UPPSALA
UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1832

Potential Hazards for Haematopoietic Stem Cell Donors

SIMON PAHNKE

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2022

ISSN 1651-6206
ISBN 978-91-513-1471-6
URN urn:nbn:se:uu:diva-471647

Dissertation presented at Uppsala University to be publicly examined in H:son Holmdahl-salen, Akademiska sjukhuset, Ing 100, Uppsala, Friday, 20 May 2022 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Nina Worel (Medical University Vienna, Vienna, Austria).

Abstract

Pahnke, S. 2022. Potential Hazards for Haematopoietic Stem Cell Donors. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1832. 61 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1471-6.

The aim of this thesis has been to increase our knowledge about the allogeneic stem cell donation procedure and the associated risks for stem cell donors.

In a first study (paper I), we described the donation procedure and short-term side effects of 1957 donors included in the Nordic Register of Haematopoietic Stem Cell Donors. Donors of bone marrow or peripheral blood stem cells experienced side effects such as bone/muscle pain, headache and /or fatigue in more than 90% of cases, with symptoms lasting less than one week for the majority of donors. Bone marrow donors had side effects of longer duration, experienced more fatigue, and were more likely to need sick leave longer than one week. Related donors were older than unrelated donors, had more comorbidities, and more frequently needed a central venous catheter and/or multiple apheresis during peripheral blood stem cell donation.

For a second study (paper II), we analysed global survey data from the World Marrow Donor Association (WMDA), regarding the use of biosimilar versions of stem cell mobilising drug filgrastim. A third of donor registers (10/30) had adopted the use of biosimilar filgrastim, with the majority doing so during the last five years. A review of studies of biosimilar filgrastim use for healthy donor stem cell mobilisation, showed biosimilar drugs to exhibit similar pharmacokinetic and pharmacodynamic properties to the reference product Neupogen®. No differences in stem cell mobilising capacity or adverse events were found. The study resulted in the endorsement by WMDA of the use of biosimilar filgrastim for stem cell mobilisation in healthy donors.

In two studies (paper III and V) of almost 1100 donors, we linked data from multiple Swedish national registers to investigate if peripheral blood stem cell donation with the use of granulocyte-colony stimulating factor (G-CSF) is associated with an increased risk of cancer or cardiovascular disease. No increased risk of cancer, haematological malignancies or cardiovascular disease was found, after a median follow up of close to 10 years.

In a national survey of 210 potential stem cell donors, using validated mental health screening tools (paper IV), we found female gender, lower age, and an increased level of worry for one-self in regards to becoming a donor, to be associated with lower mental health, and higher levels of anxiety.

Keywords: stem cell donor, stem cell transplantation, cancer, haematology

Simon Pahnke, Department of Medical Sciences, Haematology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-513-1471-6
URN urn:nbn:se:uu:diva-471647 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-471647)

“It always seems impossible until it's done”
Nelson Mandela

List of Papers

The thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Pahnke, Simon**, G. Larfors, U. Axdorph-Nygell, A. Fischer-Nielsen, E. Haastrup, D. Heldal, M. Itala-Remes, J. E. Johansson, M. Kauppila, S. Lenhoff, P. Ljungman, R. Niittyvuopio, A. Sandstedt, and H. Hägglund. "Short-Term Side Effects and Attitudes Towards Second Donation: A Comparison of Related and Unrelated Haematopoietic Stem Cell Donors." *J Clin Apher* (Aug 18 2017).

II. **Pahnke, Simon,** T. Egeland, J. Halter, H. Hägglund, B. E. Shaw, A. E. Woolfrey, and J. Szer, "Current Use of Biosimilar G-CSF for Haematopoietic Stem Cell Mobilisation." *Bone marrow transplantation (Basingstoke)* (03/2018).

