 145 donors (54%) responded to the questionnaire, and were equally distributed throughout the study period when analyzed by five year intervals. Of 92 surviving transplanted siblings, 44 (48%) responded to the invitation to participate. Since the recruitment of non-donor / non-patient siblings did not result in sufficient numbers for comparative analysis (n=10), these results were not further analyzed.

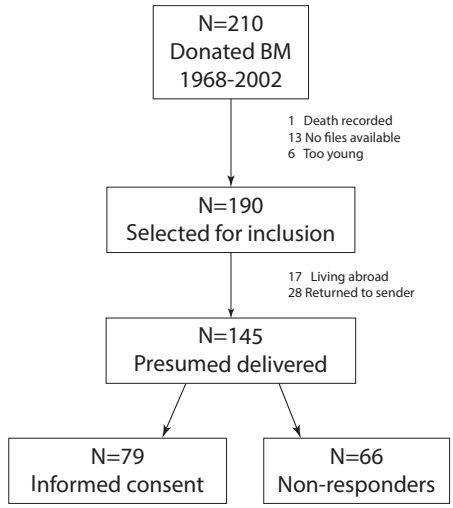

Figure 2: Inclusion and response; excluded donors: 17 donors were living abroad; 6 donors had not reached the age of 12 years at time of the study. One donor had died; 28 donors were untraceable. Thirteen files were no longer available.

At time of the study in total 85 of all recipients had died (35%). All surviving recipients (n=79), who were at least 12 years old, were invited to participate in the study. The total number of FU years was 1340.

Informed consent was received from 79 donors, including four of the donors with a medical condition at the time of donation. At time of the study 91% (71/79) of the donors considered themselves overall healthy. However, 25% (20/79) had developed medical complaints since the BM donation. One donor (donor 071) with congenital heart abnormalities mentioned stent placement at age of 16 years; donor 012 reported the prophylactic use of antibiotics due to his congenital asplenia and heart abnormality. Seven donors mentioned regular upper airway infections, and seven donors reported problems related to asthma of allergies. Furthermore three donors reported having developed autoimmune diseases (rheumatoid arthritis, hypothyroidism and Crohn's disease) since donation. Many other donors reported

non-autoimmune joint problems such as bone fractures and contusions or hospital admissions due to (minor) surgery. Two donors suffered from epilepsy and two others were anemic; none of these donors had a medical history at time of donation. Two donors required medical intervention for severe psychological problems, five suffered from long lasting fatigue. One donor reported persisting back pain since the second time she donated to her sibling. Six donors reported more than one health issue. The majority of the donors had a healthy body mass index both at time of donation and FU, although 33% of the donors were underweight at time of donation, compared to 13% of healthy Dutch children.

Health related Quality of Life (HRQOL): PedsQL, GHQ-12 and SF-36

PedsQL™ 4.0

Donors 12-18 year (n=18) were asked to complete the PedsQL. No significant differences were found between mean scores of child donors and the norm group of healthy school children. However, when taking into account the survival of the recipient, donors with a living recipient (n=13) scored significantly better on the "physical health" domain, than did donors of whom the recipient was deceased (n=5, T-test, p= 0.025). In contrast no significant correlation could be found between the sum scores of the donors and those of their recipients (n=16), suggesting that the health status of the recipient does not influence HRQoL of the donor.

General Health Questionnaire, GHQ-12

The mean total score of the adult donor group did not differ significantly from the healthy adult Dutch population. Socio-demographic and donation-related characteristics, such as marital status, education, gender and recipient survival was not associated with the mean total score or the percentage of psychopathology in the donor group.

Medical Outcome Study Short Form 36, SF-36

All donors had significantly higher (=better) raw scores in the sub domains "physical functioning" (p=0.000), "role physical" (p=0.000), "bodily pain" (p=0.000), "general health" (p=0.000), "social functioning" (p=0.000) and "mental health" (p=0.0034) compared to the general healthy Dutch adult norm group. The difference on the "role emotional" scale was close to significance (p=0.054). Since all of the sub domains, included in the "physical component summary score", differed significantly from the norm group, it was not surprising for this score to be significantly different as well (p=0.000). When comparing male to female donors, male donors scored significantly

better on the sub domains "vitality" (p=0.018) and "mental health" (p=0.030). They also scored significantly better on the "mental health summary score" (p=0.013).

Donors with a living recipient scored significantly better on the "role emotional" sub domain, compared to those with a deceased recipient (p=0.032). No mean differences were found according to education or marital status. There was a significant positive relationship between the "vitality" of the donor and the "vitality" of their recipient (p=0.030). A significant positive correlation was also found between "bodily pain" of the recipient and "mental health" of the donor (p=0.038), "general health" of the recipient and "mental health" of the donor (p=0.028) and "mental health" of the recipient and "bodily pain" of the donor (p=0.037). All of the other sub domains did not show any significant correlations (see Figure 3).

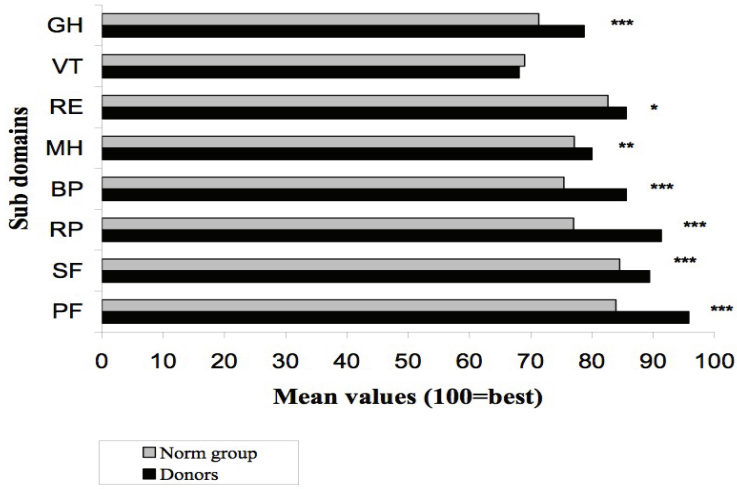

Figure 3: Figure 3: SF-36 subscale means of donors compared to the norm group
GH = general health; VT = vitality; RE = role emotional; MH = mental health;
BP = bodily pain; RP = role physical; SF = social functioning; PF = physical functioning.
*** significance at the <0.001 level; ** significance at the <0.05 level; * not significance

Discussion

This is the first study addressing the immediate effects and long-term somatic and HRQoL outcome of BM donation in a large pediatric cohort. The Leiden unit performed the first European pediatric sibling BM transplant over four decades ago. As such the unit has considerable expertise and experience in the management not only of pediatric patients, but also of child donors. We anticipated that our results may be influenced depending upon the year of donation, since the study spanned a considerable period of time. Over this period clinical practice and ethical

considerations have changed. We were able to retrieve a substantial amount of information from archived medical files and the hospital computerized information system, which similarly was not compromised by year of donation, allowing us to confidently report our long term follow-up findings. This is particularly important, as to date no other published data is available for such a comprehensive study on pediatric donors. Recently the Pediatric Diseases Working Party of the EBMT, reported the early side effects of childhood stem cell donation[35], in a prospective study. This study differs from our report as all age groups were included and both bone marrow and peripheral blood stem cell donation and FU was only 1 year post donation. However, their observations confirm our findings that large volume harvests are associated with significant reduction in hemoglobin levels and the need for allogeneic transfusion. Also children ages less than 4 years were more likely to experience events. Furthermore, in the US the RDSafe Study, which is ongoing, is collecting extensive clinical and psychosocial information from a sample of 100 pediatric stem cell donors.

Donor Eligibility

During the study period the major accepted criteria for donor eligibility were being a sibling and an HLA match. The lack of well defined criteria for pediatric donors may well explain the fact that donors were declared fit to donate despite a concurrent medical condition. Although partly explained by the early years of transplantation included in our study, our analysis and recent publications show that the care for related donors is still, even in large transplant centers, in development[12,13], compared to unrelated donors. Our study shows there is a wide variance in the management of pediatric donors, suggesting that donor eligibility criteria specifically designed for children would be helpful for pediatric transplant physicians. Potential donors with co-morbidity might place an additional burden on parental consent, which may disadvantage the welfare of the donor[1].

Laboratory results and donation procedure

The retrospective nature of our study did not permit us to investigate if donors were or were not routinely evaluated. This in part may be explained by the fact that laboratory results predating computer datasets (i.e. before 1995) were less available. Interestingly the unit policy of routine morphological BM examination of sibling donors at the time of harvest, allowed for a comprehensive review of BM, especially in relation to iron stores, irrespective of year of donation. Literature on the composition of healthy infant BM is scarce and concerns cellularity and classification of normal cells, without special attention for iron stores[36,37]. The fact that two-thirds of the reviewed BM smears showed reduced or absent iron stores, suggests that FU regarding hematological recovery, pertinent to iron status and where applicable oral

iron suppletion in young pediatric donors is necessary. This should include serological assessment of iron stores. In our study, the relationship between BM iron stores and serological parameters could not be assessed, as the latter was not routinely undertaken. It is not clear whether autologous red cell collection affected iron stores. The importance of maintaining normal iron stores is relevant in the pediatric age group, as iron deficiency has been associated with delayed neuro-cognitive development and poor school function[38], especially in early school age.

Harvesting procedure

In this study harvest volumes often exceeded 20 ml/kg (which is the standard in (un)related adult donation, equivalent to approximately 20% of total circulating volume)[19,39,40]. Although only approximately 10% could be explained by major ABO incompatibility and/or poor cell yield, we were unable to determine the reason for large volume harvests, especially in the donors donating to younger siblings included in this study. The large volumes harvested frequently resulted in a, unnecessary high cell dose for the related setting. Since 2007 our department has limited the harvest volumes to 15ml/kg donor body weight. An analysis of 43 donations undertaken since implementation showed full engraftment in 41 recipients (100% donor), stable mixed chimerism in 1 child with homozygous ß-thalassemia (transfusion independent) and 1 late rejection in a child transplanted for homozygous ß-thalassemia. Our data suggest that limiting the harvest volume does not impede successful cell yields sufficient for engraftment for the vast majority of children. Recent analysis (data not provided) in our department, shows that in the past 5 years, we have limited our collection volumes for child donor to this standard, without compromising the graft. Erythrocytes from the graft were re-infused in all donors to reduce post harvest anemia. Pertinently, in more than half of all donors in our study, when harvest volumes exceeded 15 ml/kg, allogeneic blood transfusion was necessary to compensate for the blood loss, with the additional risks involved[41,42].

Long-term FU & Health Related Quality of Life (HRQoL)

Although this study is based upon a self-reported questionnaire, this is the first attempt at documenting the donor's perception of HRQoL following childhood donation. Since there is no comparable data available, the response rate was compared published data from prospective studies (involving both related and unrelated donors). An overall response of 38% of all donors in the study period responded to the questionnaire, however, considering that only 145 invitations were presumed delivered, this figure rose to 54%. Participation in our study was equally distributed throughout the study period. In comparison, Hoelig *et al.*[43] reported a five year post donation FU response of only 42% in unrelated donors. The experience in Austria with related donors was even lower, with a response of less than 10%, ten

years post donation (personal communication A. Rosenmayr). As in all retrospective studies of a self reporting nature, the results could be influenced by the non-response bias[44]. The recollection of the donation and the period following may have been influenced by the lapse of time or the recipient's death. More than half of donors with medical problems at time of the donation responded to the questionnaire (4 out 7, see Table 2). Although continuing medical problems were reported, none were directly related to the donation procedure. The reporting of non-specific clinical problems, such as recurrent upper airway infections and joint problems are difficult to interpret, and most likely do not reflect a long term consequence of BM donation in early childhood. However, as the participants felt them sufficiently relevant to report, we included them for completion. The study was not designed to verify self reported medical conditions. With this study an attempt has been made to disclose aspects of pediatric donor care.,

On average 16 years post donation, adolescents and adults function remarkably well, both physically and mentally. Higher raw scores on the SF-36 as observed in our study have also been reported in living kidney donors[45-48]. It is unlikely that this phenomenon is directly related to the donation procedure. However, it has to be mentioned that the age range of the comparative SF-36 Dutch adult norm group (mean 43.1 yr) is higher than those of the adult donors (mean 23.9 yr) in our study, which may explain the observed differences. Male donors scoring better than female donors on "vitality" and "mental health" sub domains of the SF-36 questionnaire, is consistent with the findings of published data[30,49]. Our findings that donors whose recipient was alive, compared to donors who were bereaved, scored significantly better on the "role emotional" sub domain. This is similar to findings among living kidney donors[50], but contrary to findings of bereaved related donors in the USA[16]. One explanation of our findings may be that the impact of bereavement at a young age may cause difficulties in adaptation and emotional development in adulthood[7].

In children, donors of living recipients scored better on the "physical health" domain than did donors of a deceased recipient. The occurrence of physical problems in children has been shown to predict internalizing problems such as depression and anxiety and externalizing problems, such as aggressive or acting-out behavior at a later age[51]. Our study suggests that these problems may persist into adulthood in selected cases of child donors. Encouragingly only two donors reported severe psychological difficulties.

Although the donation procedure involves no physical therapeutic benefit for the donor, the psychological benefit of being able to help a sick family member is evident[9,16]. This might justify a limited amount of risk for a healthy child who is due to age limitations not able to give informed consent[1,25,52].

We were unable to address the issue of informed consent at the time of donation as the study was limited by its retrospective nature. However, consent in the pediatric population remains an important issue to be addressed in future studies. To what extent pediatric BM donation is still a voluntary act, is questionable. MacLeod *et al.*[9] reported that two-thirds of sibling donors had 'deliberate no choice', while the remainder felt 'forced' or coerced to participate. Contrary to the adult (un)related donor practice, informed consent is rarely requested from young children. Young children have a right to be informed[4,53] before committing them to undergo invasive procedures, especially when the intervention is not to their direct medical benefit. Careful consideration should be given at all times to weigh the balance of risks and benefits to the donor[54].

Conclusions and recommendations

BM donation in early childhood does not lead to significant physical or psychosocial impairment at a later stage in the majority of donors. However, the lack of accepted guidelines for child donor care management leads to inconsistencies in the procedures, even in a single centre. Our study highlights the importance of independent medical assessment of child donors, especially in children with pre existing medical conditions to avoid peri-donation events. The limitation of the maximum harvested volume to 15 ml/kg donor body weight prevents young children being exposed to allogeneic blood products. Our study would suggest this would not be detrimental in terms of poor cell yields, to the recipients.

Low iron stores were frequently detected in our study population, suggesting that hematological follow-up pertinent to iron status is desirable and where necessary oral iron suppletion should be prescribed.

Although this study has shown that BM donation in early childhood does not negatively affect a donor's life on long-term, it is important to weigh the risks and benefits and thus safeguard the interests of the child donor.

Conflict of interest statement

The authors declare there are no conflicts of interest.

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Part IV

Important Aspects of Unrelated Donor Search


Chapter
∞

THE IMPORTANCE OF IDENTIFYING A BACK-UP DONOR FOR UNRELATED STEM CELL TRANSPLANTATION

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MBA Heemskerk
JLWT Lie
RMY Barge
JJ Cornelissen
RM Egeler
LF Verdonck
N Wulffraat
M Oudshoorn

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Summary

The importance of identifying a back-up donor, once a primary suitable unrelated stem cell donor has been found, is often underestimated. Transplant centres erroneously count on the unrelated volunteer donors to be willing, available and medically fit for actual donation. According to our data, which includes 502 unrelated donor work-up procedures performed for 425 Dutch patients between 1987 and 2002, one of 11 work-ups ended in the primary requested donor failing to donate. Of all donor-related cancellations (n = 46), 78% of the procedures were deferred due to medical reasons and 22% due to nonmedical reasons. Most of the donors deferred for medical reasons were female (P = 0.005). In 50% of the cases for which a back-up donor was already identified, the patients were transplanted with a delay of less then 2 weeks; when no back-up donor was available, the median delay increased to 18 weeks. We strongly encourage implementing a search for at least one back-up donor in the primary search. Identifying a back-up donor can save precious time and complicated logistic rescheduling.

Introduction

Approximately one in three patients in need of stem cell transplantation has a suitable related donor[1]. The remaining patients depend on allogeneic transplantation with stem cells from an unrelated but human leucocyte antigen (HLA) compatible donor, as this has proven to be a suitable alternative[2]. Europdonor has facilitated unrelated stem cell donor searches for Dutch patients since 1987. Improving qualities of international services like Bone Marrow Donors Worldwide (BMDW) has shortened the search period over recent years. The experience of facing deferral of the chosen donor, just prior to the transplantation procedure, has led to a search policy in which we try to identify two donors for each patient. The best donor is chosen, the second best donor is released as a back-up donor. Studies performed on the availability of unrelated donors during confirmatory HLA typing stage have shown the relationship between psychological factors concerning volunteer history, recruitment and donation and the level of attrition[3,4]. Deferral of a chosen donor prior to harvest is less than optimal; without an identified back-up donor, a new search has to be performed which is time consuming and can lead to necessary extra treatment courses and hospital admissions for the patient. Until now no data has been available on the advantage of identifying a back-up donor in the first search for a patient. It is our policy to identify a stem cell donor and back-up donor for each patient whenever possible. We addressed the question whether a back-up donor saves precious time and analysed the different reasons for not completing a donor work-up procedure, with special attention given to the donors' deferral.

Materials and methods

The analysis concerned the 502 work-up procedures following unrelated donor searches for 425 Dutch patients facilitated by the Europdonor Foundation in the Netherlands, from 1987 to 2002. Patients originated from the following transplant centres: the Leiden University Medical Centre (n=204, 71 adults/133 children), Erasmus Medical Centre/Daniel Rotterdam (n=108) and the University Medical Centre Utrecht (n=113, 84 adults/29 children). Statistical analysis was performed in SPSS11 using Chi-squared test and Mann–Whitney *U* test.

Our search criteria include HLA match grade, CMV status, donor gender, donor age and ABO blood group system[1]. Confirmatory HLA typing and additional immunogenetic tests, such as Mixed Lymphocyte Culture (MLC) and Cytotoxic Lymphocyte Precursor test (CTLp), are performed with potential donors and the best-matched donor is requested for work-up. A work-up procedure involves the formal request for physical examination and preparation of a donor for stem cell harvest. The transplant centre can express the preference for bone marrow or stimulated peripheral blood stem cells with the decision being driven largely by the patient

condition and disease stage, or current transplant protocol. It depends on the policy of the donor registry and the willingness of the donor to determine if this request can and will be fulfilled. The transplant centre determines a tentative date for transplantation. The donor centre contacts the chosen donor for counselling and physical examination, and arranges the definitive date for the stem cell harvest. At the time of the work-up request of the best-matched donor, the second best donor is selected to be the back-up donor in case the first donor fails to donate. This donor is released with the remaining donors, informing the donor registry that he/she is the back-up donor. The determination to release this back-up donor to the worldwide donor pool is based on the policies of each individual donor registry; ranging from immediate release to a temporary removal from the donor pool to await the outcome of the primary donor's evaluation and consent.

Results

Between 1987 and 2002, 502 work-up procedures with unrelated stem cell donors for 425 Dutch patients were initiated. Overall, 120 work-up procedures were cancelled. In total, 359 first transplantations, 21 second transplantations and two-third transplantations were performed. In 36 of the first transplantations and 11 of the second transplantations, a back-up donor was asked to donate stem cells. The reason to request the back-up donor at the time of second transplantation was deferral of the first donor in one case and preference of the transplant centre in the other cases. In total, 492 donors were involved, 265 males, 218 females; in nine cases, the donors' gender was not reported.

Cancellations

In 15% (74/502), the work-up procedure was cancelled due to patient-related reasons, primarily because the patient was no longer eligible for transplantation. In 9% (46/502), the donor was deferred. Table 1 shows the grounds for donor deferral. They were either personal (n=10, five male and five female donors) or medical (n=36, 11 male and 25 female donors). The proportion of female donors in the latter group is higher than in the group of all requested donors (P=0.020). Reasons for donors' medical deferral were in a number of cases specified by the donor centre, although they have no obligation to do so. Female donors have an increased rate of deferral for medical reasons compared to male donors (P=0.005). In this study, pregnancy is considered a medical reason for unavailability, with regards to international regulations for donor eligibility.

Back-up donor

Confrontation with donor deferral during the work-up stage has led to our current

policy of attempting to identify a donor and a back-up donor for each patient. Overall, in 63% (305/502) of all examined work-up procedures, a potential back-up donor was identified in the initial donor search. The number of patients for whom a back-up donor was identified has improved during the past years. In the first few years (1987–1989), a back-up donor was found for only 28% of the patients. In the last 3 years (1999–2001), a back-up donor was identified for 66% of all patients. Currently, 81% of our unrelated donor searches result in the identification of a back-up donor (Table 2). In these cases, all other donors tested had too many mismatches to be acceptable.

Table 1: Reasons for donor cancellation at the time of work-up

Reasons for cancellation	Specifications	Male	Female
Nonmedical, n = 10[a]		5	5
	Unavailable	2	
	No longer interested	2	4
	Unspecified	1	1
Medical, n = 36[a]		11	25
	Obesity	1	2
	Pregnancy		5
	Malignancy		2
	Infectious disease	2	2
	Liver/kidney/thyroid failure	1	2
	Vascular	1	1
	Multiple sclerosis		1
	M Willebrand	1	
	Unspecified	5	10
Total		16	30

[a] *Female donors are deferred more often, due to medical reasons: Chi-squared test: P = 0.005.*

In 46 of all cases, the best donor was deferred after the formal request for physical examination and preparation for stem cell harvest. For 10 patients, an unrelated stem cell donor search had to be reopened. In 36 of the 46 cancelled work-up procedures, a back-up donor had previously been identified. In 35 of these cases, the back-up donor was requested to donate stem cells. A total of 29 patients were transplanted with this back-up donor, mostly without major delay. For one patient, stem cell transplantation was no longer an option. Five of the requested back-up donors were not eligible for stem cell donation due to medical reasons.

