

Chapter

11

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 regimens 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 evolvments 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 supplementation 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 past 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 system¹. Apart from a growing list of indications, the development of non-myeloablative conditioning regimens 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 registry² and it was estimated that in 2013 daily 33 unrelated stem cell products were crossing an international border³. 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 worldwide⁶, it is assumed that the therapy is still underused as curative treatment, due to various clinical and non-clinical reasons⁷. 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 preferable¹⁰. 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 preferable¹³. 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 weight¹⁶, 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 mobilization¹⁷.

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 years¹⁸. 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 useful¹⁹. Globally, 19% of the registered donors are male and younger than 36 years and only 10.5% of all donors are younger than 26 years³. 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 years²⁰. 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 efforts²⁵. 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 investigated²⁶, 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 increasing²⁹. It has been shown that commitment is lower in ambivalent donors³⁰. When asked almost immediately after registration, 35% of newly recruited donors stated that they have doubts if they would proceed to donation³¹. 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 patients³². 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 strategies³¹. 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 US³⁷. 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 population³⁷ 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 financial support. Determining the optimal size and mix of the global donor inventory involves difficult decisions balancing competing objectives and requirements²⁷. 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 phenotype⁴⁰. 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 groups⁴⁰. 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 probabilities⁴², 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 pool⁴³. 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 Registries⁴⁴ 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 HSCT⁴⁵. Over a decade later the WMDA Annual Report demonstrates that 45% of patients for whom an unrelated donor search is initiated reach HSCT². 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 deferred⁴⁶. 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 factor⁴⁷, and the period to identify a donor could (and in some cases needs) to be decreased⁴⁸. 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 search⁴⁹⁻⁵³. 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 his physical benefit demands responsibility from health professionals, and an approach where the safety of the donor comes first⁵⁴. 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 analysed⁵⁵. 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 donation⁵⁵. The WMDA have adjusted their statement with regards to the use of G-CSF in healthy volunteers⁵⁶, 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 an absolute contraindication for HSCT, but as previously mentioned, older patients have older siblings, and although age is not per se an indication for performance status⁴⁷, 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 one⁵⁸. 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 others⁵⁹. 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 obligation⁵⁹. 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 making⁶⁰. In extenso – could this imply violation of the basic 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 interests⁵⁹. 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 donate⁵⁹. 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 activity⁶¹. The American Academy of Pediatrics (AAP) has addressed ethical concerns in a policy and defined criteria that allow for the use of pediatric donors⁶². 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 proposed⁶³. 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 minors⁶⁵. 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 source⁶⁷. 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 involved⁶⁸. This was acknowledged by the transplant society with the establishment of the EBMT Donor Outcome Committee in 2012. Furthermore the FACT/JACIE Standards version 5⁶⁹ 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-up⁷². 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 donation⁷⁵. 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 management⁷⁶. 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 group⁷⁷. 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 inhibitors⁷⁸. Similar developments are on their way for chronic lymphocytic leukemia⁷⁹. If results of autologous tumor targeted T-cell therapy⁸⁰ 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 donors⁸¹. In 2013, 40% of the patients in Italy received a haploidentical graft; Bacigalupo⁸² 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 care⁸⁴, and keeping the treatment accessible⁸⁵. 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 investigation⁸⁸. 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 affordable⁸⁷. 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 diversity⁸⁹. Raising public awareness is important to reach the goal of covering HLA diversity even within a country⁹⁰. 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 transplantation⁹¹. 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 considered⁸⁹. 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 syndrome⁹⁴, 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 studied⁹⁵. 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 Eurodonor 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 research⁹⁸. The WMDA requires additional approval for donation by a donor registry and informed consent of the donor⁹⁹, 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 involved¹⁰², 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 research¹⁰³, 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' interests¹⁰⁴ and to accomplish long-term safety for future donors.

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