III. **Pahnke, Simon**, U. Axdorph Nygell, J. E. Johansson, A. Kisch, P. Ljungman, A. Sandstedt, H. Hägglund and G. Larfors. ”Cancer incidence of Swedish healthy peripheral blood stem cell donors”. *Bone Marrow Transplant. (2022 Mar 7).*

IV. Winterling, J., **S. Pahnke**, H. Hägglund, G. Larfors, S. Lenhoff, A. Kisch. ”Psychological well-being and health in potential donors of haematopoietic stem cells before donation – a Swedish national study”. *Submitted*

V. **Pahnke, Simon,** H. Hägglund, and G. Larfors. ”No increased incidence of cardiovascular disease in healthy Swedish peripheral blood stem cell donors”. *Manuscript*

Contents

Introduction 11

Allogeneic stem cell transplantation 13
- Brief history of allogeneic stem cell transplantation 15
  - Early attempts at stem cell transplantation 16
  - Current status of allogeneic stem cell transplantation 17
  - Outcomes of allogeneic stem cell transplantation 18
- Stem cell donation 20
  - Choosing a donor 20
  - Stem cell source 21
  - Short term complications after stem cell donation 22
  - G-CSF and the risk of cancer 22
  - G-CSF and risk of non-malignant diseases 24
  - Alternatives to G-CSF for stem cell mobilisation 24

Research aims 27

Methods 28
- Paper I 28
- Paper II 29
- Paper III 29
- Paper IV 31
- Paper V 32

Ethical considerations 34

Results 35
- Paper I 35
- Paper II 37
- Paper III 37
- Paper IV 38
- Paper V 39

Discussion 41
- Short-term risks and donor characteristics 41
- Long-term health risks after G-CSF and PBSC donation 42
- Psychological aspects of becoming a stem cell donor 43

Conclusions....44

Future perspectives....45

Impact of new treatments on the number of allogeneic stem cell transplantations....45

Acknowledgements....50

References....51

Abbreviations

ASH	American Society of Haematology
BM	Bone marrow
CTLA-4	Cytotoxic T lymphocyte-associated molecule-4
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
EBMT	European Society for Blood and Marrow Transplantation
FDA	The United States Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte_Macrophage colony stimulating factor
GVHD	Graft versus host disease
GvL	Graft versus leukemia
HADS	Hospital Anxiety Depression Scale
HCT	Haematopoietic stem cell transplantation
HLA	Human Leukocyte Antigen
LISA	The Longitudinal Integration Database for Health Insurance and Labour Market Studies
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death Ligand-1
NRHSD	The Nordic Register of Haematopoietic Stem Cell Donors
NMDP	National Marrow Donor Programme
PBSC	Peripheral blood stem cell
PROM	Patient reported outcome measures
SAS®	Statistical analyses software, SAS Institute Inc.
SCT	Stem cell transplantation
SF-12	Short Form-12, a 12-item, patient-reported health survey
WMDA	World Marrow Donor Association

Introduction

The starting point for the PhD thesis project was The Nordic Register of Haematopoietic Stem Cell Donors (NRHSD), initiated by main supervisor Hans Hägglund in 1998. The register was a collaboration between all six Swedish centres for stem cell transplantation, and four centres in Norway, Denmark and Finland. The register contains information on the donation procedure, side effects, anthropometric and socioeconomic data, and donors' comorbidities, for donations performed until 2014.

The register was the basis for the study presented in paper I, with a descriptive analysis of 17 years of experience of stem cell donation in the Nordic countries.

While working with the NRHSD study, I was an attending member of the European Bone Marrow Transplantation donor outcome committee. I was there asked to analyse the result of a survey initiated by the World Marrow Donor Association (WMDA), a global association of blood stem cell donor registries and cord blood bank registries, and review all published literature regarding safety and efficacy of biosimilar filgrastim, for peripheral blood stem cell (PBSC) mobilisation in healthy donors. The results of the survey and literature review are presented in paper II.

For the studies presented in paper III and V, we wanted to address longstanding concerns that the use of stem cell mobilising drugs such as G-CSF (granulocyte-colony stimulating factor) might lead to increased risks of cancer or cardiovascular disease for donors. We therefore created a cohort containing all Swedish related donors (related=donating to a sibling, child or parent) and those unrelated Swedish register donors previously registered in the NRHSD. Using linking of multiple national population based registers, the donors' long-term risk of cancer or cardiovascular disease was compared to population-based controls, the donors' siblings and to bone marrow donors. Gathering of data on the donors, applications for ethics approval and request for linkage of data from Swedish national registers was done as part of the doctoral studies, as well as all statistical analyses.