Table 2: Improvement of back-up donor identification over time

Period in time	Number of patients with a back-up donor/total number of work-ups (%)	
1987 – 1989	6/21	(29%)
1999 – 2001	121/183	(66%)
2002 – 2004[a]	214/265	(81%)

[a] *The work-up procedures until 30 June 2004 are included: Chi-squared test: $P = 2.10^{-7}$*

Table 3: The advantage in time of an initially identified back-up donor (the delay is defined as the difference between tentative and final harvest date)

	Median delay (days)	Range (days)	% Transplanted
Best donor available (n=371)	0	0-155	87%
Best donor deferred: back-up donor available (n=36)	7	1-100	63%
Best donor deferred: no back-up donor available (n=10)	129	40-555	60

The absence of a back-up donor can cause delay or even cancellation of the preferred therapy. The regular time delay in a work-up procedure is defined as the difference in days between the tentative date for transplantation at the time of the work-up request and the final transplantation date. The transplant centre proposes the tentative date for transplantation; depending on the availability of both the donor and the collection centre, the final date for collection will be determined in consultation with the transplant centre. The median delay of patients transplanted with the best donor is 0 days (range 0–155). Over 85% of the first transplantations took place within a period of less then 14 days from the tentative date.

To investigate the delay caused by the deferral of a donor during the work-up procedure, we determined the difference in the first tentative harvest date and final harvest date. In 29 patients transplanted with a back-up donor, a median delay of 7 days (range 1–100 days) occurred.

In 10 cancelled work-up procedures, no back-up donor had been identified and a new unrelated donor search had to be started. Six patients were transplanted with a median delay of 129 days (range 40–555 days). The other four patients were no longer eligible for transplantation. An overview of the advantage in time of an initially identified back-up donor is given in Table 3.

Discussion

A successful unrelated donor search does not guarantee the availability of the identified donor for stem cell harvest. During the initial search, HLA typing and additional laboratory tests are performed. The best donor is chosen and requested for stem cell donation; the second best or the so-called back-up donor is released. It is our experience that more patients are now referred to us for an urgent search, with an initial proposed time frame for transplanta- tion within 6–12 weeks. This is likely a result of our success in being able to locate donors at very short notice[5,6], and changes in current transplantation practice. A variation between 0 and 14 days in the proposed and final harvest date is considered acceptable. The policy to structurally identify a back-up donor was introduced in 1994 in our search process. Since then, the total number of identified back-up donors for Dutch patients has tripled over the years. This could be attributed to the increasing number of registered donors worldwide[7], in combination with our evidence-based search strategy.

In 46 cases, the donor centre cancelled the work-up procedure. The reasons for donor cancellation were divided into medical and nonmedical reasons. A significant number of female donors were deferred due to medical reasons (P=0.005). The preference for the selection of male donors for stem cell transplantation was discussed before in relationship to transplant-related mortality, relapse incidence and graft versus host disease[8–11]. On the basis of our findings and facts as described in the literature, the transplant centres prefer male to female donors if possible.

The reasons for a medical cancellation are not always specified, although a donor centre is free to give information to the transplant centre on this point. In a number of cases, the medical reason was specified. Obesity is a major reason for donor deferral at donor work-up stage; a donor with serious obesity should be deferred at least at the time of confirmatory HLA typing request, but more favourably at the time of recruitment for the unrelated donor registry. Donor registries should give more attention to this point.

There was no difference in donor gender in the nonmedical reasons. Being unavailable at the time of the work-up request or personal withdrawal were the main reasons. Extensive education and information of the donor might reduce this number of cancellations. In terms of volunteer history, it was found that stem cell donors who are also blood donors are less likely to drop out[3]. Generally, the transplant centre is not informed about the blood donor status of unrelated stem cell donors; therefore, we could not confirm this finding.

To determine the benefit of identifying a back-up donor in the initial search, the degree of delay in a normal work-up procedure has been established. A delay can be brought about by either donor-related or patient-related reasons. We showed that a delay caused by donor deferral could be minimised by identifying a back-up donor. The

benefit of identifying a back-up donor not only results in more patients proceeding to transplantation but also decreases the cost of overall treatment. This might be of substantial importance; the necessity for second unrelated donor search not only incurs search costs but also costs of extra treatment and hospital admission for the patient. Another aspect is the time that is needed to perform a second unrelated donor search. A number of patients will be at risk of relapse or deterioration of their disease, and will therefore no longer be eligible for stem cell transplantation if there is an untimely delay to transplantation due to donor deferral. It is yet unknown how the search procedure affects the mental state of health of the patient. It is recommended that future searches investigate the experiences of patients who are enrolled in an unrelated stem cell donor search, especially when arrangements for transplantation have been made (eg patient's conditioning regimen is started) and the transplantation is deferred due to a donor cancellation and no back-up donor is available.

Conclusion and recommendations

Donor deferral, in particular during the work-up procedure, is never welcome and can cause a serious delay. It is strongly advised that donor registries ask for basic medical information (including height and weight) at the time of recruitment, and certainly at the time of confirmatory HLA typing request, to prevent unwanted surprises. Our search strategy, including the search for a back-up donor, prevents unnecessary loss of precious time for both patient and transplant centre. With the knowledge of almost 10% donor cancellations during the work-up procedure, identifying a back-up donor should be a standard element in the search process. It is therefore strongly advised that transplant centres identify a back-up donor in the initial search and inform the donor centre about the back-up donor status at the time a donor is released. On the basis of these results, transplant physicians are now better able to inform the patient concerning the possible obstacles in the unrelated search and donor work-up procedure. The information should include a discussion of the likelihood that the identified suitable donor may not precede to actual donation.

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Chapter
9

DISSIMILAR BENEFITS OF THE INCREASE OF THE GLOBAL DONOR INVENTORY OF ALTERNATIVE DONORS AND STEM CELL GRAFTS FOR PATIENTS OF NORTH-WESTERN EUROPEAN VERSUS NON-NORTH-WESTERN EUROPEAN DESCENT

SM van Walraven
A Brand
JNA Bakker
MBA Heemskerk
S Nillesen
MB Bierings
LB Bungener
BG Hepkema
A Lankester
A van der Meer
K Sintnicolaas
JAE Somers
E Spierings
MGJ Tilanus
CEM Voorter
JJ Cornelissen
M Oudshoorn

The Lancet Haematology, under review Sep-2014

Abstract

Between 2001 and 2012 the global inventory of unrelated donors (UD) for haematopoietic stem cells increased from 7 to 21 million and the number of available cord blood units (CBU) increased to over 500,000. We addressed the question whether this expansion has resulted in a higher percentage of transplants for patients in need of UD or CBU transplantation. UD and CBU searches were evaluated for 3124 patients in the Netherlands in two cohorts (2001-2006, n=995, 2007-2012, n=2129), comparing results for patients of north western European (NWE) and non-north western European (non-NWE) origin. Endpoints were donor found and transplantation reached. Despite the substantial growth of the global donor inventory, the median number of potential volunteer stem cell donors per patient (n=7) for non-NWE patients has not improved over time, while for NWE patients the median number of potential donors increased from 42 to 71. For the period before and after 2007 an UD/CBU was identified for 91% and 95% of NWE patients respectively. For non-NWE patients these figures were 65 and 82% respectively ($p<0.0001$), due to more non-NWE patients for whom a suitable CBU could be identified. However, the degree of donor-recipient matching was significantly lower as compared to NWE patients ($p<0.0006$). Additionally, a significant reduction of the time needed to identify a UD/CBU was apparent. As a result, the percentage of patients actually reaching their intended transplant increased from 76% to 82% for NWE patients and from 53% to 69% ($p=0.0003$) for non-NWE patients. Collectively, our results show that the increase of the global inventory of UD/CBU has resulted in more transplants for patients lacking a family donor. However, the quality and quantity of potential haematopoietic stem cell grafts for patients with a non-NWE descent is still inferior, indicating an urgent need for those patients.

Introduction

Allogeneic haematopoietic stem cell transplantation (alloHSCT) is an important part of treatment in many haemato-oncological diseases. For patients lacking a matched related donor, an unrelated donor (UD) or cord blood unit (CBU) may provide a valuable alternative. Alternative donors can be identified through registries of volunteer unrelated donors or public cord blood banks. In the past decade, improvements in the identification and availability of UD and UCB have been achieved. Bone Marrow Donors Worldwide (BMDW), the file of registered unrelated donors, has almost tripled (from 7.4 million donors in 2001 to over 21 million in December 2012), while the inventory of unrelated cord blood units CBU grew from 87,000 in 2001 to over 500,000[1]. An increased knowledge of the HLA system and availability of several search related-software tools[2-5], may facilitate and speed up the efficiency of the search process[6-8]. Also, the simultaneous search for a back-up donor has been shown to minimize the delay if a donor is unexpectedly not fit or unavailable to donate[9]. With these recent improvements, we set out to address the question whether a higher percentage of patients in need of an UD/CBU may actually reach transplantation nowadays and also whether the time needed to identify an UD/CBU has decreased. The questions were addressed in a large cohort of 3365 consecutive unrelated donor searches performed between 2001-2012 in The Netherlands, including searches for 2772 Dutch patients from north-western European (NWE) descent and 352 non-north-western European (non-NWE) patients.

Patients & Methods

The patients and donor searches

Europdonor Foundation, the Dutch Stem cell donor registry coordinates the unrelated donor searches (UDS) in the Netherlands, serving a population of 16.8 million inhabitants. The number of Transplant Centres is eight adult centres and two paediatric HSCT units in 2012, and the number of new searches is currently 500 annually. All UD and CBU searches performed from 2001 until 2012 for the patients of all Dutch HSCT centres were included (n=3365, figure 1), and divided into two periods: Cohort I, 2001-2006 (n=1093) and Cohort II, 2007-2012 (n=2272), each cohort was split according to NWE and non-NWE descent. Patients were assigned to NWE or non-NWE background, based upon a self identified descent[10]. Descendants from the Netherlands, Germany, Belgium, Luxemburg, Great Britain, Ireland, and Scandinavia were considered NWE. The non-NWE group consisted of patients with genetic ancestry in Northern Africa (n=51), Sub-Saharan Africa (n=22), Turkey (n=87), Asia (n=54), Eastern Europe (n=4), Hispanic (n=9), or mixed (n=125). Data were collected from the Europdonor national search database and patients' files in the search units in Leiden and Nijmegen.

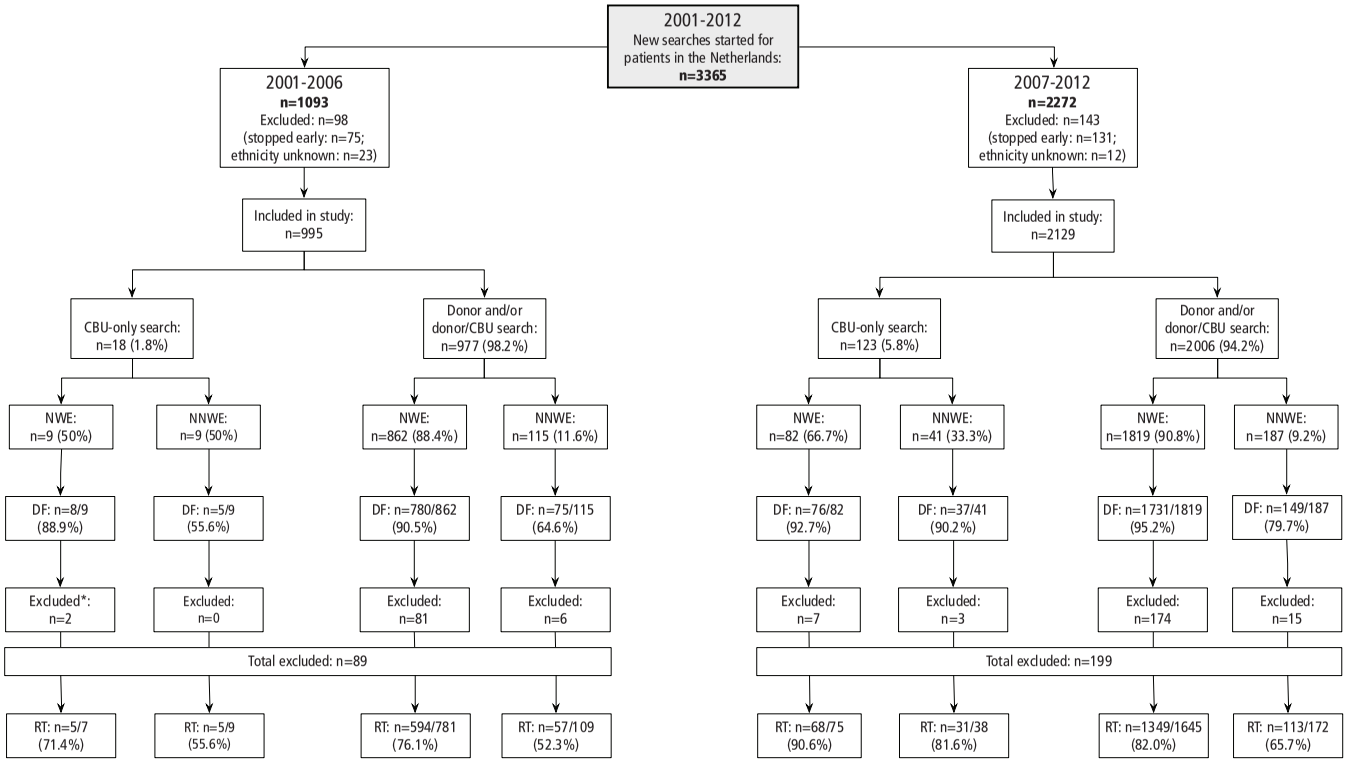

Figure 1: Overview of inclusion/exclusion in different stages of the search process
NWE = north western European; NNWE = non-north western European; DF = donor found;
CBU = cord blood unit; RT = reached transplantation
* Patients for whom the procedure was cancelled for reasons not related to the search process were excluded

Searches for combined donor/CBU and CBU-only and searches for NWE and non-NWE patients were analyzed separately.

Diagnoses were described in broad groups (Table 1); haemoglobinopathies, immunodeficiency- and metabolic disorders were subscribed to inborn errors (IE). Malignancies that could not be described to main groups were assigned to Other Malignant Diseases (OMD) and acquired non malignant diseases in Other Non Malignant Diseases (ONMD).

Patients with unknown ethnic background (n=35, of which n=14 reached transplantation) were excluded. Patients for whom a search was cancelled very shortly after initiation and for whom no donor was yet identified were excluded for the 'Donor Found' (DF) analysis (Cohort I, n=75; Cohort II, n=131). The remaining evaluable search cases (n=3124) originated from the following Transplant Centres (TC): Academic Medical Centre Amsterdam (n=131), Erasmus Medical Centre Rotterdam (n=479), Free University Medical Centre Amsterdam(n=216), Leiden University Medical Centre (n=831, of which 312 paediatric patients), Maastricht University Medical Centre (n=141), University Medical Centre Groningen (n=74), University Medical Centre Nijmegen (n=391, of which 80 paediatric patients), University Medical Centre Utrecht (n=861, of which 241 paediatric patients).

For the analysis of 'Reaching Transplantation' we excluded n=288 patients for whom a donor was found but transplantation was cancelled due to reasons not related to the search process (Cohort I, n=89, Cohort II, n=199), see figure 1. Reasons include: never reached remission/refractory disease (n=100), alternative therapy chosen (e.g. ATG for SAA or randomized for non-SCT arm in study, n=88), autologous HSCT (n=5), (extended) family donor available (n=23), indication changed / good clinical condition (n=27) and patient withdrawal (n=45). This left n=2836 searches for the analysis (n=788 NWE and n=118 non-NWE patients in Cohort I and n=1720 NWE and n=210 non-NWE patients in Cohort II).

Search strategies

The basis for the current protocol for UD/CBU search was previously described[11,12] and adjusted to new insights and better quality of the donor pool. Each new search, irrespective for UD or CBU, started with estimation of the likelihood of finding an acceptable donor, taking into consideration the match-grade or stem cell source preferences of a centre. These results are communicated with the centre and where it is unlikely to find an acceptable donor, search strategies or treatment options are adjusted to avoid unnecessary delay.

The search profile for UD is based upon confirmed HLA-typing of the patient (HLA-A, -B, -C, -DRB1, -DQB1 high resolution), including a review of family typing,

Table 1: Baseline characteristics of NWE and NNWE patients in two search periods.
Legend : ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, CLL – chronic lymphoblastic leukemia, CML – chronic myeloid leukemia, MDS – myelo dysplastic syndrome, PCD – plasma cell disorder, OMD – other malignant diseases, SAA – severe aplastic anemia, IE – inborn errors, ONMD – other non malignant diseases; *Fisher's Exact test; **Wilcoxon rank sum test; ***Chi square test.

	2001-2006 NWE	2007-2012 NWE	p	2001-2006 NNWE	2007-2012 NNWE	p
Total no of patients (n)	871	1,901		124	228	
< 16 yr (%)*	135 (15.5)	139 (7.3)	p<0.0001	41 (33.1)	66 (28.9)	n.s.
Median age, yrs	38.5	51.5	p<0.0001	13.8	19.9	p=0.002
(range)	(0.1-67.1)	(0.1-79.7)		(0.1-65.7)	(0.1-67.3)	
Median age < 16 yr (yr)	6.4	6.3	n.s.	4.5	5.3	n.s.
Median age > 16 yr (yr)	44.3	54	p<0.0001	30.6	42.0	p=0.01
Male (%)*	545 (62.6)	1131 (59.5)	n.s.	82 (66.1)	141 (61.8)	n.s.
Deviation from 50/50 ratio***	p<0.0001	p<0.0001		p<0.0001	p<0.0001	
Diagnosis (%)						
ALL	134 (15.4)	241 (12.7)	n.s.	25 (20.2)	36 (15.8)	n.s.
AML	207 (23.8)	644 (33.9)	p<0.0001	25 (20.2)	49 (21.5)	n.s.
CLL	34 (3.9)	99 (5.2)	n.s.	1 (0.8)	4 (1.8)	n.s.
CML	89 (10.2)	96 (5.0)	p<0.0001	9 (7.3)	12 (5.3)	n.s.
MDS	124 (14.2)	241 (12.7)	n.s.	11 (8.9)	19 (8.3)	n.s.
PCD	51 (5.9)	177 (9.3)	p=0.002	1 (0.8)	8 (3.5)	n.s.
Lymphoma	109 (12.5)	227 (11.9)	n.s.	4 (3.2)	19 (8.3)	p=0.0002
OMD	6 (0.7)	13 (0.7)	n.s.	1 (0.8)	0	n.s.
SAA	40 (4.6)	66 (3.5)	n.s.	7 (5.6)	18 (7.9)	p=0.03
IE & ONMD	77 (8.8)	97 (5.1)	p=0.0003	40 (32.3)	63 (27.6)	n.s.

haplotype frequencies, allele frequencies, HLA-B/C-associations, and HLA-DRB1/DQB1 associations. Ethnic background and results of BMDW regular match (mismatch runs if applicable) are taken into consideration. Where appropriate, advice for a concurrent donor search within the extended family search is given[12]. A 10/10 or 9/10 HLA matched donor was usually preferred, however, in some transplant protocols (e.g. reduced intensity regiment [RIC]), mismatched donors are not acceptable. Search profile for CBU is based on HLA-A, -B (serological (split) level) and -DRB1 at high resolution and the minimum total nucleated cell count (TNC) based upon body weight of the patient and according to local protocols is applied[13]. If no 6/6 or single mismatched units with sufficient TNC are identified, a run for two mismatches is performed, for both single and double cord searches.

In the selection of donors for verification typing, non-HLA factors (age, gender, ABO, CMV status, previous donation) are considered. Verification typing of prospective UD's is performed for HLA-A, -B, -C, -DRB1, -DQB1 high resolution by the centre; for the selection of a CBU the minimum HLA typing requirements are HLA-A and -B on serological split level and HLA-DRB1 on high resolution level, usually performed upon request by the cord blood bank. In this study, a number of patients/donors were not typed for HLA-C, due to local policies. Match-grade for these pairs (n=71 in Cohort I and n=129 in Cohort II) were considered 'unknown'.

Definitions

Donor found: a donor/CBU meeting the valid HLA matching criteria of the centre at that time. *Match-grade UD:* for UD all five high resolution typed loci HLA-A, B, C, DRB1, DQB1, were taken into consideration. A single mismatch on one of these loci is considered 9/10. *Match-grade CBU:* Only three loci (HLA-A, -B at the (split) serological level, -DRB1 at high resolution) and TNC are both taken into consideration. Generally a ≥ 4/6 match according to local protocols is applied[13]. *Length of search:* the minimal interval in days from start search to identify an acceptable donor or CBU. *No donor found:* if a search was cancelled after the median necessary time for a search in that particular year, the search remained included in the No donor found-group.

Statistical analysis

Statistical analysis was performed using R version 2.15.1 (Copyright 2012, the R Foundation for Statistical Computing). For measure of associations and differences we used Chi Square test, Fisher's Exact test (two tailed) and Wilcoxon rank sum test.

For measure of correlation we used Pearson's product-moment. A p-value of 0.05 or less was considered significant.

Results

Baseline characteristics of NWE (n=2772) and non-NWE (n=352) patients are presented in Table 1. The distribution of NWE and non-NWE patients did not significantly differ over time between both cohorts (13% non-NWE in cohort I, and 11% non-NWE in cohort II). The median age of patients increased significantly over time, mainly due to more elderly NWE patients. Non-NWE patients remained significantly younger than NWE patients in both periods ($p<0.0001$). Indications for transplantation changed over time. The proportion of patients with CML and inborn errors (IE) decreased while the proportion (elderly) NWE patients with acute myeloid leukaemia (AML) and plasma cell malignancies (PCD) significantly increased (Table 1). The distribution of ethnic backgrounds of non-NWE patients in cohorts I and II was similar. Characteristics of the search process are reported in Table 2. The median number of potential donors increased from 42 to 71 only for NWE patients ($p=0.004$) and remained at seven for non-NWE patients. A preferred CBU-only search was significantly more often performed for non-NWE patients ($p<0.0001$, Table 3).

Donor found

Significantly more UD/CBU were found in the second Cohort ($p<0.0001$) for both NWE and non-NWE patients (Table 2). In Cohort I, an UD/CBU was identified for 91% of NWE patients and 65% of non-NWE patients. In Cohort II, an UD or CBU was identified for 95% of NWE and 82% of non-NWE patients. Cord blood as an alternative stem cell source was needed more frequently for non-NWE patients in both cohorts ($p<0.0001$), although better matched (6/6) units were more often found for NWE patients ($p<0.002$, supplemental data). The amount of identified CBU's for non-NWE almost doubled over time (18%-33%).

