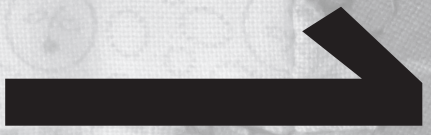
Chapter



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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