During the pursuit of the above-mentioned projects, I became interested in the psychological aspects of becoming a stem cell donor. A prospective national survey was therefore constructed by the research group, using validated questionnaires concerning different aspects of psychological well-being. The study is ongoing and aim to offer participation to all Swedish stem cell donors between 2019 and 2022, with follow up questionnaires during one year after donation. The results of the first 210 respondents of the pre-donation survey are presented in paper IV.

The focus of all the studies included in this dissertation is on the donors, and different aspects of possible risks that they are subjected to as part of their contribution to the patients´ treatment.

I believe there are several important reasons for performing the included studies. All donors are healthy volunteers that have decided to donate stem cells to another person. Some donors do so for truly altruistic reasons, to be able to help a patient in need, but others become donors under considerable emotional pressure to aid a relative with a serious disease.

It is important that risks for the donors are avoided whenever possible, and that remaining risks are known and adequately described, to allow potential donors to make an informed decision. For this, it is crucial to gain as accurate estimations as possible of the risks associated with becoming a donor.

The aim of my studies has been to add valuable information on both short and long term risks associated with stem cell donation, thereby helping prospective donors make a well informed decision on whether to donate or not.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation, also called haematopoietic stem cell transplantation, is a process in which the hematopoietic ("blood") stem cells of a patient are replaced with those of a donor, figure 1.

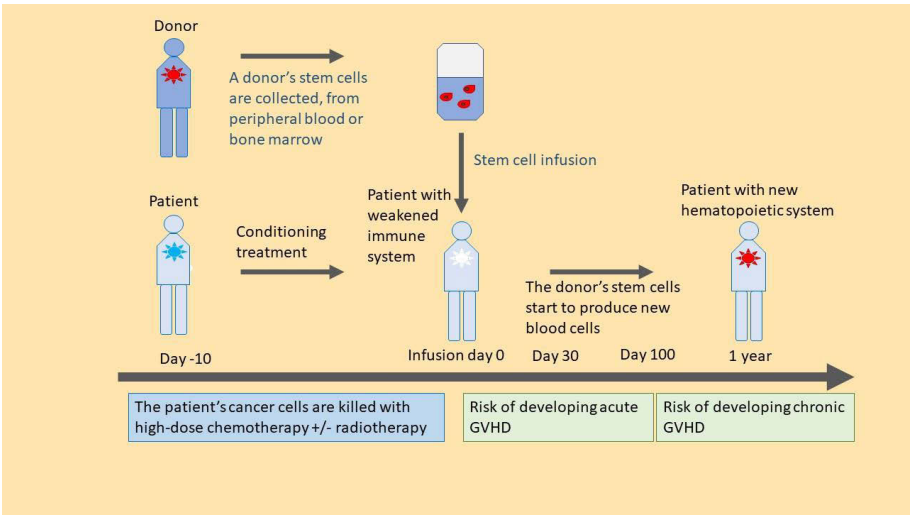

Figure 1. Flow chart of haematopoietic stem cell transplantation.
Image courtesy of Dr. H. Engler.

When used as a treatment for cancer, the patient first receives treatment with high doses of chemotherapy, with or without radiotherapy, to kill cancer cells and weaken the immune system's ability to reject the donated stem cells (1). Stem cells are then collected from a voluntary donor, either from the bone marrow, from peripheral blood or from umbilical cord blood cells stored in an blood bank. After processing of the cells, the donated stem cells are infused into the patient, through a catheter placed into a blood vessel. The stem cells then travel from the blood to the bone marrow, where they begin production of new mature blood cells.