Grade of HLA matching and non-HLA donor-recipient matching aspects

Major differences in match-grade were observed between NWE and non-NWE patients. For non-NWE patients in Cohort II compared to Cohort I, less 10/10 HLA matched or 9/10 HLA matched donors were identified. For at least 91% of NWE patients in Cohort I and 88% in Cohort II a $\geq$ 9/10 donor was found, compared to 64% of non-NWE patients in Cohort I and 58% non-NWE patients in Cohort II (Table 2).

Other characteristics that may affect transplant outcome, such as donor-recipient gender disparity reduced over time for NWE patients but not for non-NWE patients in cohort II. CMV mismatches between the pairs decreased significantly for NWE

Table 2: Characteristics in search and reaching transplantation in NWE and NNWE patients in two periods.
*Wilcoxon rank Sum test, **Fisher's Exact test,***Chi Square test.

	2001-2006 NWE	2007-2012 NWE	p	2001-2006 NNWE	2007-2012 NNWE	p
Total no of patients (n)	**871**	**1,901**		**124**	**228**	
HLA-ABDR-matches in BMDW*	42	71	p=0.0002	7	7	n.s.
median number (range)	(0-17,851)	(0-37,618)		(0-655)	(0-1,841)	
Search performed n (%)**						
Donor/CBU search	862	1,819		115	187	
CBU-only search	9 (1.0)	82 (4.5)	p<0.0001	9 (7.3)	41 (18.0)	p=0.006
Samples requested (n)*	3,889	8,450		449	813	
Median (range)	5 (1-18)	4 (1-27)	p<0.0001	4 (1-17)	4 (1-14)	n.s.
Samples received (%)	2,464 (63.4)	5,458 (65.0)		240 (53.5)	399 (49.1)	
Median	4	3	p<0.0001	3	2	n.s.
Donor/CBU found (%)**	**788 (90.5)**	**1,807 (95.1)**	p<0.0001	**80 (64.5)**	**186 (81.6)**	p=0.0007
Donor, n (%)	756 (86.8)	1,624 (85.4)	n.s.	58 (46.8)	112 (49.1)	n.s.
CBU, n (%)	32 (3.7)	183 (9.6)	p<0.0001	22 (17.7)	74 (32.5)	n.s.
No donor found	83	94	p<0.0001	44	42	p=0.0007
Donor not acceptable	7	26		2	1	
Match-grade donors (%)**						
10/10	460 (64.2)	1,158 (68.8)	p=0.03	23 (28.8)	46 (25.6)	n.s.
9/10	193 (26.9)	326 (19.4)	p=0.0003	28 (35.0)	59 (32.8)	n.s.
<9/10	32 (4.5)	17 (1.0)		7 (8.8)	1 (0.6)	
Cord Blood	32 (4.5)	183 (10.9)	p=0.0001	22 (27.5)	74 (41.1)	n.s.

Table 2 (continued): Characteristics in search and reaching transplantation in NWE and NNWE patients in two periods. *Wilcoxon rank Sum test, **Fisher's Exact test,***Chi Square test.

	2001-2006 NWE	2007-2012 NWE	p	2001-2006 NNWE	2007-2012 NNWE	p
Match-grade unknown, n (%)	71 (9.0)	123 (6.8)		n.a.	6 (3.2)	
Donor age, median (range)	34 (18-58)	35 (18-59)	n.s.	34 (30-57)	37 (19-57)	n.s.
Donor gender, male (%)	361 (63.2)	753 (60.3)	n.s.	21 (48.8)	43 (52.4)	n.s.
Sex matched	365 (63.9)	871 (69.8)		23 (53.5)	42 (51.2)	
Sex mismatched**	206 (36.1)	377 (30.2)	p=0.01	20 (46.5)	40 (48.8)	n.s.
Male patient - female donor	98 (17.2)	192 (15.4)	n.s.	16 (37.2)	25 (30.5)	n.s.
Female patient - male donor	108 (18.9)	185 (14.8)	p=0.02	4 (9.3)	15 (18.3)	n.s.
CMV (known for n couples)	**381**	**1,126**		**31**	**70**	
Matched (%)	237 (62.2)	817 (72.5)		21 (67.7)	49 (70.0)	
CMV mismatched**	144 (37.8)	309 (27.5)	p=0.0002	10 (32.3)	21 (30.0)	n.s.
Patient negative - donor positive	51 (13.4)	122 (9.9)	p=0.02	1 (3.2)	6 (8.6)	n.s.
Patient positive - donor negative	93 (24.4)	187 (16.6)	p<0.0001	9 (29.1)	15 (21.4)	n.s.
Length search in days*						
Start - donor found (median)	43	34	p<0.0001	56	36	p=0.0005
Range	(2-393)	(1-276)		(7-123)	(1-290)	
Excluded (see P & M)**	83	181	n.s.	6	18	n.s.
Included for reaching transplantation analysis	**788**	**1,720**		**118**	**210**	

Table 2 (continued): Characteristics in search and reaching transplantation in NWE and NNWE patients in two periods.
*Wilcoxon rank Sum test, **Fisher's Exact test, ***Chi Square test.

	2001-2006 NWE	2007-2012 NWE	p	2001-2006 NNWE	2007-2012 NNWE	p
Reaching Transplant, n (%)**	**599 (76.0)**	**1,417 (82.3)**	p=0.0003	**62 (52.5)**	**144 (68.6)**	p=0.0003
BM / PBSC	571 (95.3)	1,248 (88.1)	p=0.0003	43 (69.4)	82 (56.9)	p <0.0001
CBU	28 (4.7)	169 (11.9)	p<0.0001	19 (30.6)	62 (43.1)	n.s.
With back-up donor/CBU	68 (11.4)	157 (11.1)	n.s.	2 (3.3)	13 (9.0)	p=0.01
Time to transplantation (days)						
Donor found - infusion	68	54	p<0.0001	48	53	p<0.0001
Start - infusion	113	91	p<0.0001	109	92	p=0.0008
If CBU	102	85	p<0.0001	91	81	p<0.0001
Transplant cancelled, n (%)	**189 (24.0)**	**304 (17.7)**		**57 (48.3)**	**66 (31.4)**	
Clinically deteriorated	95 (12.1)	175 (10.2)	p=0.0008	9 (7.6)	18 (8.6)	n.s.
Donor referred, no back-up	4 (0.5)	9 (0.5)	n.s.	2 (1.7)	5 (2.3)	n.s.

patients but not for non-NWE patients. The median time to identify a donor for a combined donor/CBU search in NWE patients in Cohort I was 43 days and in Cohort II 34 days and also considerably improved in Cohort II for non-NWE patients (median of 56 and 36 days in Cohort I and II respectively, Table 3).

A CBU-only search was performed upon request of the centres for 18 patients of Cohort I (2%) and 123 patients of Cohort II (6%). Preferred CBU-only searches were in both cohorts significantly more often performed for non-NWE patients. A preferred CBU search despite a fully matched UD available was less often performed for non-NWE patients (one and two patients in cohort I and II respectively). For NWE patients this occurred for five and 17 patients in cohort I and II, respectively.

For the group of 288 excluded patients (see patients and methods), searches were not longer (median 42 days and 35 days respectively). For n=127/995 patients (13%) in Cohort I and n=136/2124 (6%) patients in Cohort II, no acceptable UD/CBU was identified. The median search time was longer in comparison to the donor found group ($p<0.0001$, data not shown)

Reaching transplantation

Despite a successful donor search, procedures were cancelled by the TC for 89 patients in Cohort I and 199 patients in Cohort II, because the patient clinically deteriorated or died (see Table 2). There was no correlation between length of search and whether or not a transplant was actually performed. The percentage of patients being transplanted increased significantly over time with NWE patients more often reaching their intended transplantation. In total 76% (n=599/788) NWE and 53% (n=62/118) non-NWE eligible patients in Cohort I and 82% (n=1417/1720) NWE and 69% (n=144/210) non-NWE eligible patients in Cohort II reached transplantation. The increase for non-NWE patients from 53 to 69% was statistically significant ($p<0.0003$). Overall NWE patients were transplanted with better matched donors (figure 2), and CBU as stem cell source was significantly more frequent in non-NWE patients.

Back-up donor

In Cohort I, 70 patients (9.3% of NWE and 5.5% of non-NWE patients) and in Cohort II 170 patients (9.8% of NWE and 7.8% of non-NWE patients) received stem cells from a back-up donor (n=234) or a back-up cord blood unit (n=6). Apart from the chosen donor being deferred or no longer available during work up, in both cohorts in four cases the TC decided to switch to the back-up donor, because the identified donor was only able or willing to donate bone marrow, where PBSC was preferred. In one case the donor did not show up on day of aphaeresis. In 10 cases (Cohort I n=3, Cohort II=7) a new search for a back-up donor had to be initiated, causing an

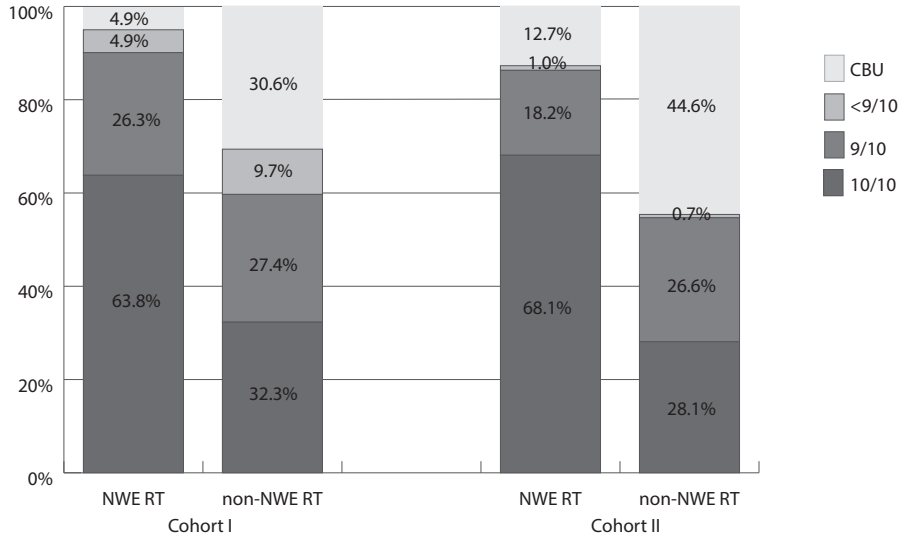

Figure 2: Match-grade donor in NWE and non-NWE patients reaching transplantation (match-grade unknown for n=52 in NWE 2001-2006, n=84 in NWE 2007-2012, and n=5 in non-

median delay of 15 days (range 0-412 days) to transplantation, compared to median 9 days range 1-181 days) if a back-up donor was available. In 27 cases the match-grade of the requested back-up donor was lower than the originally identified donor.

Discussion

In the last decade, significant investments[14] have been made to increase the worldwide haematopoietic stem cell donor pool and to improve the quality of donor HLA typing. However, there is still concern about the availability of alternative donors, especially for patients of non-European descent[15]. We addressed the question whether the expansion of the global donor inventory has resulted in a higher percentage of transplants for patients in need of an unrelated donor or cord blood transplantation and which patients benefitted in particular. Overall we observed a higher percentage of transplants in both NWE and non-NWE patients, for whom a search was started in the period 2007-2012, when compared to the search period before 2006. However, despite the significant increase of volunteer UD, non-NWE patients showed only little benefit and 30% of transplants in this group was performed with CBU, compared to 10% in NWE patients. Although overall more donors were found, the probability to identify a 10/10 matched donor for non-NWE patients has not improved, while a significant advantage for NWE patients (Table 3) has become apparent.

Gragert et al recently reported their theoretical population-genetics based

Table 3: Major differences between results for NWE and non-NWE patients in two periods. *Wilcoxon rank Sum test, **Fisher's Exact test,***Chi Square test.

	2001-2006		p	2007-2012		p
	NWE	NNWE		NWE	NNWE	
Age (median, yrs)*	38.5	13.8	p<0.0001	51.5	19.9	p<0.0001
Diagnosis (%)**						
AML	23.8	20.2	n.s.	33.9	21.5	p<0.0001
PCD	5.9	0.8	p=0.02	9.3	3.5	p=0.002
IE & ONMD	8.8	32.3	p<0.0001	5.1	27.6	p<0.0001
Median donors in BMDW (n)*	42	7	p<0.003	71	7	p<0.0006
CBU only search (%)**	1	7.3	p<0.0001	4.4	41	p<0.0001
CT samples received (%)*	63	53	p=0.05	65	49	p<0.0001
Length of search (days)	43	56	p=0.01	34	36	p=0.02
Donor/CBU found (%)***	90.5	64.5	p<0.0001	95.1	81.2	p<0.0001
10/10 (%)	64.2	28.8	p<0.0001	68.8	25.6	p<0.0001
9/10 (%)	26.9	35	p<0.02	19.4	32.8	n.s.
CB as stem cell source (%)	4.7	27.6	p<0.0001	10.1	39.8	p<0.0001

model showing the likelihood of finding a well matched UD or CBU for patients of different ethnic background in the USA[15]. Donor availability, inconsistent typing results and donor medical eligibility were taken into account. The model is based on donor and cord blood data in their registry (approximately 50% of the global inventory), and showing the likelihood of identifying an UD/CBU for both white Europeans and African-American patients, which is over 95%. Using 100% of the global inventory[1], we found for 95% of NWE patients and only 81% of non-NWE patients an acceptable UD/CBU with a match-grade of at least 7/8. The difference may be explained by the clinical nature of our study, implying that we searched for actual patients. The assumption of Gragert et al that the donor population represents a true reflection of the patient population is possibly overestimate the probability of finding an acceptable UD/CBU in particular for non-NWE patients. Furthermore, a mismatched donor or CBU is not always an acceptable alternative. Despite availability of mismatched UD or CBU the outcome of the UDS would be No Donor Found. All patients for whom no donor was found in our study had one or more rare alleles or uncommon HLA-B-C/DRB1-DQB1 associations or a combination of these, often originating from a mixed racial background. Currently, for a Dutch NWE patient a median number of 71 potentially matched donors are listed, often allowing selection for characteristics such as donor age, gender and CMV status, factors that may improve transplant outcome. In contrast, we found that the number of potentially

matched donors for our non-NWE patients remained low: a median number of seven UD per patient. These results confirm that non-NWE patients still lag behind because of limited registered, available and suitable non-NWE donors within the national and international registries[16-20] and are more likely to be transplanted with less optimal HLA matched donors or CBUs[17,21].

Length of search and reaching transplantation

A significant shorter search time for both NWE and non-NWE patients was observed in more recent years, which appeared to be associated with a reduction of cancelled procedures. Cancellation, due to clinical deterioration of the patient after an UD/CBU was identified, was approximately 30% in the period 1991-2000[11], but only 10% in the years after 2007. It emphasizes the importance of time, in particular in adult patients with high risk leukaemia[22-24]. Future development of HLA next generation sequencing techniques are expected to enhance the quality of the global UD inventory[25,26] even more. In combination with provision of additional donor characteristics, it allows TC's to request stem cell donors that are completely typed on high resolution and fulfil additional criteria, thereby minimizing the length of search virtually to one day, and facilitating transplantation within a month from UDS initiation. Such a combined request for verification typing and stem cell donation is occurring more frequently in recent years. Further potential saving of time may be achieved in the period between donor identification and transplantation. Early recipient HLA typing[27], estimation of the likelihood to identify a donor and efficient search protocols allow for optimum time planning, thus reducing the time to transplantation to a minimum[7,8,28-31].

Cord blood as stem cell source for non-NWE patients.

An increasing percentage of actual transplantations was observed for non-NWE patients in the most recent period, which appeared due to a higher number of CBU transplants. Cord blood is currently increasingly applied in patients with very poor risk acute leukaemia, needing an immediate transplant after having obtained remission, or children with IE, other than haemoglobinopathies[12,32]. CBU's are almost instantly available and requires less-stringent HLA matching criteria, but on the other hand is associated with a higher rate of graft failure and retarded haematopoietic recovery[33,34] Recent studies have suggested better outcome following unrelated CBU using grafts with higher cell numbers, or double CBU grafts, and/or better matched grafts[35-39]. Although the probability of finding an CBU with at least a 4/6 match increased over time for non-NWE patients, the degree of matching in non-NWE patients appeared still significantly less than in NWE patients in our study, indicating that non-NWE patients continue to receive suboptimal donor grafts. In concordance with Gragert et al[15], our findings in successive cohorts of non-NWE patients strongly

underpin the urge to expand the global inventory, but especially focusing on donors and grafts from ethnic minorities.

Conclusion

Collectively, we conclude from this large retrospective study that the increase of the global inventory and the major efforts and investments to improve the search-process have resulted in a strong benefit for NWE patients. However, the probability to identify a well matched UD for non-NWE patients has not increased in time and non-NWE patients more often rely on CBU as an alternative stem cell source. In addition, the match-grade for both UD and CBU is less optimal for non-NWE patients. Finally, we observed that improved efficiency of the donor search time is associated with overall more NWE and non-NWE patients reaching their intended transplantation.

Contributors

SMvW, MBAH, AB and MO designed the study. MO and AB supervised the analysis. SMvW and SN collected data. SMvW, AB, JJC and MO interpreted data. SMvW and JNAB performed statistical analysis. SMvW wrote the manuscript. AB, MO, JNAB, MBAH, SN, MBB, LBB, BGH, AL, AvdM, KS, JAES, ES, MGJT, CEMV contributed to the drafting of the report. JJC critically reviewed the report and contributed to the final drafting. All authors agreed with the final version of the manuscript.

Declaration of interest

We declare no competing interests.

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Chapter
10

REMUNERATION OF HEMATOPOIETIC STEM CELL DONORS: PRINCIPLES AND PERSPECTIVE OF THE WORLD MARROW DONOR ASSOCIATION

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Abstract

Hematopoietic stem cell transplantation is a curative procedure for life-threatening hematologic diseases. Donation of hematopoietic stem cells (HSCs) from an unrelated donor, frequently residing in another country, may be the only option for 70% of those in need of unrelated hematopoietic stem cell transplantation. To maximize the opportunity to find the best available donor, individual donor registries collaborate internationally. To provide homogeneity of practice among registries, the World Marrow Donor Association (WMDA) sets standards against which registries are accredited and provides guidance and regulations about unrelated donor safety and care. A basic tenet of the donor registries is that unrelated HSC donation is an altruistic act; nonpayment of donors is entrenched in the WMDA standards and in international practice. In the United States, the prohibition against remuneration of donors has recently been challenged. Here, we describe the reasons that the WMDA continues to believe that HSC donors should not be paid because of ethical concerns raised by remuneration, potential to damage the public will to act altruistically, the potential for coercion and exploitation of donors, increased risk to patients, harm to local transplantation programs and international stem cell exchange, and the possibility of benefiting some patients while disadvantaging others.

Background

Hematopoietic stem cell transplantation (HSCT) has been in use since the 1960s and is a proven cure for patients with hematologic and metabolic disorders and immune deficiencies. A necessity for performing HSCT is that the donor and the recipient have identical or close to identical human leukocyte antigen (HLA) phenotypes. The first allogeneic HSCTs were performed with HLA matched related donors only. There is a 25% chance that 2 siblings inherit the same HLA phenotypes, and ~30%-35% of patients will have an HLA identical sibling or closely matched family donor. For patients requiring an allograft who do not have a related donor, an HLA matched unrelated donor or cord blood unit has been an option for 4 decades.

The single most important donor factor in determining transplantation outcome is the degree of HLA matching between patient and donor[1,2]. The HLA system displays extreme polymorphism, such that for many patients, there may be few if any other persons who will match their unique HLA type. To assist patients in finding a potential unrelated donor, registries of HLA typed volunteer donors were first established in the early 1970s. It was soon realized that the opportunity for finding a matched donor would be significantly enhanced by creating a mechanism for searching donor registries in other countries. This was achieved by the formation of Bone Marrow Donors Worldwide in 1988. Bone Marrow Donors Worldwide provides a centralized database containing information on the HLA phenotypes of virtually all unrelated donors (adult and umbilical cord blood, a source also rich in hematopoietic stem cells [HSCs]), allowing the entire international inventory to be searched in one single location.

Currently, there are more than 14.9 million registered unrelated donors internationally, in 64 stem cell donor registries from 44 countries and in 44 organizations of cord blood banks from 26 countries[3]. In 2008, more than 11,500 patients worldwide received an HSC transplant from an unrelated donor. Greater than 44% of those patients used a donor or cord blood unit from another country[4], emphasizing the benefit of international cooperation in all aspects related to the procurement, transport, and use of these stem cell products.

Despite the number of adult donors already registered and the growing numbers of publicly stored cord blood units worldwide, many patients in need of an HSCT still cannot find an acceptable HLA matched donor because they have a rare HLA phenotype. The inability to find an HLA match for specific patients has led to the development of strategies to enhance the registries by increasing both the number and diversity of the donors listed[5,6].

Remuneration of donors is sometimes proposed as a means of incentive so more persons join and donate HSCs. In this context, the issue of remuneration of HSC donors has been raised in a lawsuit filed in the United States District Court in October 2009[7].

In that case, the plaintiffs sought to overturn the prohibition against remuneration for marrow donors found in the National Organ Transplant Act[8], arguing that the prohibition limited access to persons who might donate if they were remunerated.

The question of remuneration of donors is also currently being openly debated in the context of solid-organ donation. For example, the concern about international trafficking of organs and organ donors has recently led the World Health Organization (WHO) to issue a declaration opposing the international exchange of organs[9]. In 2008, in the United States, legislation was prepared that gave states the right to provide remuneration of organ donors as a means to address the organ shortage[10]. Although this legislation was ultimately not introduced, it is reasonable to expect that developments in the organ donation arena will have implications for donors of HSCs as well.

The WHO first formally considered the issue of remuneration for organ, tissue, and blood donation in 1991, taking the position that the human body and its parts should not be subject to commercial transactions[11]. This was reaffirmed by the WHO in 2008 through the restatement of a set of Guiding Principles[12]. The European Union has also taken a position against remuneration in the donation of human tissue and cells[13]. Many countries and other jurisdictions have taken similar positions[14,15].

The World Marrow Donor Association (WMDA) was established to develop international guidelines and policies to ensure unrelated donor and stem cell product safety and to encourage proactive international collaboration toward harmonizing regulatory standards[16]. The WMDA has consistently maintained a policy against remuneration of donors[17,18]. This position is based on the general consensus of its member organizations that a truly volunteer donor-based system would be the most effective and safe way to develop donor registries. Studies have shown that, although donors express several motivations when asked[19], altruism, the selfless regard or concern for the wellbeing of others, is the fundamental principle behind donation[20].