Stem cell transplantation is primarily used as a treatment for life threatening haematological malignancies such as acute leukaemia, myelodysplastic syndrome and lymphoma, but also for some non-malignant diseases of the bone

marrow, thalassemia, sickle cell disease and primary immune deficiencies, offering a potential cure for patients that otherwise have few other treatment options.

Although offering the potential for cure, stem cell transplantation comes with significant risks for the patient. These can be from side effects from the chemotherapy, mainly in the form of infections, or the development of Graft-versus-host disease, GVHD. GVHD is a condition where the new immune system, derived from the donors stem cells, attack the patient's body, causing inflammation and tissue damage. In severe forms, it can cause irreversible organ damage, and can, both in its acute (within the first 100 days) and chronic form, be fatal or lead to chronic debilitating conditions (2).

Treatment of patients with allogeneic haematopoietic stem cells would not be possible without a donor willing to donate the stem cells necessary for the procedure. The likelihood of a successful transplantation is dependent on finding a donor with a high degree of compatibility between the donor's immune cells and the patient's cells. This is measured as the similarity, or match, of a group of proteins called human leukocyte antigens, or HLA (3).

The HLA are protein markers found on the cell surface of almost all human cells and play an important role in the immune system's ability to recognise which cells belong to the body and which do not. A person inherits their HLA in pairs from their parents, each pair made up of one HLA inherited from each parent. A person's unique combination of different HLA is referred to as their HLA type.

Close relatives are those most likely to have an HLA type similar to, or matching, the patients. There is a 25% chance that a sibling of a patient will be a complete match, while children and parents of a patient will match half of the patients HLA markers.

About 70% of patients will not have a fully matching family donor (3). Through the establishment of an international network of large registers of voluntary unrelated donors, un unrelated donor can be found for 30-70% of patients, but is dependent on the HLA type, and thereby the ethnic origin, of the patient (3, 4).

Together with new treatment protocols allowing transplantation from haploidentical donors, i.e., donors that match one half of the patients HLA markers, and the availability of stem cells stored in umbilical cord blood banks, most patients without a fully matching family donor can today find a suitable donor.

Figure 2. Depiction of the bull Donn Cuailnge

Detail from mural by Belfast artist Desmond Kinney.

Photo by William Murphy, reproduced by permission under CC BY-SA 2.0

Anecdotally, the first mention of what might be considered an allogeneic bone marrow transplantation can be found in the Celtic *An Táin Bó Cuailnge* – an 8th century epic saga central to early Irish literature. When the hero of the saga, *Cethern mac Fintain*, is mortally wounded in the defence of the Gaelic kingdom of Ulster and their most valuable asset, the stud bull *Donn Cuailnge*, figure 2, he is saved by being placed for three days and nights in a mash of animal bone marrow[i] (5).

[i] "And Cethern was placed in the marrow-mash for the space of three days and three nights, and he began to soak up the marrow-mash which was about him. And the marrow entered into his wounds and gashes, his sores and many stabs. Then after three days and three nights he arose from the marrow-mash, and thus it was that he arose but were saved by being succumbed in the bone marrow"5. Táin Bó Cúalnge, the Book of Leinster CELT, the Corpus of Electronic Texts [Available from: https://celt.ucc.ie/published/T301035/text032.html.

Early attempts at stem cell transplantation

The first scientific description of an attempt at performing allogeneic stem cell transplantation was published in the Annals of internal medicine in 1939 (6), of a 19-year-old woman with aplastic anaemia treated with bone marrow obtained from her brother, figure 3. At the time of her death three days later, no clinical benefits or side effects had been noted.

In 1956, E. Donnall Thomas' group performed attempts at stem cell transplantation in six patients (7). Besides a possible effect on the haemoglobin level in one patients, no beneficial effects could be seen in the patients and possible engraftment was detected in only two of the patients. Thomas was in 1990 awarded the Nobel Prize in Physiology or Medicine for his work on organ and cell transplantation.

Apart from difficulties in achieving during engraftment of donor stem cells in the recipient, it soon became clear that if engraftment was successful, most recipients developed what was initially called "secondary disease". Symptoms of diarrhoea, weight loss, hepatic failure and skin lesions were thought to occur due to a reaction between donor cells and the host's tissues, a graft-versus-host reaction (8-10), and are now often referred to as graft versus host disease (GVHD).