In light of the current debate about remuneration, the WMDA formed a task force to review the question and to develop a policy statement in this matter for its consideration and adoption. Here, we discuss why volunteer persons who provide HSCs to unrelated recipients should not be paid for their humanitarian act.

Common terms

Hematopoietic stem cells (HSCs) mean hematopoietic stem cells derived from bone marrow and peripheral blood unless stated otherwise.

Reimbursement means payments for out-of-pocket expenses incurred by the donor, replacement of lost wages or time off, or payment for medical expenses incurred by or on behalf of the donor related to the donation.

Remuneration means payment of something of value to a donor or other party in exchange for HSCs over and above reimbursement for out-of-pocket expenses.

Ethical considerations

The question of remuneration for donation raises certain ethical concerns. The essential act at issue is the decision by an unrelated person to undergo a medical procedure for the benefit of someone else. A significant body of work has developed around the ethical issues involved in such an exchange, especially in the context of solid-organ donation[21] and use of donors as research subjects[22].

Three ethical principles in particular are often the focus of inquiry. The first is the principle of dignity, which is that the transfer of part of a human body is distinct from that of a product or service and requires unique considerations so as not to devalue human life through commercialization of organ, tissue, and blood. The second principle is that the donor should not be subject to unnecessary or unreasonable harm. Finally, any system of distribution should be fundamentally fair. In particular, no segment within society should benefit at the expense of another segment or permit coercion of any kind in the process of acquiring HSCs.

Dignity

The concept of dignity is premised on the view that the human body should be treated as having intrinsic value apart from the potential economic value that might be placed on organs, tissue, or blood by someone in need. This notion is founded in both religious and philosophical considerations. Many religions hold that the body is a sacred gift from a higher being and a person has the duty to protect or conserve that gift[23]. Any harm to the body is a violation of that duty, except in the case of protecting the person from further harm[24]. From a philosophical perspective, reference is often made to the teaching of Immanuel Kant whose formulation that society should "treat humanity ... always as an end and not as a means only"* is often cited as the basis to conclude that the payment for body parts is a misuse of a human being because it views the provider as a source of supply for the person in need and not a distinct human being[25]. By considering only the economic value of a donated organ, tissue, or blood, the potential exists that markets for body parts will be created. In such a setting, the sale of a body part is seen as devaluing human life by implying that a person's worth is based on the material value of the body rather than as a rational human being. Donation without remuneration is generally permitted in the religious setting as an act of charity benefiting a fellow human, whereas in the philosophical setting the nonremunerated donation is seen as an

*) I. Kant, Werke, hrsg. von W. Weischedel; Band IV, Grundlegung zur Metaphysik der Sitten, S. 61. Darmstadt: Wissenschaftliche Buchgesellschaft; 2005. "Handle so, dass du die Menschheit, sowohl in deiner Person, als in der Person eines jeden andern, jederzeit zugleich als Zweck, niemals bloss als Mittel brauchest".

altruistic act for the benefit or another rather than as a commodification of one human for the befit of the other.

The concept of dignity must be balanced with the person's right to make decisions about his or her own body, reasonably free from the control of society. However, although recognizing that the person has the right to make decisions about his or her own body within a wide spectrum of behavior, society has an interest in avoiding behavior that has certain social consequences that include undermining widely and deeply held views about the value of life[26]. The overriding concern is that the person be valued as a distinct human being.

In the context of dignity, a further argument for remuneration is often advanced as it relates to access to health care for economically disadvantaged populations in which minority ethnic groups tend to be overrepresented In the case of organ donation, denying compensation on the basis of human dignity may deny access to those minority populations that would benefit from donation from persons within the same ethnicity. If that group would respond to compensation, the argument goes, the harm is offset by the benefit to people in the same ethnic group[27]. This has some resonance in regard to unrelated donor HSCT because patients will probably find a donor within their own ethnic group, and registries struggle to find donors within their minority populations. To sustain this view, it must be argued that the economic value derived from the sale of body parts is more important than upholding the concept of personal and societal dignity of human beings. But this is precisely the trade-off that undermines the value that society puts on the human being. It may also lead to the further commodification of the person or disadvantaged group by opening up the potential of remuneration for other body parts, further undermining the value of the person or population[28].

Harm to donor

As noted earlier, the act of donation is to submit to a medical procedure for which the person will not derive any direct benefit. Thus, any harm that might result will not be offset by a benefit to the person undergoing the procedure, except for the sense of satisfaction derived from an altruistic act. Therefore, care must be taken to minimize the potential of harm and to fully disclose any risk to the donor so as to ensure that the decision to donate is made freely and willingly. The decision to take the risk inherent in the procedure must be made without any undue influence or pressure[29].

There is a general agreement that donor registries should have donor safety as their first priority[18,30-32]. Any medical or psychosocial condition that increases the risk to donor has to be thoroughly investigated, resulting either in deferral or approval for donation.

Guidelines for donor risk assessment and deferral are used in conjunction with an individual medical and psychosocial assessment of donor eligibility to make sure that a donor is not asked to take unacceptable risk[33]. If the risk is known to the donor, remuneration has the potential of creating a calculation in which the short-term economic benefit is overvalued compared with the risk being taken by the remunerated donor[34]. The potential for remuneration may also cause the prospective donor to withhold personal health information for fear of being disqualified from donation, preventing an accurate risk assessment and disclosure of risks specific to that donor. As a related matter, the promise of remuneration raises the question of whether the decision to donate is really voluntary when the donor is under some duress due to significant personal economic concerns.

Harm to the donor could occur when the cost to the donor in lost wages, medical bills associated with the donation, or incurring other out-of-pocket expenses would adversely affect the donor. It is widely recognized that the donors should be reimbursed for these types of expenses and are not considered remuneration for purposes of this discussion.

Fairness

Fairness is the concern that the burden of donation not fall on a particular group or class, especially when the benefit accrues to a different group or class. Concern about exploitation of populations underlies both the WHO Guiding Principles and the Declaration of Istanbul[9]. When payment is used as an inducement to provide organs or tissue, it is argued that a wealthier population will exploit poorer populations that will be more susceptible to the perceived short-term gain from the exchange while overlooking the long-term risks and psychosocial implications as discussed further in "Limited benefit of remuneration to donors".

Exploitation of patients is another concern, especially in the HSCT setting. The donor is in the potentially unique situation of being the only possible donor who matches the HLA of the patient, providing significant leverage over the patient; that is, the donor would have the ability to name the price, and market principles would not apply. The donor would have the ability to name his or her price. Patients undergo a preconditioning regimen in the days leading up to the HSCT, which eradicates or suppresses their own hematopoietic system and makes them totally dependent on the cells from the donor to generate a new donor-derived hematopoietic system. The administration of a commercialized donation system while the patient's life hangs in the balance could seriously jeopardize the patient.

Evidence of the exploitative potential of a remuneration-based system has been seen in other settings. For example, in the United States a potential related donor sought compensation for a commitment to donate[35]. At the time when called to

donate, the potential donor extracted further payment. Tragically, the potential donor ultimately refused to donate. Regardless of the final outcome in this case the situation shows the potential vulnerability of a recipient if the basis of the exchange is financial and not altruistic.

Finally, it has been asked that because personnel and institutions involved in HSC donations are paid for their services, why not the donors[36]? This question, however, does not seem relevant, because donors are already reimbursed for their out-of-pocket expenses and compensated for income-loss while away from work for donation reasons. The donors therefore continue to earn their salary like all others involved in the donation, but they earn it despite their absence from work.

Other considerations

Safety of patients

Remuneration has the potential of interfering with this process of risk assessment to the detriment of the patient. In a system that uses remuneration, some persons could find the monetary remuneration so significant that they might hide relevant medical or psychosocial information or both[37,38].

A process that might induce a potential donor to be less forthcoming in response to the screening questionnaire may result in a patient being placed at risk for the transmission of diseases from the donor. Additional screening and testing may reduce, but cannot eliminate, the possibility of harm to the patient.

Although there may be times when the potential of the transmission of disease is outweighed by the benefit to the patient, that decision must be made with the full knowledge of all potential risks to the patient so that a truly informed decision can be made. The prospect of remuneration may cause the donor to provide information late in the process to increase the chance of being selected to donate. Anything that interferes with full disclosure of that potential risk early in the process may needlessly put a patient at risk.

In a similar context, the question of safety to patients in blood donation has resulted in the development of the interna- tional consensus that blood donation be voluntary and uncompen- sated to protect the patient, as most recently evidenced in the Melbourne Declaration[39] of the WHO, which called on "all governments to achieve 100% voluntary nonremunerated donations by 2020 as the cornerstone of their blood policies"[40].

Limited benefit of remuneration to donors

The effect of financial incentives on HSC donor life circumstances is probably minimal and transient. Evidence from the Iranian system of paying unrelated donors for kidneys led a past president of Organ Procurement Transplantation Network in the United States to state that "The experience in Iran and elsewhere suggests that the poor remain poor following a ... sale and then with one less kidney"[41].

Not only are the financial incentives offered for HSCs unlikely to change the donors' life circumstances, but donors in these circumstances are also unlikely to accrue the known lasting psychosocial benefits of HSC donation. There is ample evidence that unremunerated unrelated HSC donors experience enhanced well-being from altruistic donation and incorporate the donation experience into their self-concept. One of the first large investigations of 849 unrelated bone marrow donors found that many donors felt that by donating bone marrow, they were actualizing a central trait in their identity having to do with willingness to help others[42]. Many of these donors believed that the centrality of this helpfulness trait made them distinct from others and more willing to assist. Donors often identified the source of this focus on helping as stemming from a strong emphasis on generosity and altruism within their family of origin.

A second investigation with a similar group of 493 unrelated bone marrow donors found that high proportions of donors reported (1) that they felt like better persons for having donated (71%), (2) that marrow donation made them feel more worthwhile (67%), (3) that donating marrow was a high point in their lives that made everything seem more meaningful (75%), and (4) being proud of having donated (96%)[43]. These extremely positive feelings about donation are directly linked to donors' willingness to engage in future altruistic acts, including donation, and to recommend donation to others. More than 90% of donors in this and other investigations report that they would be willing to donate again if they were asked, and if given the opportunity, they would strongly encourage others to donate. In fact, these self-benefits of the marrow donation process were in many cases greater than those observed for living related kidney donors. This is because, unlike in the case of living related donation, the unrelated donor is under no obligation to the recipient and does not stand to tangibly gain from their donation. Thus, these donors are often viewed as exceptional and as having gone above and beyond the call of duty by family, friends, and coworkers[43].

Evidence suggests that a further potential benefit of the altruistic motivations that lead to unremunerated donation and the positive feelings resulting from the donation itself is that donors may come to view themselves as "medical donors," a self-image that may increase their willingness to engage in other forms of medical donation (eg, blood donation, cadaver organ donation[19]). This will probably be lost

in a system that offers remuneration. Finally, it is a general experience that stem cell donors frequently are willing to accept considerable discomfort without complaining, probably because the act of donation has been so meaningful and valuable for the donor. Perhaps this kind of attitude also can promote a speedy recovery.

Effect on existing registries

Commercialization of donors through remuneration may also create a disincentive for those who are altruistically motivated from joining or continuing to participate on the registry. This behavior has been observed in the blood donation setting[44]. Similarly, it has been observed that the expectation of rewards can undermine the intrinsic value derived from the behavior, reducing interest in participating[45], or reduce motivation to continue with participation once the reward is received[46]. In the latter case, sometimes referred to as "the overjustification effect" a reward paid for the initial donation may result in less motivation to provide a second donation, which is needed in some of the transplantation cases. It is not clear what effect offering payment for HSC donation would have on the overall numbers of persons willing to provide HSCs. However, the motivations for willingness to provide HSCs would be altered, and a significant reduction in the number of donors willing to donate is highly probable for 2 reasons. First, the very nature of stem cell donor registries (only a small fraction of registered donors will ever donate, and there can be years or even decades between registration as stem cell donor and donation) makes it difficult to motivate persons to register through financial rewards for donation. Second, the positive psychosocial effects of donation as described earlier have been successfully used by many donor centers and registries as part of their recruitment strategies. In a setting with donor remuneration, these strategies could not be used anymore. Thus, the offer of remuneration could adversely affect both the willingness of those already on the registry to continue as well as the recruitment of new persons to the registries.

Effect on international exchange

The current system of international exchange is based on the willingness of all participating registries to adhere to a common set of standards and guidelines. These standards are informed by a common set of ethical, legal, and practical concerns. Remuneration also raises the concern that the donor who is paid may believe he or she has a lingering economic right if the unit is not used for the intended purpose. WMDA addresses this concern indirectly by requiring that a donation not be cryopreserved as a matter of practice. In the rare instances when a product is saved and not used for the intended patient, the uncertainty created by the potential of other uses when the product was sold for a specific use would be unacceptable. Variation in country ownership laws would create further uncertainty in international

exchange. If the WMDA were to adopt a standard that allows for use of a remunerated donor, those countries that prohibit remuneration or have standards that do not permit remuneration for safety or other reasons would need to screen out donors from countries that permit remuneration. This could create a 2-tiered system of registries and would complicate the current system of international exchange. The effect would be to reduce the potential pool of donors for patients in some countries and undermine the cooperation among the registries.

Recommendation

The price assigned to the value of human donation is literally the value of life, which cannot be expressed in monetary terms. Donor remuneration raises difficult ethical issues, has the potential to damage the public will to act altruistically, and may involve coercion and exploitation of donors. It may also place patients at increased risk, negatively affect local transplantation programs and international stem cell exchange, and may benefit some patients while disadvantaging others. These concerns have resulted in several national and regional registries as well as legislative and regulatory bodies worldwide to oppose remuneration for the donation of HSCs as well as organ and blood. The WMDA, therefore, concludes that remuneration for HSC donors is undesirable and may be deleterious to the international transplantation community of both patients and donors.

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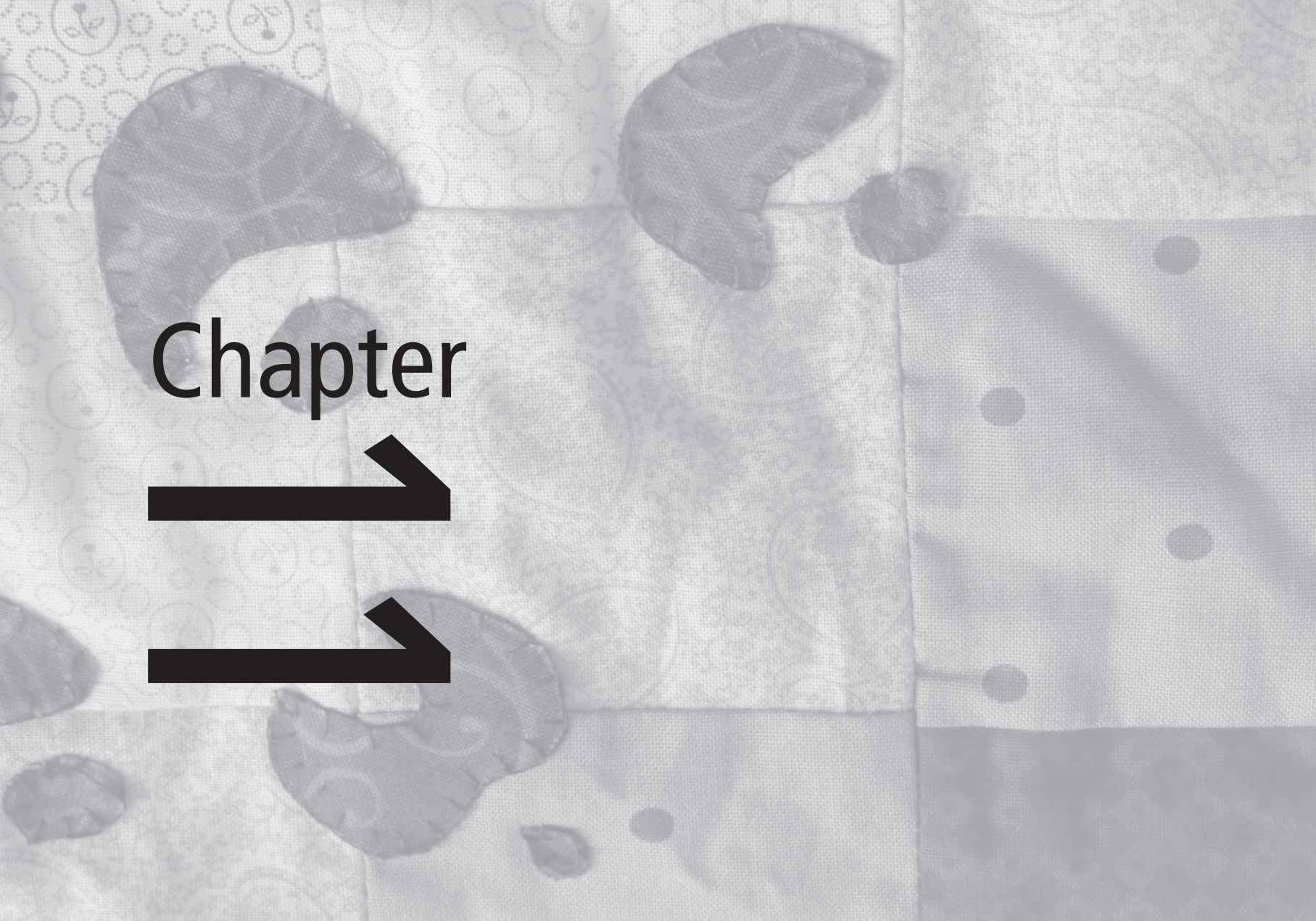
Part V

Summary and Discussion


Chapter

SUMMARY, GENERAL DISCUSSION, AND FUTURE PERSPECTIVES

This thesis focuses on the experience of stem cell donation by unrelated and related donors (minors and adults), aspects of donor care management, and the process of the unrelated donor search. The theme linking these topics is providing patients in need of HSCT with the best stem cell product without impairing the safety of the donor. In this chapter the results of our findings are summarized and put into perspective with regards to current practice and future developments.

Summary

Since the first successful allogeneic hematopoietic stem cell transplantations (HSCT) were performed in 1968, the number of disorders potentially curable with donor derived blood stem cells, has substantially increased, namely hematological malignancies, immunodeficiencies, inborn errors and metabolic diseases. Originally stem cells were harvested from bone marrow, but the availability of recombinant human granulocyte colony stimulating factor (G-CSF) enabled collection of stem cells from peripheral blood (PBSC). Furthermore, banked umbilical cord blood has become an important resource of stem cells.

Although HSCT has become a standard of care procedure, the practice is dynamic with continuous efforts to develop less toxic conditioning regiments and to reduce severe Graft versus Host Disease (GVHD). Furthermore ongoing studies are seeking new therapeutic options to harness donor immunity by use of their mononuclear cells (MNC) to combat relapse of malignant diseases and uncontrollable (viral) infections. These evolvements can directly affect the burden for the donor. Care for anonymous stem cell donors is well organized by unrelated donor registries, based upon the standards of the World Marrow Donor Association (WMDA). However, these regulations do not apply to the related donor. The Ethics and Clinical Working Group of the WMDA shared their expertise in donor care management with the European Group for Blood and Marrow Transplantation (EBMT) in 2010, on the principles and recommendations of donor recruitment, counseling, follow-up and adverse events registration (chapter 2). It was a first attempt to raise awareness for related donor care. The main challenge is that the donor and recipient are relatives, placing the potential donor at risk for coercion. Health care professionals involved in counseling and care of related donors should find the optimal balance between donor's commitment and patients' needs. The establishment of protocols concerning counseling, evaluation of donor's health, reporting adverse events and offering long term follow-up for related donors was also the subject of the first Donor Outcome Workshop in 2009, initiated by the Late Effects Working Party of the EBMT. The goal of this Workshop was to seek consensus for global standardized donor data collection on immediate side effects and long term follow-up (chapter 3). Such a large international cohort of donor data would allow for defining the risks of hematopoietic stem cell donation in other than unrelated volunteer donors. With the scarce available literature (usually

case observations or retrospective descriptive analyses) and the lack of randomized controlled trials, it is often impossible to determine a causal relationship in reported incidents. Theoretical concerns about long term effects of the administration of G-CSF in healthy individuals or the influence of multiple donations have not been addressed in prospective studies because, among other reasons, it is difficult to find funding to cover the overall cost of long term donor follow-up. We performed a retrospective study on a cohort of 268 donors who donated G-CSF mobilized stem cells in the period 1996-2006 to a relative in the Leiden University Medical Centre. The study focused on donor eligibility criteria and cardio vascular and malignancy events at follow-up (chapter 4). Since strict criteria for donor health were not yet established in the early days of PBSC donation, we used criteria of the Dutch unrelated donor registry and National Marrow Donor Program to establish in retrospect whether donors were deferrable or eligible, and found that 15% of donors (n=40) would have been deferred for donation to an unrelated individual stranger. Short-term adverse events did not differ in incidence reported in cohorts of unrelated donations. At long term follow-up, nine malignancies and 14 cardiovascular incidents were reported. These incidences were within the range of the age-and sex-matched general Dutch population, suggesting that there is no additional long term risk for cardio vascular diseases or malignancies in family donors. However, the incidence of vascular complications were substantially, albeit non-significantly, lower in NMDP eligible donors, questioning the validity of the general population as control group, despite correction for age and gender.

The need for registration of Serious Events and Adverse Reactions (SEAR) became apparent with the introduction of G-CSF administration to healthy volunteers. Besides SEARs the WMDA also addressed issues regarding patient safety, (chapter 5). A registry for Serious Products Events and Adverse Reactions [S(P)EAR] was established. S(P)EAR not only highlights risks to the patient related to the product, but also damage to the stem cells due to unsafe transportation. Submitted S(P)EAR's can, depending on severity, be reported to the donor registry and transplant society (involved in the care of related donors) in a Rapid Alert. Although registration of S(P)EAR is only mandatory for WMDA accredited registries, all donor registries are invited to (anonymously) submit any S(P)EAR.