It was not until the discovery of the human leukocyte antigens (HLA) during the 1960s, enabling matching of donors and recipients regarding important aspects of their immune system, that interest increased. The HLA are cell surface proteins found on nucleus-containing cells in the body; involved in the regulation of the immune system. HLA proteins interact with the immune system mainly by presenting intra- or extracellular protein fragments, eliciting an immune system activation (11). The mechanism is an important part of the defence against infections but also against cancer cells (12).

By the end of the 1970s, survival and proliferation of the donor's cells in the patient - engraftment, could be achieved in more than 90 % of leukemia patients, although relapse-free survival beyond one year was achieved in only about 1 in 10 patients (13).

Until the beginning of the 1990s, sibling donors was almost exclusively the source of stem cells, with cells obtained through multiple aspirations of bone marrow, usually from the posterior iliac crests during general anaesthesia. The successful transplantation of bone marrow from an unrelated donor in 1980, widened the availability of possible stem cell donors and transplantation activity increased (14). The number of transplants from unrelated donors since

then gradually increased, and has equalled those from related donors during the last 15 years (15).

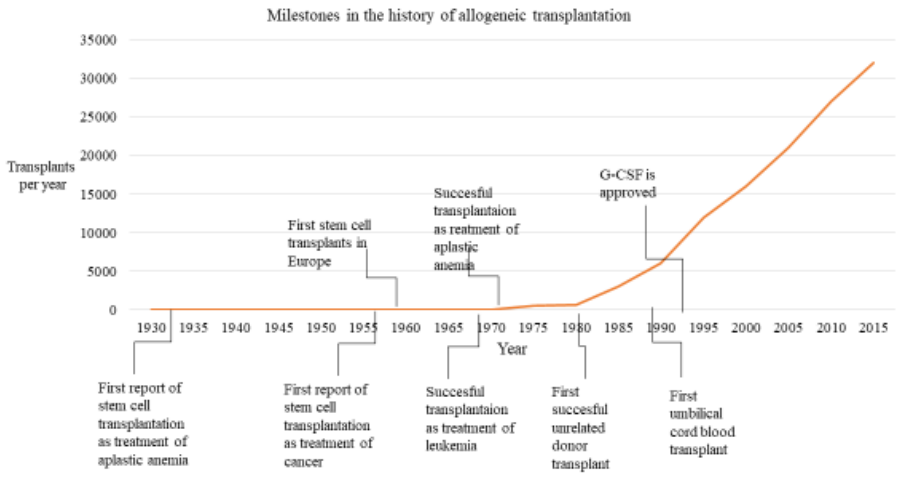

Figure 3. Timeline of major events in the history of allogeneic haematopoietic stem cell transplantation, and estimated yearly number of transplants performed worldwide

Drugs that mobilise haematopoietic stem cells into the peripheral blood were developed during the 1990s, most notably the cytokine G-CSF. This made it possible to collect peripheral blood stem cells (PBSC) through apheresis and has since replaced bone marrow donation as the main form of donation (15).

Current status of allogeneic stem cell transplantation

Allogeneic stem cell transplantation is today an established treatment option mainly for haematological malignancies, such as acute myeloid leukaemia, acute lymphatic leukaemia, myelodysplastic syndrome and lymphoma, but also for some non-malignant disorders, such as bone marrow failure syndrome, hemoglobinopathies, and inherited metabolic disorders, figure 4. Annually more than 30000 allogeneic transplantations are performed worldwide, with numbers globally increasing each year (15, 16).

The transplantation of blood stem cells from a healthy donor has two main effects for the recipient. First, it makes it possible for a patient to be treated with chemotherapy at doses that would otherwise not be tolerated, because of lethal effects on the patient's bone marrow. Secondly, immunological effects of the new immune system will help suppress or eradicate remaining malignant cells, a so-called graft versus leukemia effect (GvL) (17, 18). This immunological mechanism comes with the risk of developing GVHD, where the new immune system from the donor attacks and damages the recipient's organs. Acute GVHD occurs in a significant proportion of stem cell recipients and is together with chronic GVHD a major cause of mortality and morbidity in stem cell transplanted patients (19).