In pediatric HSCT, when no acceptable donor or cord blood unit can be identified, the use of a parent being haplo-identical to the patient is not uncommon (chapter 6). Parents who donate to their child fulfill a dual role, as caregiver and donor, and their experiences were not yet reported. From in-depth qualitative interviews with 13 parents, four main themes revealed, 'Hope and Fear', 'Need for Information', 'Do Anything for Your Child' and 'Transplant Outcome'. These themes were present in all stages of the process (decision making; donation process; reflection). Their role as a donor was for most parents of minor importance, and the fact that they felt

they had no choice but to donate was a recurrent element in interviews. A proposal for a multicentre European study for long term follow-up of parental donors was approved by the EBMT working parties on Late Effects and Pediatric Diseases.

Not only parents can donate to their children, children can act as donors to provide bone marrow to a sibling as of very young age. We undertook a retrospective study to investigate a cohort of 210 donors who donated before the age of 13 years in the Leiden University Medical Centre between 1968 and 2002 (chapter 7). Donors, on average 16 years post donation, were invited to participate in a long-term follow-up and health related quality of life study. Although medical problems were reported, none were clearly related to the donation procedure. Two donors mentioned severe psychological difficulties. Bone marrow donation in early childhood does not lead to significant physical or psychosocial impairment in the majority of donors. However, clear eligibility criteria and guidelines for donor care management were lacking. Obvious, independent medical assessment is required for counseling of pediatric donors and, in case of a preexisting medical condition, additional advice should be requested from a specialist to determine if the risk of general anesthesia and bone marrow donation is acceptable. Despite the presence of medical conditions questioning harm of donation, none of the children were deemed unfit to donate, while no documentation on follow-up of these children could be found. A review of (n=107) bone marrow reports and aspirates revealed low (46%) or absent (15%) iron stores, without clear documentation of iron suppletion after bone marrow donation. In 62% of the children, the collection of bone marrow exceeded 15 ml/kg donor body weight and more than half of these received allogeneic blood transfusions. Post-transfusion screening for red cell alloantibody formation was not performed. The results of the study underscore the need for international guidelines for care management of the pediatric stem cell donor.

The search for an unrelated donor requires, besides expertise of human leukocyte antigens (HLA), also familiarity with international rules and regulations for stem cell donation. Delay during the donor search is undesired, especially during the work up procedure and should be prevented. Approximately 10% of the donors are deferred or is not available when asked to donate stem cells. Identification of a back-up donor during the initial search is an effective way to avoid loss of precious time and inconvenience for all parties involved. However, physicians should always inform their patients that a donor might be deferred after counseling. Based upon reasons for deferral at work up, donor centres are advised to perform an eligibility health check when a donor is requested to provide samples for verification typing, in particular when there are reasons to doubt that the donor may be declared suitable, such as severe obesity or a wish for pregnancy (chapter 8).

Over time, searching for an unrelated donor or cord blood unit has become more

complicated. The still ongoing unraveling of the HLA system, adding thousands of new alleles and cumulative potential combinations for phenotypes requires continuous adaptation and training of search coordinators. Besides, clinical developments have resulted in the use of double cord blood units for transplantation, necessitating a different way of matching (chapter 9). Prolonged time between donor search and transplantation negatively influences the outcome. Despite efficient activities to reduce the length of search to a minimum, search time to identify a match will be longer when no donors are available. For patients with a north western European (NWE) background, the number of potential donors in the worldwide inventory Bone Marrow Donors Worldwide (BMDW) has increased in the paste decade to a median of 70 available matched donors, whereas for patients from a non-NWE descent, the number of potential donors remains fixed to a median of 7 donors. Moreover non-NWE donors were more often unavailable at time of verification typing. The fact that a remarkable amount of non-NWE patients reach transplantation is because donors / cord blood units with a lesser match-grade are accepted.

Similar as in other health care areas increasing attention for quality aspects and enhanced interest in the rules, regulations and ethical aspects of stem cell donation have recently come to light, attracting the attention of professionals and the public (chapter 10). The remuneration of stem cell donors was the target of a lawsuit filed in 2009 against the National Organ Transplantation Act in the USA. Plaintiffs disputed that the legislation forbidding remuneration of stem cell donors would deter potential donors from registration as a donor and thus decrease the chances of finding a match for a patient. Through intense international collaboration patients can receive a stem cell product, often collected from a donor in another country or continent. One of the basic principles that donors are not to be paid for their act is documented in the standards of the WMDA. Thus (parts of) the human body has no economic value, and should be treated with the dignity it deserves. At the time of the lawsuit, a taskforce of the WMDA extensively argued the case why stem cell donation should remain voluntarily and non-remunerated. Stem cell donation is an act of humanity and impossible to value in monetary terms, and is literally a gift of life. The introduction of payment is not only a potential risk for coercion and exploitation of donors, but can also potentially harm transplantation programs and the international exchange of stem cell products.

General discussion and future perspectives

The use of allogeneic hematopoietic progenitor cells has become a treatment option of choice for patients with defined congenital or acquired disorders of the hematopoietic system[1]. Apart from a growing list of indications, the development of non-myeloablative conditioning regiments has cleared the way to HSCT as a potential cure for an increasing amount of (mainly elderly) patients. As a result, the median

age of sibling donors has increased and due to current stricter adherence to eligibility criteria they are more often declared not suitable for donation and more often an unrelated donor or cord blood unit is needed. Currently, in over 50% of all allogeneic HSCTs the graft is provided through a donor registry[2] and it was estimated that in 2013 daily 33 unrelated stem cell products were crossing an international border[3]. In the past decade (2004-2013) the number of UD increased with an average of 10.1% per year; the average having only increased slightly in the last three years due to the inclusion of Brazilian and Chinese donors. The global CBU inventory has grown on average with 14.6% per year[4,5]. Despite a significant increase of the HSCT activity worldwide[6], it is assumed that the therapy is still underused as curative treatment, due to various clinical and non-clinical reasons[7]. Considering these facts, it is pertinent to investigate what is further required to ensure maximal utilization of this potentially curative modality of treatment.

The optimal donor pool: young, male, diverse and available

The preferences of transplant centres (TCs) for the 'ideal donor' are subject to change. Stem cells of older donors as compared to younger donors were reported to have adverse impact on overall survival in patients with certain hematological malignancies[8,9], and it has even been suggested that a younger UD rather than an older sibling is preferable[10]. With time and evaluation, opinions have also varied as to the preference for a sex matched donor, in particular for a male recipient[11,12]. A recent analysis of a large cohort in adult male patients transplanted for acute leukemia showed no difference in leukemia free survival, but a higher risk for acute GvHD when receiving donor stem cells from a male unrelated donor leading to the conclusion that a female sibling is preferable[13]. In light of the fact that a sufficient cell dose is of major importance for transplant outcome, an observation that is consistent over time[14,15], and since male donors provide quantitatively better grafts in terms of cells harvested based on body weight[16], the commonplace preference for male donors may be explained. However, also in male donors, increasing donor age is still associated with a modest negative effect on stem cell mobilization[17].

In their annual report 2012/2013 the Canadian registry OneMatch mentions that three quarters of stem cell donations are derived from male donors younger than 36 years[18]. This trend is also seen in the Netherlands where currently 70% of donors requested for verification typing are male. Not only has the worldwide unrelated donor pool increased significantly over time, so has the average age of the registered donors. As a direct consequence donors are more often deferred for medical reasons and thus less useful[19]. Globally, 19% of the registered donors are male and younger than 36 years and only 10.5% of all donors are younger than 26 years[3]. Considering age and gender, the current global inventory would not meet the criteria for the optimal donor pool, challenging donor registries to be creative and find cost-

effective solutions. Lowering the age for recruitment has been recently introduced in the United Kingdom (16 years) and in Canada (17 years). The Canadian registry focuses their recruitment on male donors, younger than 35 years[20]. Recruitment of younger UD as of 16 years of age might be beneficial, however, due to local legislation, may not be feasible in each country. When focusing on younger donors, registries need to adjust their established operating procedures as was reflected by representatives of the Canadian and British registries during the WMDA Fall meeting in 2013. The lack of 'life-experience', for instance with informed consent procedures and doctor's appointments require age appropriate counseling methods[21,22]. Also, the administration of G-CSF to minors might not be authorized in all countries. In the Netherlands for example, there is no consensus about the administration of G-CSF to healthy minors.

Despite the steady increase of UD/CBU in Bone Marrow Donors Worldwide (BMDW), the mainstream of the UD/CBU is being registered in the north western European (NWE) and north American registries[23,24]. As such, this might be the limiting factor of access to transplantation for patients with a non-NWE background seeking a matched donor. Strategies aiming to increase the HLA diversity of the donor pool could be successful in overcoming the present limitations, supplemental to ethnic minority donor recruitment efforts[25]. Apart from recruitment, strategies aimed at retaining donors listed on the registry are becoming frequently more necessary. Since the reasons for donor unavailability were first investigated[26], the amount of donors in the USA not being available when they are contacted has increased to almost half of their donor pool[27,28], and this number is increasing[29]. It has been shown that commitment is lower in ambivalent donors[30]. When asked almost immediately after registration, 35% of newly recruited donors stated that they have doubts if they would proceed to donation[31]. Characteristics like gender, duration of registration, and ethnic background are not only indicators for attrition, but also have a cumulative effect, negatively affecting chances for patients[32]. Part of the solution to help more patients reach HSCT might be working towards an optimal global donor pool. Recruitment among blood donors guarantees a higher probability of willingness and suitability for stem cell donation. However, level of commitment in new (non-blood donor) prospective donors is also identifiable; specifically ambivalence in potential donors is strongly associated with attrition and this and other parameters could be used to modify recruitment strategies[31]. Although the chance of Dutch non-NWE patients to reach HSCT has increased over time to approximately 70%, their options to identify an acceptable UD within almost 25 million listed UD are dramatically lower both in quantity and quality, than for NWE patients and have not improved over time (this thesis). The underrepresentation of non-NWE donors in the pool is lowering the likelihood for non-NWE patients to find and receive an optimal matched graft[25,27,31-36]. Gragert et al. recently reported

a theoretical model, based upon population genetics, estimating the likelihood of finding a well matched UD or CBU for white European patients and for patients with other ethnic backgrounds in the US[37]. The model was based upon the donor and cord blood inventory of the National Marrow Donor Program (NMDP), which represents approximately 50% of all registrations worldwide, and taking availability and medical eligibility into account. They claimed a likelihood of over 95% for identifying an unrelated donor or cord blood unit for white Europeans and African-American patients. In our retrospective analysis, we were able to identify an acceptable stem cell source for 81% of non-NWE patients. The assumption of Gragert et al. that the donor population represents a true reflection of the patient population[37] possibly overestimates the probability of finding an acceptable UD/CBU in particular for non-NWE patients. Besides, a mismatched donor or cord blood are not always acceptable alternatives depending on the specific transplant protocol. Patients for whom no acceptable donor was identified in our study often originated from a mixed racial background. Donors with mixed genetic ancestry are probably least represented in the worldwide donor inventory. The importance of a donor's availability, especially in young male donors (since they are most likely to be requested) and ethnic minority groups is essential to explain during recruitment[31,32]. It is necessary to revise recruitment strategies to prevent newly recruited donors from dropping out at any time during the verification typing and pre-donation process. Most donor registries have focused on the volume of their donor pool, but there is an urgent need to address the issue of donor attrition, since avoiding waste of money and efforts in this direction of recruitment can no longer be ignored[29,38]. The startling fact that over 10% of registry donors is even unable to be located at time of a blood sample request, could be addressed in an awareness campaign (through social media, flyers or newsletters). Donor registries are unable to function as trackers and delays in the search could have serious consequences for patients, and these can be prevented.

S, M, L, XL – donor registries

Currently there are a few ultra-large registries (with over 1 million registered donors) and a majority of small (<20,000 donors) and medium-sized registries (<100,000 donors)[39]. Taking into consideration that the majority of products (>80%) is annually provided through five of the larger registries, of which two XL registries (responsible for 67% of all products)[3], the vulnerability of countries with S and M registries is evident. They have become dependent on stem cell products donated by foreign donors. It is unclear why the majority of requests is sent to the XL registries, since donors with 'common HLA phenotypes' are most likely present in their own national registries. It could be argued that national registries should be able to provide a certain percentage of stem cell products for their national patients. As a result of these developments and the economic crisis, S and M registries are facing difficult

times and for new registries in emerging countries it is almost impossible to start up without sufficient financiel support. Determining the optimal size and mix of the global donor inventory involves difficult decisions balancing competing objectives and requirements[27]. However, the need for new registries, in particular in emerging countries, is obvious since they add unique HLA phenotypes to the global donor inventory. Where in recent years approximately one in fifteen donors provided a new phenotype, the contribution of new registries such as the Brazilian registry added to BMDW in 2011, resulted for that year one in ten donors adding a new phenotype[40]. In virtually all countries CB inventories have a much higher relative contribution of new HLA phenotypes to BMDW than the donors. It was stated in the BMDW annual report 2012 that CB banks are thus more successful in recruiting units from minority groups[40]. A certain amount of these new phenotypes might originate from unique mixed ethnic backgrounds. This is extremely important for a number of those patients who would otherwise not have access to HSCT by lack of an acceptable (cord blood) donor. Yearly stem cells of less than 0.1% of all registered donors and approximately 0.8% of CBU are actually used for transplantation[3,41]. Completeness of HLA typing has a strong impact on donation probabilities[42], since donors who are types on high resolution are more likely to be requested. A possible explanation for the use of CBU being approximately tenfold higher than the proportion of available adult donors being utilized might be the phenotypic diversity and potential faster availability of CBU. The promising advantage of cord blood as a stem cell source for non-NWE patients underlines the importance of banking of high quality cord blood units for allogeneic transplantation, and in doing so compensating for the lack of minority donors in the donor pool[43]. With the overall relatively small proportion of stem cell donors actually donating yearly, it is important to critically consider this before adding 'more of the same HLA' to the global donor pool. The introduction of next generation sequencing (NGS) will reduce the cost, while resolution of HLA typing is higher and determination of further parameters (blood group, CMV, KIR, etc.) easily possible, thus adding higher quality donors to the global donor pool. A Group of European Medium Sized Registries[44] are attempting to seek joined solutions for the challenges.

Reaching HSCT – clinical and non-clinical factors

In 2001 it was reported that overall only one third of eligible patients reached HSCT[45]. Over a decade later the WMDA Annual Report demonstrates that 45% of patients for whom an unrelated donor search is initiated reach HSCT[2]. This is most likely a subset of all eligible patients. A recent prospective study reported that an unrelated donor search for only 51% of patients without a family donor was initiated, without a clear explanation as to the reasons for the remaining patients being deferred[46]. Reasons for not reaching transplantation are various; HSCT might be offered too

late during therapy[7,46] with clinical deterioration, in particular for intermediate/high-risk leukemia patients, as probably the main disturbing factor[47], and the period to identify a donor could (and in some cases needs) to be decreased[48]. The major non-clinical factor determining restraint of transplant is undoubtedly the lack of donors for non-NWE patients. We have proven for our Dutch patients that efficiency of the search process can affect feasibility of reaching transplantation to 70%, by reducing the amount of searches cancelled due to clinical deterioration of the patient to approximately 10%. To perform a search as efficient as possible donor registries have developed tools and methods to shorten the UD/CBU search[49-53]. Sharing such awareness and insights between donor registries and transplant centres might play a key role in improving transplantation figures.

Safeguarding donors: the global approach

Safety of stem cell donors considers mainly the suitability of the donor undergoing the procedure. Whether the donor is an infant or an adult, an anonymous person or a family member, their well-being and interests must always be kept in mind as a duty of care. Treating a healthy donor with an agent that is not of in his physical benefit demands responsibility from health professionals, and an approach where the safety of the donor comes first[54]. With the introduction of Granulocyte Colony Stimulating Factors (G-CSF) in healthy volunteer individuals, the issue of (in particular) long-term safety has been addressed. In a recent study the short-term and long-term Serious Adverse Events (SAE) of both bone marrow and peripheral blood stem cell donation were analysed[55]. It was remarkable that the risk of short-term SAE was threefold higher in bone marrow donors. From the more long-term follow-up data it was confirmed that unrelated donors do not have an increased risk to develop a malignancy, auto-immune disease or thrombosis within three months after donation[55]. The WMDA have adjusted their statement with regards to the use of G-CSF in healthy volunteers[56], however, although these comparisons have been stratified for age and gender with the general population, other confounders were generally not corrected for. It is also not known whether this statement equally applies for the related donor population, since the overall health in the unrelated donor population is probably better than in the related donor group or even the general population. For patients, older age no longer seems to be a absolute contra-indication for HSCT, but as previously mentioned, older patients have older siblings, and although age is not per se an indication for performance status[47], co-morbidities, and thus reasons to declare a person unsuitable for donation, are more often seen in elderly donors (this thesis). It is known that co-morbidities in related donors (RD) are more often accepted since 'related donors are willing to take a greater risk'[57]. The medical profession assumed for a long time that family members are naturally motivated by the prospect of saving the life of a loved one[58]. It would subscribe the

altruistic character and the principle of beneficence referred to as an aspect of human nature, that motivates to act in the interest of others[59]. From this perspective it could be justified by the thought of Kant, that if a family donor really chooses to donate out of affection, his act would lack moral worth, because it would not be based on an obligation[59]. However, it is unclear whether the above mentioned assumption of traditional altruistic thinking would make a relative feeling obliged to donate or deter him from free decision making[60]. In extenso – could this imply violation of the basis ethic principle of autonomy, ascribing the right to choose and act freely? Violating or ignoring a person's autonomy is to treat that person merely as a means to an end, that is, in accordance with other requirements without regard to that person's own interests[59]. In that light, the assumption could be an expression of the utilitarian view, that is, if the chance of the transplantation success is likely greater than the probability of the family donor to experience any harm, it is the donor's obligation to donate[59]. The situation where the donor has not yet reached the age of adulthood or is not able to assent or to give informed consent, is even more complicated. If proxy consent for donation is given by a parent or a legal representative, this might implicate that the donor is used as means to an end, which would be contradictory with the principles of Kant's second formulation of the categorical imperative: the action is considered unacceptable, because the individual's physical integrity is ignored and his dignity diminished by locating his value in a donation activity[61]. The American Academy of Pediatrics (AAP)has addressed ethical concerns in a policy and defined criteria that allow for the use of pediatric donors[62]. Although the AAP has advised to have a system in place where (legal or ethical) approval is required prior to donation, it was argued that this might not sufficiently protect the interests of the pediatric donor and modification of the policy with more emphasis for the donor's rights, competence, and consent was proposed[63]. Harvesting stem cells is a medical procedure that potentially imposes risks and violates the bodily integrity of the donor. The argument of 'best interest' remains questionable, since the outcome of the HSCT, and thus the potential benefit for the donor can not be predicted. The debate on quality of life versus medical emancipation became public with the novel 'My Sister's Keeper'[65], where a 13 year old girl lived with the knowledge that she was conceived to rescue her sister, suffering from leukemia. She literally became the 'altruist by proxy-donor'[66], seeking for legal medical emancipation after multiple donations, and prior to donating her kidney. The novel made clear that abstaining the right of decision-making leaves the basic principle of autonomy worthless, even in minors[65]. Apart from the AAP policy, strict regulations or guidelines for practice with respect to the suitability, treatment, and follow-up of minor donors are still lacking. Even small policy changes could be beneficial for minor donors. For example, limiting the volume of bone marrow to be harvested from young donors could prevent them from requiring blood transfusions. Furthermore, HSCT outcome in children with high-risk leukemia has improved over time, regardless of donor source[67]. Also, during the

decision-making process, the search for an alternative donor (if time allows for) should be considered.

Internationally there now is a leading opinion that the suitability of the stem cell donor is of importance for all parties involved[68]. This was acknowledged by the transplant society with the establishment of the EBMT Donor Outcome Committee in 2012. Furthermore the FACT/JACIE Standards version 5[69] explicitly addresses donor care issues. Since then initiatives to develop and implement more strict guidelines for related donor care have been reported[70,71]. Awareness for the interests of the related donors was raised through international collaboration. The World Health Organization (WHO) has addressed the need for protecting the health and welfare of living donors including appropriate long-term follow-up[72]. Interestingly, a comparable discussion is being held in the field of living kidney donors, where governmental support is considered essential to set up a national system for life-long donor follow-up[73,74]. The Worldwide Network for Blood and Marrow Transplantation (WBMT), a non-governmental organisation focusing on collaboration between existing international societies was established to promote excellence in stem cell transplantation and donation[75]. Through several successive Donor Outcome Workshops consensus was sought for suitability donor outcome data and lately the need of in particular pediatric and elderly donors were specifically addressed, with the aim of providing written consensus guidelines (Vienna 2013). The development of a European Union funded Master in Donor Health Care (a Dutch initiative) is also underscoring that care for the donor of organs, tissues, and cells is taken seriously.

With regards to serious (product) events and adverse reactions (S(P)EAR), the WMDA has developed a reporting system, adding to the high quality standards of donor care management[76]. One of the major advantages of the WMDA S(P)EAR system is the possibility to send out a 'Rapid Alert' to communicate in a timely matter with the donor registries and transplant community, whenever appropriate. For the related donors no such system is yet in place. There is a strong justification for bringing the related donor care in line with those for unrelated donors, especially in addressing adverse events in this group[77]. The establishment of a reporting system to cover adverse events of all living donors globally would be a major achievement and there is a substantial need to further investigate and develop this global challenge.

Future considerations – estimating the need for unrelated donors

The dynamic field of HSCT is continuously subject to changes. New drug developments and stem cell treatment protocols are rapidly following each other and being explored. Besides HLA matched related and unrelated UD and CB the use of targeted (autologous) immune cells for cancer treatment is under investigation. The extent of involvement and the final role of allogeneic donors in the future is thus unclear

and this directly affect the activities of all donor registries. Chronic myeloid leukemia (CML) was less than two decades ago only curable by HSCT and patients are now successfully treated with tyrosine kinase inhibitors[78]. Similar developments are on their way for chronic lymphocytic leukemia[79]. If results of autologous tumor targeted T-cell therapy[80] can be confirmed in larger randomized controlled trials this may ultimately lead to a decrease of the proportion of HSCTs.

Another development is the renewed interest in transplantation with related haploidentical donors, followed by a high dose Cyclophosphamide given early after HSCT to reduce the incidence of Graft versus Host disease and graft rejection, resulting for leukemia in at least comparable outcome as with HLA identical or matched unrelated donors[81]. In 2013, 40% of the patients in Italy received a haploidentical graft; Bacigalupo[82] mentioned a 10% reduction of the financial cost in his transplant centre while increasing the number of transplantations performed by 20%.

Regional differences in use of allogeneic donors are large, and associated with national income, thus widening the gap between more or less affluent countries[3,83]. As an additional effect of the economic crisis, TCs need to investigate ways to cut the costs of HSCT, without depriving the standard of quality care[84], and keeping the treatment accessible[85]. Although in-hospital patient days are the main part of expenditure, cost of unrelated donor selection and stem cell products, in particular the cost of (double) cord blood, are also subject to discussion[84,86,87]. The cost effectiveness of HSCT with the several available stem cell sources (including haplo identical stem cells) is under investigation[88]. A concern that was expressed is that in countries where a fixed-rate system for reimbursement is negotiated with health insurance companies, transplantation with double cord might become prohibitive. It was suggested to look into ways to keep the use of cord blood both profitable and affordable[87]. The current discussion is focused on the pricing of stem cell products in general, and of cord blood in particular. A 'one-price-policy' or a price based upon the TNC of a unit (smaller units – lower prices) would positively affect patients (money is no longer an argument not to choose the best match). There is evidence that increasing the ethnic diversity of cord blood inventories lead to more patients reaching HSCT (this thesis) demonstrating cord blood banks the need to develop policies to increase ethnic diversity[89]. Raising public awareness is important to reach the goal of covering HLA diversity even within a country[90]. The likelihood of CBUs to be used over time is besides HLA, directly related to the total nucleated cell count (TNC)[91]. Units with higher TNC are more likely to be selected for transplantation[91]. It is known that non-NWE units often contain less TNC, probably related to shorter labor time but their contribution to the diversity should be considered[89]. Other policies to make units better serviceable are the provision of maternal HLA typing, since a beneficial effect of non-inherited maternal antigens (NIMA) and inherited paternal antigens (IPA) of a cord blood have shown a positive impact on engraftment

and relapse risk and a reduced graft versus host disease[92,93]. Also, the efficacy of matching cord blood on high resolution HLA-A, -B, -C and -DRB1 was recently shown to be associated with lowest non-relapse mortality after transplantation with cord blood for acute leukemia and myelo-dysplastic syndrome[94], indicating that complete high resolution typing of new cord blood units is important.

Donors and (future) research

Over the past decades motivations, experiences, and perspectives of being a stem cell donor and donating stem cells, have been studied[95]. Recently the introduction of new mobilizing agents and the use of bio-similars have created a need for donors to remain subject of prospective studies[96,97]. Donor retention, recruitment strategies, and safety of stem cell donation in particular by the related donors of all ages remain subject of interest for future research. The Leiden University Medical Centre is one of the oldest HSCT centres in Europe, and the basis of Europdonor Foundation, the Dutch National Stem Cell Donor Registry, providing the opportunity to perform long-time follow-up studies in unrelated and related, pediatric, and adult donors. Such long-term effects of stem cell donation include also cognitive, emotional, and psychosocial factors. Course of Life questionnaires completed by our pediatric donor cohort will undergo final analysis in the near future, allowing more insights into the transition into adulthood after bone marrow donation in early childhood. Furthermore, we will report on pain management investigated in a prospective cohort of related and unrelated donors. The relation between stress and mobilization and the Sense of Coherence are further subjects to be analysed in above mentioned donor cohorts. All donors included in our studies gave informed consent and the study was approved by the Ethical Review Board of the Leiden University Medical Centre. However, situations can occur where donors indirectly become a research subject (i.e. the donation is part of an experimental or research protocol). By donating stem cells, donors have proven to be altruistic and thus most likely would agree with their involvement in clinical research[98]. The WMDA requires additional approval for donation by a donor registry and informed consent of the donor[99], which might cause a delay in transplantation. The procedures associated with experimental therapy (not considered standard of clinical care) also increased clinicians' awareness to the fact that donors are individuals with legitimate rights[100,101]. It remains challenging to harmonize the interests of all parties involved[102], in particular if multiple or prolonged donations are involved in the protocol. It is important to address the acceptability of exposing a donor to a research protocol for the benefit of the recipient, and give advice according to the international standards on human research[103], also to prevent extensive delay, caused by an additional independent protocol review performed on behalf of a donor registry. The role of the unrelated donor might become less explicit in the future, but donation of stem cells by family donors will probably continue. It

is in the interest of all parties involved to find the best balance between patients' needs and donors' interests[104] and to accomplish long-term safety for future donors.

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Chapter
17

SAMENVATTING, DISCUSSIE EN TOEKOMST PERSPECTIEVEN

In dit proefschrift worden de ervaringen van stamceldonatie door onverwante en verwante donoren (minderjarigen en volwassenen) beschreven, alsmede de verschillende aspecten van de zorg voor de donor en het proces van het zoeken naar een (onverwante) donor. De veiligheid van de donor staat hierbij steeds centraal. In dit hoofdstuk worden de verschillende onderwerpen samengevat en in een breder perspectief besproken in het licht van huidige en toekomstige ontwikkelingen.

Samenvatting

De eerste succesvolle allogene transplantatie, dat wil zeggen met bloedvormende stamcellen afkomstig van een donor, werd in Europa uitgevoerd in 1968 in Leiden. Sinds 1980 is het aantal indicaties voor hematopoietische stamceltransplantatie (HSCT) exponentieel toegenomen. Behalve voor de behandeling van hematologische maligniteiten, wordt de therapie met donorstamcellen ook toegepast bij erfelijke aangeboren afwijkingen, zoals afweerstoornissen (immuundeficiënties), niet kwaadaardige afwijkingen van het bloed (ernstige aplastische anemie, sikkelcelanemie, thalassaemie) en stofwisselingsziekten. Aanvankelijk werden de stamcellen (onder algehele anesthesie) geoogst uit beenmerg door middel van puncties in de bekkenrand of het borstbeen. Met de ontwikkeling van recombinante humane groeifactoren in de jaren '90, werd het mogelijk om grote aantallen stamcellen te mobiliseren: na subcutane toediening van Granulocyte Colony Stimulating Factor (G-CSF) verplaatsen de bloedstamcellen zich vanuit het beenmerg naar de bloedsomloop en kunnen als perifere bloedstamcellen (PBSC) met behulp van aferese worden geoogst. Een transplantaat met PBSC bevat meer stamcellen en bloedvormende voorlopercellen met als gevolg een sneller herstel van vooral granulocyten en trombocyten bij de patiënt. Hierdoor is er minder risico op infecties en ernstige bloedingen in eerste periode na transplantatie. Een transplantaat met PBSC heeft daarom vaak de voorkeur van de behandelend arts boven beenmerg. Navelstrengbloed is in de afgelopen jaren een belangrijke nieuwe bron geworden.

In de afgelopen decennia is HSCT voor veel aandoeningen de standaard behandeling geworden. De praktijk is echter dynamisch en continu onderhevig aan veranderingen. Wetenschappelijk onderzoek is gericht op methodes om de toxiciteit van de voorbehandeling voor de transplantatie (de zgn. conditionering) te minimaliseren en de kans op ernstige afstotingsreacties door de donorcellen (Graft versus Host Disease, GvHD) te beperken. Daarnaast wordt onderzocht op welke wijze gebruik kan worden gemaakt van het afweermechanisme van de donor. Toediening van immuuncellen van de donor kan een belangrijke rol spelen bij de behandeling van terugkeer van de oorspronkelijke ziekte of oncontroleerbare virale infecties na de transplantatie. De ontwikkelingen van deze nieuwe behandelmethodes kunnen gevolgen hebben voor wijze waarop het donatieproces verloopt en dus ook voor de donor.

De zorg voor de anonieme stamceldonor wordt uitgevoerd door de stamceldonorbanken (Registries), en is vastgelegd in de standaarden van de World Marrow Donor Association (WMDA). Voor familiedonoren worden deze standaarden niet toegepast. Donatie is een vrije keuze, maar een familieband tussen de donor en de ontvanger kan de keuzevrijheid in gevaar brengen en zelfs leiden tot een gedwongen keuze. Professionals, betrokken bij de zorg voor familiedonoren, moeten gedurende het gehele proces streven naar een optimale balans tussen de belangen van zowel patiënt als donor. Gedurende de eerste Donor Outcome Workshop in 2009, een initiatief van de Late Effecten Working Party van de EBMT, was de zorg voor de familiedonor het belangrijkste onderwerp. Doel van de bijeenkomst was om overeenstemming te bereiken voor een wereldwijd gestandaardiseerd protocol voor het vastleggen van algemene donor data, ernstige bijwerkingen en incidenten van het proces van donatie en langetermijneffecten (hoofdstuk 3) De Ethics en Clinical Working Groups van de WMDA, die de belangen van de onverwante donoren behartigen zijn in 2010 in overleg getreden met de European Group for Blood and Marrow Transplantation (EBMT), met als doel om de uitgangspunten en aanbevelingen voor de zorg van de familiedonor (werven, informeren, begeleiden en melden van ernstige bijwerkingen of incidenten) meer te harmoniseren (hoofdstuk 2). Dit was de eerste poging om internationaal aandacht te vragen voor de zorg voor familiedonoren. Een groot internationaal cohort van familiedonoren biedt mogelijkheden om specifiek voor deze groep de risico's van stamceldonatie te inventariseren. Literatuur op dit gebied is schaars en bestaat uit observaties, gevalsbeschrijvingen of retrospectieve analyses. Prospectief en gerandomiseerd onderzoek is niet verricht. Causale verbanden in de gerapporteerde incidenten zijn hierdoor onmogelijk te bevestigen of ontkennen. De kosten voor meerjarige follow-up voor de familiedonor worden niet gedekt door de verzekering. Gebrek aan financiële middelen maakt het daarnaast onmogelijk om de effecten van het toedienen van G-CSF aan gezonde personen of de invloed van multipele donaties op lange termijn wetenschappelijk te onderzoeken. Wij hebben een retrospectieve studie verricht* in een cohort van 268 donoren die tussen 1996-2006 PBSC hebben gedoneerd aan een familielid in het Leids Universitair Medisch Centrum. De studie concentreerde zich op de medische geschiktheid van de donor en op cardiovasculaire incidenten en maligniteiten gedurende de follow-up (hoofdstuk 4). Bij gebrek aan criteria voor goed- of afkeuring van de familiedonor, werden de bevindingen van de medische keuring van de donoren vergeleken met de criteria voor onverwante donoren van de Nederlandse stamceldonorbank Europdonor en de Amerikaanse National Marrow Donor Program (NMDP). Op deze manier werd getracht achteraf vast te stellen of een familiedonor terecht of onterecht goedgekeurd was voor stamceldonatie. Ongeveer 15% van de donoren zou zijn afgekeurd als zij onverwante donor waren geweest. Kortetermijnbijwerkingen waren vergelijkbaar met die van in de literatuur bekende cohorten van onverwante stamceldonoren.

* Sanquin Blood Supply study grant PPOC 08-008

In de langetermijnfollow-up werden negen maligniteiten en 14 cardiovasculaire incidenten gerapporteerd. In vergelijking met de Nederlandse populatie vielen deze aantallen binnen de normale grenzen voor leeftijd en geslacht.

De noodzaak voor registratie van ernstige bijwerkingen en incidenten (Serious Events and Adverse Reactions - SEAR) werd voor het eerst duidelijk bij de introductie van toediening van G-CSF aan gezonde personen (hoofdstuk 5). Daarnaast werd door de WMDA ook al snel de patiëntveiligheid betrokken in dit systeem door het vastleggen van incidenten met producten (Serious Product Events and Adverse Reactions - SPEAR). Bij de registratie van SPEAR wordt naast het directe risico voor de patiënt ook melding gemaakt van schade aan een product ten gevolge van (incorrect of onveilig) transport. Indien een gemelde S(P)EAR dermate ernstig is dat onmiddellijke rapportage gewenst is kan door middel van een 'Rapid Alert' een bericht verspreid worden naar stamceldonorbanken en transplantatiecentra wereldwijd. Anonieme melding van S(P)EAR's is verplicht voor stamceldonorbanken die WMDA geaccrediteerd zijn, maar ook niet geaccrediteerde stamceldonorbanken worden aangemoedigd om incidenten te melden.

Voor kinderen met beenmergziekten is het niet ongebruikelijk om, als geen acceptabele donor of navelstrengbloed eenheid kan worden gevonden, een van de ouders stamcellen te laten doneren (hoofdstuk 6). De ervaringen van ouders die stamcellen doneerden aan hun kind waren nog niet eerder gerapporteerd. Uit diepte interviews met 13 ouders kwamen belangrijke thema's naar voren: 'Hoop en Vrees', 'Behoefte aan Informatie', 'Alles doen voor je Kind'. Deze thema's werden gedurende het gehele proces (besluitvorming – donatie – reflectie) herkend. De donorrol was voor de meeste ouders van ondergeschikt belang; het feit dat zij voelden geen andere keus te hebben dan stamcellen te doneren werd in veel interviews verwoord. Een voorstel voor een Europese studie naar langetermijneffecten bij ouders die stamcellen aan hun kind hebben gedoneerd is goedgekeurd door de EBMT. Naast ouders en volwassen familieleden kunnen kinderen als donor optreden voor een zieke broer of zus. Wij hebben een retrospectieve studie gedaan naar 210 donoren die tussen 1968 en 2002 beenmerg hebben gedoneerd in het Leids Universitair Medisch Centrum (hoofdstuk 7). De leeftijd van de donoren varieerde van 0,5 – 12 jaar op het moment van donatie. Gemiddeld 16 jaar na donatie werden de donoren uitgenodigd om deel te nemen aan een langetermijnfollow-up studie. Gezien het observationele karakter van de studie kon geen causaal verband worden vastgesteld tussen gemelde medische problemen en de donatieprocedure. Twee donoren hebben ernstige psychosociale problemen gemeld. Er kon worden geconcludeerd dat beenmergdonatie op jonge leeftijd niet leidt tot significante lichamelijke of psychische problemen op de lange termijn. Ook in deze studie viel het ontbreken van vastomlijnde criteria voor medisch goed- of afkeuren van de donor op. Inmiddels is aanbevolen (JACIE Standards 5th Edition) om de medische keuring van een donor

door een onafhankelijke arts te laten verrichten. Bij twijfel over de geschiktheid van de potentiele donor of bij een (historisch) onderliggend lijden zou aanvullend advies moeten worden gevraagd van een specialist. Op deze wijze kan worden vastgesteld of het risico van algehele anesthesie en beenmergdonatie acceptabel zijn. In bovengenoemde studie echter, werd geen van de kinderen afgekeurd als donor, hoewel een aantal van hen een ernstige medische voorgeschiedenis had, wat in een aantal gevallen leidde tot complicaties tijdens het proces van donatie. Follow-up van de kinddonoren was beperkt gedocumenteerd. Van 107 donoren werden de beenmerguitstrijkjes opnieuw beoordeeld en vergeleken met het rapport. Bijna de helft van de donoren (46%) had lage ijzerreserves en bij 15% was ijzerreserve afwezig; documentatie over suppletie van ijzer na de beenmergdonatie ontbrak. Bij 62% van de donoren werd meer beenmerg geoogst dan 15 ml/kg lichaamsgewicht, en meer dan de helft van deze kinderen ontving een transfusie met donorbloed. Posttransfusie screening voor allo-antilichamen werd niet verricht. De resultaten van de studie onderstrepen de noodzaak voor (inter)nationale richtlijnen voor de zorg en begeleiding van kinddonoren.

Het zoeken (de search) naar een onverwante donor vereist naast expertise op het gebied van weefseltypering (humaan leukocyten antigeen – HLA), ook kennis van internationale wetten en regelgeving rondom stamceldonatie en transport. Vertraging gedurende het proces, vooral wanneer een donor is gekozen en gevraagd om stamcellen te doneren, is ongewenst (hoofdstuk 8). In een retrospectieve studie werd onderzocht wat de toegevoegde waarde van een back-up donor was. Ongeveer 10% van de geselecteerde donoren werd afgekeurd of was niet beschikbaar op het moment dat hij/zij werd gevraagd stamcellen te doneren. Het simultaan zoeken naar een back-up donor gedurende de initiële donorsearch is een effectieve manier gebleken om vertraging te voorkomen voor alle partijen die betrokken zijn bij de transplantatie. Het is van belang dat artsen, wanneer zij hun patiënten informeren dat er een donor is gevonden, er ook op wijzen dat een donor medisch kan worden afgekeurd. Met betrekking tot de oorzaken voor het afkeuren van donoren werden stamceldonorbanken geadviseerd om al vroeg in het stadium van de procedure tot de donatie vast te stellen of een donor mogelijk ongeschikt is en kans heeft om afgekeurd te worden. Indien er sprake is van bijvoorbeeld ernstig overgewicht, een medische voorgeschiedenis of zwangerschapswens kan aanvullend onderzoek soms noodzakelijk zijn om de geschiktheid of beschikbaarheid van de donor vast te stellen.

In de afgelopen jaren is het zoeken naar een onverwante donor of navelstrengbloedeenheid steeds ingewikkelder geworden (hoofdstuk 9). De ontdekking van nieuwe allelen van het HLA-systeem leidt tot nieuwe potentiele combinaties voor fenotypes en vereist voortdurende scholing van search coördinatoren. Klinische ontwikkelingen, zoals het selecteren en toedienen van twee navelstrengbloedeenheden aan één patiënt, vereisen specifieke kennis en

vaardigheden met betrekking tot matchalgoritmes. Een langere tijd tussen diagnose en transplantatie kan de uitkomst van transplantatie negatief beïnvloeden. Efficiëntie om de lengte van het zoekproces naar een onverwante donor of navelstrengbloed eenheid tot een minimum beperken is van belang. Voor patiënten met een noordwest Europese (NWE) achtergrond is het aantal potentiele donoren in het wereldwijde bestand Bone Marrow Donoren Worldwide (BMDW) in het laatste decennium bijna verdubbeld. Voor patiënten met een niet-noordwest Europese (non-NWE) achtergrond is het aantal potentiele donoren sinds het begin van deze eeuw stabiel laag gebleven. Daar komt bij dat non-NWE donoren vaker niet beschikbaar zijn. Uit een analyse van alle Nederlandse onverwante donor searches van de afgelopen 12 jaar blijkt dat toch een aanzienlijk aantal non-NWE patiënten transplantatie bereikt. Dit is te danken aan het feit dat zij vaker met navelstrengbloed kunnen worden getransplanteerd (waarvoor minder stringente matchcriteria kunnen worden toegepast).

Ethische aspecten, de ontwikkeling van lokale, nationale en internationale richtlijnen en regelgeving op het gebied van gezondheidszorg en stamceldonatie zijn in de afgelopen jaren een steeds voornamere rol gaan spelen, en trekken onverwacht soms ook de publieke aandacht (hoofdstuk 10). Het toestaan van een financiële vergoeding voor stamceldonatie was in 2009 de reden voor een kort geding, dat in de Verenigde Staten van Amerika werd aangespannen tegen de National Organ Transplantation Act. De aanklager betoogde dat de bij wet verboden betaling op stamceldonatie nieuwe potentiele donoren zou weerhouden zich te registreren, ten gevolge waarvan patiënten minder kans zouden hebben om een passende donor te vinden. De Wereld Gezondheidsorganisatie (WHO) heeft zich op het standpunt gesteld dat cellen en weefsels van het menselijk lichaam geen economische waarde hebben en derhalve niet kunnen en mogen worden beschouwd als een handelsproduct. Ook in de grondbeginselen van de Standaarden van de WMDA is vastgelegd dat voor een altruïstische stamceldonatie niet betaald mag worden. Een WMDA Taskforce heeft in een reactie op deze rechtszaak uitvoerig gemotiveerd waarom stamceldonatie ook in de toekomst vrijwillig en onbetaald moet blijven. Stamceldonatie is een humanitaire daad, die niet in geld is uit te drukken en die voor een patiënt letterlijk een 'Gift of Life' kan betekenen. Met het bieden van geld voor donatie van stamcellen of andere weefsels of organen om een donor te verleiden tot donatie worden situaties gecreëerd, waarbij beslissingen soms niet geheel onafhankelijk en vrijwillig kunnen worden genomen. Intensieve internationale samenwerking heeft het mogelijk gemaakt om patiënten wereldwijd te voorzien van stamcelproducten. De introductie van een financiële vergoeding voor stamceldonatie zou een ernstige bedreiging kunnen vormen voor de continuïteit van deze internationale uitwisseling en daarmee de kans op genezing van patiënten.

Discussie en toekomstperspectieven

Allogene hematopoietische stamceltransplantatie is de standaard behandeling voor een groeiend aantal aandoeningen van het bloed- of de bloedvormende organen[1]. De ontwikkeling van minder toxische voorbereidingsschema's (ook wel non-myeloablatieve conditionering of Reduced Intensity Conditionering genoemd), heeft ertoe geleid dat de therapie ook veilig kan worden toegepast bij oudere patiënten, die zo een kans op genezing kan worden geboden. Met het stijgen van de gemiddelde leeftijd van de patiënt, neemt ook de gemiddelde leeftijd van de familiedonor toe. Strikter hanteren van keuringscriteria heeft tot direct gevolg dat meer familiedonoren worden afgekeurd voor stamceldonatie, waardoor er meer vraag is naar stamcellen van onverwante donoren en navelstrengbloedeenheden. Op dit moment wordt in meer dan de helft van alle allogene stamceltransplantaties een transplantaat van een onverwante donor of navelstrengbloed gebruikt[2]. Dagelijks passeren ongeveer 33 stamcelproducten een internationale grens[3]. In de afgelopen 10 jaar (2004-2013) is het aantal geregistreerde onverwante donoren jaarlijks met gemiddeld 10% toegenomen (tussen 2011-2013 is dit percentage zelfs iets hoger door de toetreding van de Braziliaanse en Chinese stamceldonorbanken tot het wereldwijde bestand). Het wereldwijde bestand van navelstrengbloedeenheden is gemiddeld met 14,6% per jaar gegroeid[4,5]. Hoewel ook de toename van het aantal hematopoietische stamceltransplantaties (HSCT) wereldwijd aanzienlijk is[6], wordt aangenomen dat de therapie door verschillende oorzaken nog onvoldoende vaak wordt toegepast[7]. Het is daarom belangrijk om te onderzoeken wat er nodig is om deze potentieel curatieve therapie globaal en maximaal te kunnen benutten.

Kenmerken van het optimale donorbestand: jong, man, divers en beschikbaar

De eisen die transplantatie centra (TC) stellen aan de 'ideale donor' zijn aan veranderingen onderhevig. Er is vaak voorkeur voor de jongere donor; stamcellen van oudere donoren leiden tot een minder goede ziektevrije overleving van patiënten met een hematologische maligniteit[8,9]. Er is zelfs gesuggereerd om de voorkeur te geven aan een jongere onverwante donor boven een oudere familiedonor[10]. Door de tijd heen is er wisselend voorkeur geweest voor een donor met hetzelfde geslacht als de patiënt, in het bijzonder voor een mannelijke patiënt. In een recente studie bij volwassen mannen met acute leukemie werd gekeken naar het verschil tussen transplantatie met een zus of met een mannelijke onverwante donor. Er kon geen verschil in ziektevrije overleving worden aangetoond[11,12]. Het risico op acute Graft versus Host Disease (GvHD, omgekeerde afstoting) was echter significant hoger in de groep die met de mannelijke onverwante donor was getransplanteerd, waaruit de voorkeur voor stamcellen van de vrouwelijke familie donor werd geconcludeerd[13]. Het aantal toegediende stamcellen in een transplantaat is steeds als een belangrijke

factor aangemerkt voor transplantatieuitkomst[14,15]. Dit kan een verklaring zijn voor de voorkeur voor mannelijke donoren, van wie door een relatief groter lichaamsoppervlak gemiddeld meer stamcellen kunnen worden geoogst[16]. Echter, ook bij mannen heeft een hogere leeftijd een negatief effect op stamcel mobilisatie[17]. In het jaarverslag 2012/2013 van de Canadese stamceldonorbank OneMatch wordt de voorkeur van TC voor jonge mannelijke donoren als opvallend gemeld: 75% van de geleverde stamcelproducten was afkomstig van mannelijke donoren jonger dan 36 jaar[18]. Ook in Nederland wordt deze trend gezien: ruim 70% van de aanvragen voor een bloedmonster voor verificatie van de HLA typering ter voorbereiding voor transplantatie is voor een mannelijke donor. Het wereldwijde donorbestand is weliswaar aanzienlijk toegenomen in de afgelopen jaren, ook de leeftijd van de geregistreerde donoren is gemiddeld hoger geworden. Een gevolg hiervan is dat donoren vaker op medische grond niet beschikbaar zijn voor stamceldonatie en dus eigenlijk onbruikbaar[19]. Wereldwijd is 19% van de geregistreerde donoren man en jonger dan 36 jaar en slechts 10% van alle donoren (ongeacht geslacht) is jonger dan 26 jaar[3]. Uitgaande van leeftijd en geslacht voldoet het wereldwijde bestand op dit moment niet aan de criteria voor het optimale donorbestand. Stamceldonorbanken staan voor de uitdaging om te zoeken naar kosteneffectieve oplossingen. Het verlagen van de leeftijd voor registratie zou een oplossing kunnen zijn. In Groot Brittannië (registratie vanaf 16 jaar) en Canada (registratie vanaf 17 jaar) is dit in 2013 geïntroduceerd. De Canadese stamceldonorbank richt zich vooral op het werven van mannelijke donoren jonger dan 35 jaar[20]. Het rekruteren van jongere donoren heeft echter ook een keerzijde: stamceldonorbanken zien zich gedwongen om hun voorschriften en werkwijzen aan te passen. Tijdens de WMDA Fall Meeting in 2013 werd gerapporteerd dat onvoldoende 'levenservaring' en de onbekendheid met bijvoorbeeld procedures voor geïnformeerde toestemming (informed consent) bij jonge donoren, aanpak op maat bij (medische) begeleiding en dus extra training van de staf die hiermee is belast vereisen[21,22]. Het toedienen van G-CSF aan donoren jonger dan 18 jaar is niet in alle landen toegestaan; in Nederland is bijvoorbeeld geen consensus over de toediening van G-CSF aan gezonde personen jonger dan 18 jaar.

Hoewel het wereldwijde bestand Bone Marrow Donoren Worldwide (BMDW) gestaag groeit, is het merendeel van de donoren en navelstrengbloedeenheden geregistreerd in noordwest Europa (NWE) en noord-Amerika[23,24]. Dit vormt een beperkende factor voor patiënten met een niet-noordwest Europese (niet-NWE) achtergrond, voor wie een donor moet worden gevonden. Naast het werven van donoren met een niet-NWE achtergrond zijn meer strategieën nodig om de HLA-diversiteit van de donorpool met succes te kunnen vergroten[25]. Naast het verwerven van nieuwe donoren is het minstens zo belangrijk om actief te streven naar het behoud van beschikbare donoren. In de Verenigde Staten wordt al sinds eind jaren

'90 onderzoek gedaan naar de redenen waarom donoren niet langer beschikbaar zijn[26]. Sinds die tijd is in de Verenigde Staten het aantal donoren dat tijdens een eerste contact niet beschikbaar is toegenomen tot bijna de helft van het totale bestand[27,28] en dit aantal loopt nog steeds op[29]. Ambivalentie ten aanzien van donatie wordt daarbij genoemd als een belangrijke oorzaak voor het verminderd of niet langer beschikbaar willen zijn[30]. Uit onderzoek blijkt dat kort na de registratie meer dan een derde van nieuwe donoren aangeeft twijfels te hebben over stamceldonatie en niet weet of hij zal doneren indien gevraagd[31]. Specifieke kenmerken zoals (vrouwelijk) geslacht, lengte van de periode dat een donor geregistreerd staat en etnische achtergrond zijn cumulatieve 'risico factoren' voor verminderde beschikbaarheid[32]. Het optimaliseren van het wereldwijde donorbestand kan bijdragen aan de wens om een groter aantal patiënten te kunnen transplanteren. Rekruteren onder bloeddonoren geeft bijvoorbeeld meer zekerheid over beschikbaarheid op termijn en (medische) geschiktheid van de donor. Voor nieuwe niet-bloeddonoren zouden wervingsmethoden kunnen worden aangepast, waarbij gebruik wordt gemaakt van deze wetenschap en andere parameters[31].

Nederlandse patiënten met een niet-NWE achtergrond hebben nu een kans van 70% om getransplanteerd te worden. Hun kansen om een acceptabele onverwante donor te vinden onder de bijna 25 miljoen geregistreerde donoren is echter aanzienlijk minder, zowel in kwaliteit als in kwantiteit, dan voor patiënten met een NWE achtergrond en is eigenlijk in de afgelopen 10 jaren niet verbeterd (dit proefschrift). Daar komt nog bij dat de beschikbaarheid van niet-NWE donoren in beginsel al lager is dan van NWE donoren, wat de kans op het vinden van een optimale donor eens te meer verkleint[25,27,31-36].

Gragert en collega's hebben recent een theoretisch model gepresenteerd waarmee zij de kans op het vinden van een goed passende donor of navelstrengbloedeenheid voor blanke Europeanen en andere bevolkingsgroepen in de Verenigde Staten hebben berekend[37]. In dit op populatiegenetica gebaseerde model, wordt gebruik gemaakt van de beschikbare donors en navelstrengbloedeenheden van de National Marrow Donor Program (ongeveer 50% van het wereldwijde bestand), rekening houdend met de beschikbaarheid van donoren. Geconcludeerd wordt dat voor meer dan 95% van de patiënten met een (blanke) Europese of Afrikaanse achtergrond een onverwante donor of navelstrengbloedeenheid kan worden gevonden. In onze retrospectieve analyse werd echter voor 81% van de niet-NWE patiënten een acceptabele donor gevonden, waarbij vaker een mismatch moest worden geaccepteerd. De aanname van Gragert cs. dat de donorpopulatie een reflectie is van de patiëntenpopulatie[37] heeft mogelijk tot een overschatting van de kansen op een acceptabele donor of navelstrengbloedeenheid geleid. Daarbij is niet in ieder transplantatieprotocol een mismatched donor of navelstrengbloedeenheid een acceptabele stamcelbron. Patiënten in onze studie waarvoor geen acceptabele

donor kon worden gevonden hadden vaak een gemengde etnische achtergrond. Donoren met een gemengde etnische achtergrond zijn waarschijnlijk het minst vertegenwoordigd in het wereldwijde bestand. Het is daarom van groot belang dat beschikbaarheid van donoren, vooral van jonge mannelijke donoren (aangezien zij de grootste kans hebben om gevraagd te worden), en donoren uit de niet-NWE groep als aandachtspunt wordt benadrukt tijdens donorwervingscampagnes[31,32]. Dit betekent dat de stamceldonorbanken niet alleen moeten kijken naar de omvang van hun bestand, maar ook bestaande strategieën voor donorwerving moeten herzien om een betere beschikbaarheid van (nieuwe) donoren te bewerkstelligen. Het niet-beschikbaar zijn van vooral de nieuwe donoren na kostbare wervingsacties kan niet langer worden gerechtvaardigd[29,38]. Via social media, folders en nieuwsbrieven kan onder de aandacht worden gebracht dat 10% van de donoren onvindbaar is op het moment dat er een verzoek is een bloedmonster af te staan, met mogelijke negatieve gevolgen voor patiënten voor wie een donor wordt gezocht. Een oproep om bij wijziging van adres ook altijd de stamceldonorbank te informeren kan voorkomen dat het zoeken naar een donor voor de patiënt geen ongewenste en onnodige vertraging oploopt.

S, M, L, XL - donor registries

Op dit moment zijn er enkele zeer grote stamceldonorbanken (met meer dan 1 miljoen geregistreerde donoren) en een meerderheid van kleine (<20.000 donoren), middelgrote (20.000-100.000 donoren) en grote stamceldonorbanken (>100.000 donoren)[39]. Het overgrote deel (>80%) van de onverwante stamcelproducten wordt jaarlijks geleverd door vijf van de grotere stamceldonorbanken, waarvan twee zeer grote (samen 67% van alle producten). Dit maakt duidelijk hoe kwetsbaar de landen met de kleine en middelgrote stamceldonorbanken zijn. Zij zijn voor hun patiënten afhankelijk geworden van stamcelproducten die door buitenlandse donoren worden gedoneerd. Het is onduidelijk waarom ook de meerderheid van de aanvragen aan de zeer grote stamceldonorbanken zijn/worden gericht, aangezien het aannemelijk is dat donoren met een 'gangbare/frequente HLA typering' ook in de nationale stamceldonorbank te vinden moeten zijn. Men kan zich afvragen of nationale stamceldonorbanken niet in staat zouden moeten zijn om een bepaald percentage van de eigen patiënten van nationale stamcelproducten te voorzien. Mede door de moeilijke economische tijden en de toenemende kwaliteitseisen in de afgelopen jaren hebben de kleine en middelgrote stamceldonorbanken het zwaar en is het voor nieuwe stamceldonorbanken nagenoeg onmogelijk om zonder financiële steun te starten. Bij het vaststellen van de optimale omvang en samenstelling van het wereldwijde donorbestand, moet de balans worden gevonden tussen concurrerende belangen[27]. Nieuwe stamceldonorbanken, in het bijzonder in ontwikkelende landen, zijn van belang als het gaat om het toevoegen van nieuwe unieke HLA-fenotypes

aan het wereldwijde bestand. In de afgelopen jaren had gemiddeld één op de 15 nieuwe donoren een nieuw uniek HLA-fenotype. De bijdrage van bijvoorbeeld de Braziliaanse stamceldonorbank die in 2011 ging participeren in BMDW maakt duidelijk wat de toegevoegde waarde van een nieuwe stamceldonorbank is: in dat jaar had één op de 10 nieuwe donoren een uniek HLA-fenotype[40]. Opvallend is dat navelstrengbloedbanken een relatief groter aandeel in de nieuwe HLA fenotypes hebben in vergelijking tot donoren in datzelfde land. Navelstrengbloedbanken hebben kennelijk meer succes bij het rekruteren onder niet-NWE groepen[40]. Een deel van de nieuwe fenotypes in navelstrengbloedeenheden is ontstaan door een gemengde etnische achtergrond. Dit is van groot belang voor de groep patiënten waarvoor anders geen acceptabele donor of navelstrengbloedeenheid zou kunnen worden gevonden.

Jaarlijks worden stamcellen gedoneerd door 0,1% van alle geregistreerde donoren en worden ongeveer 0,8% van de navelstrengbloedeenheden gebruikt voor transplantatie[3,41]. Volledigheid en uitgebreidheid van HLA typering van de donor is rechtstreeks van invloed op de kans om voor donatie te worden gevraagd[42]. Een verklaring voor het relatief intensievere gebruik van navelstrengbloedeenheden (er wordt naar verhouding 10x zo veel van gebruikt) is mogelijk de grotere diversiteit en potentieel snellere beschikbaarheid. Daarbij komt de minder stringente noodzaak tot gelijkheid voor de HLA groepen van navelstrengbloed en patiënt als mogelijke verklaring voor dit verschil. De verwachte voordelen van navelstrengbloed als stamcelbron voor niet-NWE patiënten onderschrijft het belang van het opslaan van navelstrengbloedeenheden van hoge kwaliteit, waardoor het tekort aan donoren met een niet-NWE achtergrond in het wereldwijde bestand kan worden gecompenseerd[43]. Het is van belang om dit gegeven en het feit dat minder dan 1% van de geregistreerde donoren jaarlijks daadwerkelijk stamcellen doneert, kritisch te beschouwen voordat 'meer donors met dezelfde HLA' worden toegevoegd aan het internationale donorbestand[43].

Met nieuwe laboratoriumtechnieken zoals 'Next Generation Sequencing (NGS) zullen de kosten van hoge resolutie HLA-typering aanzienlijk worden verminderd en kunnen ook andere gegevens (bloedgroep, CMV, KIR, etc.) eenvoudig worden bepaald, waarmee kwalitatief hoogwaardige donoren kunnen worden toegevoegd aan het donorbestand. De Group of European Medium Sized Registries is opgericht, met als doel om gezamenlijk oplossingen te zoeken voor deze uitdagingen[44].

Bereiken van transplantatie – klinische en niet-klinische factoren

In 2001 werd slechts een-derde van alle patiënten, die waren aangemeld voor stamceltransplantatie, ook daadwerkelijk getransplanteerd[45]. Ruim 10 jaar later meldt het WMDA jaarverslag dat 45% van alle patiënten voor wie een

onverwante donorsearch is gestart wordt getransplanteerd[2]. Dit is waarschijnlijk een onderschatting van het totaal aantal patiënten dat in aanmerking komt voor transplantatie. Een recente prospectieve studie rapporteerde dat een onverwante donorsearch werd gestart voor 51% van alle patiënten zonder familie donor, zonder een duidelijke verklaring wat er met de overige 49% gebeurde[46]. Ondanks een geslaagde donorsearch, gaan transplantaties niet altijd door. De meest voorkomende oorzaak om een transplantatie te annuleren is klinische verslechtering (recidief), vooral bij patiënten met hoog risico leukemie[7,46,47]. Tijd is een cruciale factor: bij diagnose verrichten van HLA typering en de patiënt op tijd aanmelden voor het zoeken naar een donor zijn belangrijk[46]. Maar ook de tijd die nodig is om een donor te zoeken: die kan (en moet in sommige gevallen) teruggedrongen worden[48]. De belangrijkste niet-klinische factor voor niet-NWE patiënten voor het niet bereiken van transplantatie is zonder twijfel het gebrek aan donoren. Wij hebben voor Nederlandse patiënten aangetoond dat een efficiënt uitgevoerde onverwante donorsearch leidt tot een hoger percentage getransplanteerde patiënten en het terugdringen van het aantal annuleringen ten gevolge van klinische achteruitgang van de patiënt tot ongeveer 10% (dit proefschrift). Om een onverwante donor search zo efficiënt mogelijk uit te voeren zijn inspanningen van alle partijen die hierbij betrokken zijn en optimale samenwerking met TCs vereist. Stamceldonorbanken hebben methodes en hulpmiddelen ontwikkeld om de search te verkorten[49-53]. Het delen van informatie en inzichten tussen stamceldonorbanken en TCs kan een belangrijke rol spelen in het verbeteren van transplantatiecijfers.

Veiligheid van donoren: de wereldwijde aanpak

Veiligheid van stamceldonoren betreft vooral de medische geschiktheid van de donor voor de donatieprocedure. Of de donor een kind of volwassene is, verwant of onverwant, er mag niet worden voorbijgegaan aan de belangen van de donor – dat is de (ethische) plicht van de zorgverlener. De behandeling met een medicament of het onder algehele anesthesie brengen zijn niet in het fysieke belang van de donor en vereisen verantwoordelijkheid van de zorgverlener en een attitude waarbij de veiligheid van de donor op de eerste plaats komt[54]. Bij de introductie van het gebruik van Granulocyte Colony Stimulating Factor (G-CSF) in gezonde personen werd het belang van de veiligheid onderkend, in het bijzonder op lange termijn. In een recente studie zijn de ernstige bijwerkingen (Severe Adverse Events, SAE) op korte en langere termijn bij de verschillende vormen van donatie (BM en PBSC) geanalyseerd[55]. Opvallend was dat de bevinding dat het risico op een SAE drie maal hoger is in beenmergdonoren. Van belang is de conclusie dat voor een onverwante donor op de lange termijn geen verhoogd risico op het ontwikkelen van trombose, een maligniteit of auto-immuunziekte is gevonden[55]. Het is onduidelijk of de bevindingen ook gelden voor de verwante donorpopulatie; fysieke gezondheid van onverwante donoren is

waarschijnlijk beter dan van familiedonoren.

Voor patiënten is leeftijd niet langer een contra-indicatie voor HSCT. Zoals eerder opgemerkt hebben oudere patiënten ook oudere broers/zussen. En hoewel leeftijd niet noodzakelijkerwijs een indicatie is voor lichamelijke conditie[47], hebben ouderen vaker co-morbiditeit of een onderliggend lijden en dus vaker reden om niet geschikt voor stamceldonatie te worden verklaard (dit proefschrift). Echter, co-morbiditeit wordt voor familiedonoren vaker geaccepteerd, simpelweg omdat 'familiedonoren bereid zijn om een hoger risico te aanvaarden'[56]. Lang werd door medische beroepsgroep aangenomen dat familieleden van nature gemotiveerd zijn om het leven van een dierbare te redden[57]. Het zou het altruïstische karakter en het principe van 'goed doen' als aspect van de menselijke aard benadrukken, om te handelen in het belang van anderen[58]. Indien een familiedonor kiest om te doneren vanuit de liefde voor een familielid, heeft vanuit het perspectief van Kant zijn daad geen morele waarde, omdat er geen sprake is van een verplichting[58]. Het is echter onduidelijk wat het gevolg is van de eerder genoemde aanname van traditioneel altruïstisch denken; kan dit betekenen dat een familielid zich 'verplicht' voelt om te doneren, en hem weerhouden van de mogelijkheid om een vrije keuze te maken[59]. Betekent dit wellicht dat het ethisch principe van autonomie, dat het recht op een vrije keuze onderschrijft, met voeten wordt getreden? Indien het principe van autonomie wordt genegeerd dan wordt een persoon gebruikt als middel om een doel te bereiken, zonder daarbij rekening te houden met de belangen van die persoon[58]. Vanuit die optiek zou de aanname uitdrukking kunnen geven aan het nuttigheidsbeginsel, zoals dat is geformuleerd door Bentham: als kan worden aangenomen dat de kans op het slagen van een stamceltransplantatie redelijkerwijs groter is dan de kans op het ondervinden van enige schade door de familiedonor, dan is het de plicht van de donor om te doneren[58]. De situatie wordt gecompliceerd indien de donor een kind is en nog niet kan instemmen of toestemmen met donatie. Toestemming bij volmacht, door de ouders of wettelijk vertegenwoordiger kan dan betekenen dat het kind als middel wordt gebruikt om het doel, genezing van een broertje of zusje, te bereiken. Dit is niet in overeenstemming met het principe van Kant's tweede formulering van de categorische imperatief: de actie wordt beschouwd als onacceptabel omdat de integriteit en waardigheid van het individu (de kinddonor) worden aangetast[60]. In het kader van stamceldonatie door kinderen heeft de American Academy of Pediatrics (AAP) een aantal ethische aspecten beschreven en criteria gedefinieerd om het gebruik van kinderen als stamceldonor te rechtvaardigen[61]. Hoewel de AAP adviseert te streven naar een protocol voor (wettelijke of ethische) goedkeuring voorafgaand aan de donatie, blijft het de vraag of de belangen van de kinddonor hiermee voldoende worden beschermd[62]. Er is een voorstel gedaan om het protocol aan te passen, waarbij meer aandacht aan de rechten, het besef en de toestemming van het kind wordt gegeven[62]. Het oogsten van stamcellen is een medische ingreep

met potentiele risico's en aantasting van de integriteit van het lichaam van de donor. Het argument van 'het eigen belang' blijft daarbij omstreden, aangezien de uitkomst van de transplantatie en dus de meerwaarde voor de donor niet vooraf kan worden voorspeld[63]. Het debat over kwaliteit van leven en medische emancipatie werd ook bij het publiek actueel door de publicatie van 'My Sister's Keeper' ('De Tweede Dochter')[64], waarin een 13-jaar oud meisje leeft in de wetenschap dat zij is verwekt om het leven van haar zusje, dat leidt aan leukemie, te redden. Zij is letterlijk de 'donor bij volmacht'[65], en gaat, na meerdere stamceldonaties en voor zij besluit een nier te doneren aan haar zusje, op zoek naar het recht op medische emancipatie[64]. Door het verhaal wordt het duidelijk dat het principe van autonomie geen waarde heeft als voorbij wordt gegaan aan de beslissingsbevoegdheid van de donor, ook als dat een kind is. Op de beleidsnota van de AAP na, bestaan er geen strikte regelgeving of richtlijnen voor de medische geschiktheid, behandeling en follow-up voor kinderen die stamcellen doneren. Relatief kleine aanpassingen in lokale praktijkvoering kunnen al een groot verschil betekenen voor kinddonoren. Het terugbrengen van het maximum volume van te oogsten beenmerg bijvoorbeeld, kan voorkomen dat een kinddonor een bloedtransfusie nodig heeft (dit proefschrift). Daar komt bij dat uitkomst van transplantatie bij kinderen met hoog risico leukemie in de afgelopen jaren, aanzienlijk is verbeterd ongeacht de bron van stamcellen[66]. In een gestructureerd proces van besluitvorming zou kunnen worden overwogen om gebruik te maken van een alternatieve stamcelbron, zoals een onverwante donor of navelstrengbloedeenheid (indien de tijd dat toelaat).

De mening dat de medische geschiktheid van de (familie) stamceldonor in het belang is van alle betrokken partijen, wordt ook internationaal gedragen[67]. Dit is bevestigd door de oprichting van de EBMT Donor Outcome Committee in 2012 en vanaf de FACT/JACIE Standards versie 5[68] is de zorg voor de donor expliciet benoemd. Dientengevolge zijn initiatieven ontplooid om zorg voor de familiedonor strikter te reguleren en implementeren[69,70]. Nut en noodzaak van goede zorg voor stamceldonoren inclusief langetermijnfollow-up is ook door de Wereld GezondheidsOrganisatie (WHO) erkend[71]. Opmerkelijk is dat een vergelijkbare discussie wordt gevoerd voor het welzijn van levende nierdonoren; financiële steun van de overheid wordt daarbij als essentieel beschouwd voor het opzetten van nationale systemen voor levenslange follow-up[72,73]. Het Worldwide Network for Blood and Marrow Transplantation (WBMT) is opgericht om de samenwerking tussen bestaande organisaties op het gebied van bloed- en stamceldonatie te stroomlijnen en stamceltransplantatie en -donatie wereldwijd te bevorderen[74]. In Donor Outcome Workshops is internationale consensus bereikt over criteria voor medische geschiktheid, waarbij tijdens de laatste bijeenkomst vooral het opstellen van richtlijnen met internationale consensus van stamceldonatie op oudere of jongere leeftijd werden besproken (Wenen, 2013). De ontwikkeling van een Europese Master

in Donor Health Care, een Nederlands initiatief met steun van de Europese Unie, is een ander voorbeeld waaruit duidelijk wordt dat de zorg voor orgaan-, weefsel- en stamceldonoren een professie is die ook internationaal serieus wordt genomen.

Op het gebied van ernstige incidenten en bijwerkingen heeft de WMDA een rapportagesysteem. Het eerdergenoemde S(P)EAR waarschuwingssysteem geeft een goede indicatie van ernstige complicaties bij onverwante donoren/producten. Om de ernstige bijwerkingen bij familiedonoren te registreren bestaat geen systeem. Om meer inzicht te krijgen in de familiedonoren is het van belang om ook voor deze groep de ernstige bijwerkingen en incidenten te rapporteren[75]. Het opzetten van een wereldwijd systeem waarin ernstige bijwerkingen en incidenten bij alle levende donoren van weefsels en/of organen worden gerapporteerd en geregistreerd moet nader worden onderzocht omdat dit tot een enorme verbetering in de zorg voor de donor zal leiden.

De toekomst – hoe lang zijn onverwante donoren nog nodig?

Het veld van HSCT is dynamisch en voortdurend onderhevig aan veranderingen, die directe gevolgen kunnen hebben voor de stamceldonorbanken. Ontwikkeling van nieuwe medicamenten en protocollen voor behandeling met stamcellen volgen elkaar snel op. Naast het gebruik van familiedonoren, onverwante donoren en navelstrengbloedeenheden wordt nu ook de optie van behandeling met doelgerichte (autologe) T-cellen onderzocht. Genezing van chronische myeloide leukemie (CML) was minder dan 20 jaar geleden alleen te bereiken met een allogene stamceltransplantatie. De ontdekking van een nieuwe therapeutische benadering met tyrosine-kinase inhibitors reduceerde voor het merendeel van deze patiënten de behoefte aan stamceltransplantatie[76]. Vergelijkbare ontwikkelingen worden gezien op het gebied van chronische lymfatische leukemie (CLL)[77]. De potentie van behandeling met autologe T-cellen om doelgericht de tumor aan te vallen, is onlangs gerapporteerd[78]. Indien de resultaten van dit onderzoek kunnen worden bevestigd kan dat uiteindelijk leiden tot een afname van het aantal stamceltransplantaties. Een andere ontwikkeling is de hernieuwde belangstelling voor beenmergtransplantatie met haploidentieke familie donoren, gevolgd door hoge dosis cyclofosfamide kort na transplantatie, om de kans op afstoting en GvHD te voorkomen. De uitkomsten van dergelijke transplantaties zijn nagenoeg vergelijkbaar met die van transplantaties met HLA-identieke familiedonoren of onverwante donoren[79]. In 2013 werd 40% van alle HSCT patiënten in Italië met stamcellen getransplanteerd van een haploidentieke donor. Bacigalupo gaf aan dat de kosten van het stamceltransplantatieprogramma hiermee met 10% konden worden verlaagd, terwijl het aantal transplantaties met 20% was toegenomen[80].

Regionale verschillen in het toepassen van stamceltransplantaties met onverwante

donoren zijn groot en geassocieerd met het nationaal inkomen, waardoor het verschil tussen de rijke en arme landen steeds groter wordt[3,81]. Een bijkomend gevolg van de economische crisis, is de noodzaak voor transplantatiecentra om te onderzoeken hoe de kosten van transplantatie kunnen worden verminderd, zonder afbreuk aan de kwaliteit van zorg[82,83]. Het aantal ligdagen in het ziekenhuis is de grootste kostenpost, maar de kosten van de onverwante donorsearch, een stamcelproduct en in het bijzonder de kosten van navelstrengbloedeenheden zijn ook onderwerp van discussie[82,84,85]. De kosteneffectiviteit van stamceltransplantatie met verschillende stamcelbronnen (inclusief haploidentieke stamcellen) wordt op dit moment onderzocht[86]. In sommige landen geven de verzekeringsmaatschappijen een vaste vergoedingen, met het gevolg dat transplantatie met navelstrengbloed niet langer tot de mogelijkheden behoort. Het is in het van belang van niet-NWE patiënten dat er gezocht wordt naar manieren om het gebruik van navelstrengbloed betaalbaar en rendabel te laten blijven[87] (dit proefschrift). De huidige discussie concentreert zich op de prijs van stamcelproducten in het algemeen en van navelstrengbloed in het bijzonder. Zowel een 'vast prijsbeleid', of een prijs die is gebaseerd op het aantal cellen in een navelstrengbloedeenheid (kleinere eenheid – lagere prijs) zou ten goede komen aan de patiënt: geld is niet langer een argument om niet de beste match te kiezen. Er zijn aanwijzingen dat de toename van etnische diversiteit in het wereldwijde navelstrengbloedbestand er toe leidt dat meer patiënten kunnen worden getransplanteerd (dit proefschrift). Navelstrengbloedbanken zouden hun wervingsmethoden nog meer kunnen aanpassen om de HLA-fenotype diversiteit nog verder te vergroten[87]. Bekendheid bij het grote publiek stimuleren is daarbij van groot belang om het doel te bereiken, ook binnen de mogelijkheden van een individueel land[88]. De waarschijnlijkheid dat een navelstrengbloedeenheid wordt gebruik is, naast de HLA-typering, direct gerelateerd aan het aantal cellen (TNC) die de eenheid bevat[89]. Eenheden met een hoger aantal TNC hebben meer kans om geselecteerd te worden voor transplantatie[89]. Het is bekend dat niet-NWE eenheden vaker minder TNC bevatten, mogelijk houdt dit verband met de relatief kortere tijdsduur van de bevalling, maar de toegevoegde waarde van de diversiteit moet niet worden onderschat[87]. Een andere mogelijkheid om een navelstrengbloedeenheid breder toepasbaar te maken is het beschikbaar stellen van de moederlijke HLA typering. Navelstrengbloedeenheden die de niet-geërfde maternale antigenen (NIMA) of geërfde paternale antigenen (IPA) gemeen hebben met de patiënt, hebben een positief effect op transplantatie uitkomst: de kans op recidief is kleiner en ook de mate van GvHD is minder[90,91]. Een recente studie heeft aangetoond dat het matchen van navelstrengbloed op hoge resolutie voor HLA-A, -B, -C en -DRB1 geassocieerd is met de laagste mortaliteit na transplantatie bij patiënten met acute leukemie en myelodysplastisch syndroom[92]. Navelstrengbloedbanken zouden kunnen overwegen hun (nieuwe) eenheden op hoge resolutie te laten typeren.

Donoren en (toekomstig) onderzoek

In de afgelopen decennia zijn motivatie, ervaringen en opvattingen van stamceldonoren en stamceldonatie onderzocht en beschreven[93]. Introductie van nieuwe middelen voor mobilisatie van stamcellen en het gebruik van zogenaamde biosimilars heeft geleid tot discussie en de vraag naar mogelijkheden van prospectieve studies waarbij ook gezonde niet-donoren worden geincludeerd[94,95]. Beschikbaarheid van donoren, wervingsstrategieën en veiligheid van vooral de familiedonor blijven belangrijke onderwerpen voor toekomstig onderzoek. Langetermijneffecten van stamceldonatie zijn echter niet louter voorbehouden aan fysieke uitkomst, maar ook cognitieve, emotionele en psychosociale factoren moeten worden onderzocht. De analyse van de Levensloopvragenlijst die is afgenomen bij ons cohort kinddonoren zal worden afgerond, waarbij wij meer inzicht hopen te krijgen in de ontwikkeling van jong volwassenen die hebben gedoneerd op jonge leeftijd. Daarnaast zal een analyse op het gebied van 'omgaan met pijn' worden verricht, in een prospectief cohort van onverwante en familiedonoren. Ook de relatie tussen stress en stamceldonatie en Levensoriëntatie zullen worden geanalyseerd. Alle donoren die hebben deelgenomen in onze studies hebben schriftelijke toestemming gegeven en deze studies in donorbelang zijn goedgekeurd door de Commissie Medische Ethiek van het Leids Universitair Medisch Centrum. Er kunnen situaties ontstaan waarbij donoren indirect worden betrokken in een klinische studie (bijvoorbeeld wanneer de donatie deel uitmaakt van een experimenteel behandelprotocol). De aanname dat donoren door stamcellen af te staan aantonen dat zij in belang van de patiënt handelen, en dus ook instemmen met deelname aan wetenschappelijk onderzoek[96] gaat voorbij aan de autonomie van de donor. De WMDA heeft gesteld dat in dat geval goedkeuring van het protocol door de stamceldonorbank en aanvullende toestemming van de donor nodig zijn[97], hoewel dat mogelijk kan leiden tot vertraging in het proces ten nadele van de patiënt. De opstelling van de WMDA heeft geleid tot inzicht bij behandelaren van patiënten, dat donoren, net als patiënten, rechten hebben[98,99]. Het blijft een uitdaging om de belangen van alle partijen te harmoniseren[100], in het bijzonder omdat dit een onbevooroordeelde benadering vereist van degenen die een studieprotocol, waarin ook een rol is gereserveerd voor stamceldonoren, moeten beoordelen en goedkeuren. Hier is zeker een mogelijkheid voor verbetering: medisch ethische commissies of wetenschapscommissies moeten de rol en veiligheid van ieder individu (patiënt en donor) dat betrokken is in de studie overwegen, in het bijzonder wanneer er meerdere of verlengde donaties zijn opgenomen in het protocol. Het is belangrijk om bij de goedkeuring van een studieprotocol ook expliciet de gevolgen en aanvaardbaarheid voor de donor te benoemen en te adviseren conform de internationale WHO standaarden voor menselijk onderzoek[101], zodat vertraging, veroorzaakt door aanvullend onafhankelijke beoordeling van een studieprotocol door een stamceldonorbank wordt voorkomen. Het is onzeker hoe nadrukkelijk de

rol van de onverwante donor in de toekomst zal zijn, maar familiedonoren blijven een belangrijke rol spelen. Het zoeken naar de beste balans tussen de noodzaak voor de patiënt en het belang van de donor[102] blijft daarom actueel voor alle betrokken partijen zodat ook op lange termijn de veiligheid van donoren kan worden gewaarborgd.

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Part VI

Appendices

Appendices

DANKWOORD, CURRICULUM VITAE, LIST OF PUBLICATIONS, LIST OF ABBREVIATIONS, LIST OF CO-AUTHORS

Dankwoord

De weg naar het doctoraat is een lange weg, en zelden zonder oneffenheden. Voor mij zijn het welzijn en de veiligheid van de donor van hematopoietische stamcellen steeds de onvoorwaardelijke drijfveren geweest om door te gaan. Het is allemaal begonnen in 1991 toen ik op de polikliniek kindergeneeskunde geconfronteerd werd met kinderen die beenmerg doneerden aan een broertje of zusje met (veelal) leukemie. Dat intrigeerde me onmiddellijk: hoe leg je dat uit aan een kind, dat hij een medische ingreep moet ondergaan terwijl hij niet ziek is? Het was het begin van een lange zoektocht naar antwoorden op steeds nieuwe vragen, die allemaal draaiden om die ene persoon: de donor van stamcellen.

Het is daarom niet meer dan correct om in de allereerste plaats een woord van dank te richten tot de honderden donoren die bereid zijn geweest om te participeren in de verschillende onderzoeken: de ouders die stamcellen doneerden aan hun kinderen, de mannen en vrouwen die aan een broer of zus of een onbekende ontvanger doneerden, de 'kinderen' die zelfs tot 40 jaar na donatie bereid bleken te zijn om hun veelal indrukwekkende ervaringen met mij te delen, en de bloedplaatjesdonoren die als controlepersonen de vragenlijsten invulden. Zonder hun hulp was dit boek er niet gekomen, ik ben ze heel veel dank verschuldigd.

De promotor en co-promotoren hebben in de afgelopen jaren ieder op hun eigen manier een belangrijke rol gespeeld in mijn leven, en mij steeds geinspireerd om steeds weer nieuwe paden van onderzoek in te slaan. Anneke Brand, rots in de branding, steun en toeverlaat bij nacht en ontij. Steeds als ik bij jou was geweest (vaak aan het eind van de dag), was vermoeidheid niet meer belangrijk en had ik hernieuwde energie om weer op een andere manier tegen een dataset aan te kijken, wat soms verrassende resultaten opleverde. Machteld Oudshoorn, steeds kritisch en nauwkeurig - iedere tabel werd door jou nagerekend tot achter de komma, ieder percentage gecheckt tot het klopte. Onze gezamenlijke interesse in de HLA-aspecten van de onverwante donorsearch leverde vaak stof voor studie en discussie op. Daarnaast ben je natuurlijk de beste bron als het gaat om een snoei-, plant-, of ander advies voor de tuin! Lynne Ball, collega maar vooral dierbare vriendin; ik bewaar dankbare herinneringen aan de avonden achter de computer tijdens het onderzoek naar de ervaringen van ouders en kinderen die doneerden, en onze reizen naar de EBMT en WMDA bijeenkomsten.

De medewerkers van het Centrum voor Stamceltherapie van het LUMC verdienen een pluim: zij informeerden de donoren over de studie en verzamelden de vragenlijsten en bloedmonsters, en waren behulpzaam bij het opzoeken van oude transfusiegegevens. Peter, Ingrid, Anja, Lona, Dominique, Ineke, Ed, Edwin, Paulien, Joost, Yolanda en Jacqueline: heel veel dank voor jullie zeer gewaardeerde inzet!

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De vele (inter)nationale collega's wil ik danken voor hun inzet en betrokkenheid en als coauteur. Mede dank zij uw inspanningen is er consensus voor de ontwikkeling van optimale zorg voor de donor.

A big Thank You to my international colleagues Bronwen Shaw and Galen Switzer, who became true friends over the years. Your support and advice have been so valuable.

Tony, collega, vriendin en nu ook paranimf. Dank je wel voor je vriendschap in goede en minder goede dagen. Ik hoop dat we nog heel veel samen zullen ondernemen.

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Lieve Jack, door de jaren heen heb je me steeds weer moed gegeven als ik dacht dat het nooit zou lukken, of stikte in een statistische berekening! Jij bleef erin geloven, en kreeg gelijk. Dank ook voor al je digitale inspanningen: mede dank zij jou is het een prachtig boekje geworden.

Curriculum Vitae

Suzanna M. (Anne-Marie) van Walraven was born in 1958 in Heerlen and grew up in Gouda and Oegstgeest. She attended the Stedelijk Gymnasium and Louise de Coligny Scholengemeenschap in Leiden, and achieved her HAVO diploma in 1977. In the same year she started her career as nurse (Juliana Kinder Ziekenhuis, The Hague, NL 1977-1981) and specialised in anaesthetics (Christelijke Vereniging Het Diaconessenhuis, Leiden, NL, 1981-1985). She worked in the emergency room of the Leiden University Medical Centre (1985-1986) and after the birth of her daughters Sanne (1986) and Leonore (1989) specialised in haematology and paediatric stem cell transplantation (Leiden University Medical Centre, 1991-1997). She served as search coordinator and search consultant at Europdonor Foundation (1997-2006). After finishing her MSc in Nursing (University of Cardiff, UK, 2003), she started a research project for a doctoral dissertation, focusing on different experiences and aspects of stem cell donation and the unrelated donor search. She worked four years in the paediatric stem cell transplantation unit of the Leiden University Medical Centre (2006-2010) as physician assistant, and received her MPA in 2009 (Hogeschool Utrecht, NL). Until 2014 she managed the Transplant Centre Coordination Unit at Europdonor Foundation, the department that is responsible for the unrelated donor searches for Dutch patients.

Since 1998 Anne-Marie is actively participating in the World Marrow Donor Association (WMDA) as member of several subcommittees and task forces, and chair of the (former) Ethics Working Group. In 2011 she organised the 2nd Donor Outcome Workshop on behalf of the Worldwide Network of Blood and Marrow Transplantion (WBMT) in Leiden. In 2012 she was appointed member of the Donor Outcome Committee of the European Group for Blood and Marrow Transplantation (EBMT). Anne-Marie is chair of Hematon SCT, a group within the Dutch organisation looking after the interests of patients with blood cancer. She has been involved in the editorial staff of the Dutch Magazine for Physician Assistants, since its foundation in 2012. Currently she is working for the Dutch office for Hemo- and Biovigilance TRIP (Transfusion and Transplantation Reactions in Patients), and involved in the development of the WMDA eLearning program. In her free time she loves to travel and collect fabric from all over the world for her patchwork and quilt projects.

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2014 C Anthias, SM van Walraven, BS Sørensen, G Nicoloso-de Faveri, M Fechter, J Cornish, A Bacigalupo, CH Mueller, M Boo, BE Shaw. Related hematopoietic cell donor care: Is there a role for unrelated donor registries? Bone Marrow Transplantation, 2014 (under review).

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List of abbreviations

AAP	American Academy of Pediatrics
ABMTRR	Australiasian Bone Marrow Transplant Recipient Registry
ALL	Acute lymphoblastic leukaemia
AML	Acute myelogenous leukaemia
ANOVA	Analysis of variance
APBMT	Asia Pacific Blood and Marrow Transplantation Group
ARA	American Rheumatism Association
ATG	Anti-thymocyte globulin
BM	Bone marrow
BMDW	Bone Marrow Donors Worldwide
BMI	Body mass index
BW	Body weight
CBS	Dutch Central Bureau of Statistics
CBU	Cord blood unit
CD34+	Cluster of differentiation 34 positive
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	Chronic lymphoblastic leukaemia
CML	Chronic myelogenous leukaemia
CMO	Chief Medical Officer
CMV	Cyto megalo virus
CTLp	Cytotoxic lymphocyte precursor test
CVC	Central Venous Catheter
CVD	Cardio vascular disease
CWG	Clinical Working Group
CXCR-4	C-X-C chemokine receptor type 4
DF	Donor found
DKMS	Deutsche Knochenmarkspenderdatei (German bone marrow donor center)
DLI	Donor lymphocyte infusion
DNA	Desoxyribo nuclein acid
DRWG	Donor Registries Working Group

DVT	Deep vein thrombosis
EBMT	European Group for Blood and Marrow Transplantation
EDS	European Donor Secretariat
EMBMT	Eastern Mediterranean Blood and Marrow Transplantation Group
EMDIS	European Marrow Donor Information System
EPO	Erythropoietin
FFP	Fresh frozen plasma
G-CSF	Granulocyte colony stimulating factor
GHQ	General Health Questionnaire
GVHD	Graft versus Host Disease
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HOVON	Haemato Oncology Foundation for Adults in the Netherlands
HPC	Hematopoietic progenitor cells
HRQoL	Health related quality of life
HSC	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
IBMTR	International Bone Marrow Transplant Registry
ICD	International Classifications of Diseases
IDRC	International Donor Registry Conference
IE	Inborn errors
IPA	Inherited paternal antigens
IQR	Interquartile range
ISCT	International Society for Cellular Therapy
JACIE	Joint Accreditation Committee ISCT & EBMT
KIR	Killer-cell immunoglobulin-like receptor
LDH	Lactate dehydrogenase
LEWP	Late Effects Working Party
LUMC	Leiden University Medical Centre
MDS	Myelo dysplastic syndrome
MLC	Mixed lymphocyte culture
MNC	Mononuclear cells
MSC	Mesenchymal stromal cells

NGS	Next generation sequencing
NIMA	Non-inherited maternal antigens
NMDP	National Marrow Donor Program
Non-NWE	Non-north western European
NWE	North western European
OMD	Other malignant diseases
ONMD	Other non-malignant diseases
PBSC	Peripheral blood stem cells
PCD	Plasma cell disorders
PE	Physical examination
PedsQL	Pediatric Quality of Life Inventory™
PEG-G-CSF	Pegylated granulocyte colony-stimulating factor
PLT	Platelet
RDSafe	Related donor safety study
RIC	Reduced Intensity Conditioning
RT	Reached transplantation
SAA	Severe aplastic anemia
SAE	Severa adverse event
SAR	Serious adverse reaction
SBSC	Swiss Blood Stem Cells
SCT	Stem cell transplantation
SEAR	Serious events and adverse reactions
SF-36	Medical Outcomes Study Short Form-36
SMR	Standardized morbidity ratio
SPEAR	Serious product events and adverse reactions
SPSS	Statistical Packages for the Social Sciences
TC	Transplant centre
TIA	Transient ischemic attack
TNC	Total nucleated cell count
UCB	Unrelated cord blood unit
UCL	Utrecht Coping List
UD	Unrelated donor
UDS	Unrelated donor search

UPN	Unique patient number
URD	Unrelated donor
WBC	White blood cell
WBMT	Worldwide Network for Blood and Marrow Transplantation
WHO	World Health Organisation
WMDA	World Marrow Donor Association

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Cover illustration: "Crossing Borders" - this quilt (designed and made by the author) represents both stem cells migrating from marrow to periphery and stem cell products dispersing over the globe (machine patchwork, hand application and hand quilting). More information on this quilt: http://piecesandpatches.nl

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