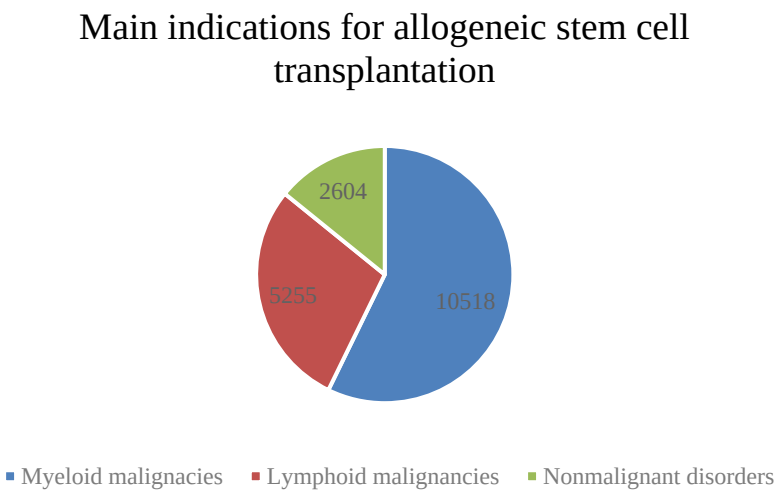

Figure 4. Indications for allogeneic stem cell transplantation, and number of transplantations, in EBMT associated countries, 2019. An additional 29 patients were treated for solid tumours, and 157 patients were transplanted for other indications (9).

Outcomes of allogeneic stem cell transplantation

Outcomes after allogeneic transplantation have improved over time; a recent retrospective analysis of EBMT data showed minor increases in overall survival during the time period 2001 – 2015, figure 5 (20).
In a retrospective review of 1148 patients transplanted 2003-2007, relapse or malignant disease progression was reported for roughly 25% of patients, with an overall survival of about 75% at day 200 post-transplant, and 50% after 7 years. Acute GVHD grade III-IV was experienced by 14% (21).

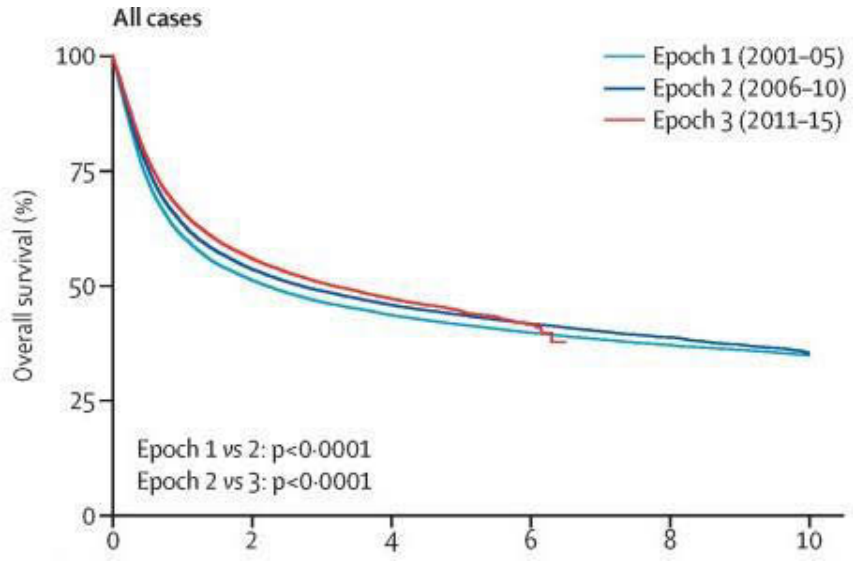

Figure 5. Overall survival of 106 188 allogeneic stem cell transplant patients, divided by year of transplant.
Epoch 1, 2001-2005: 23 249 patients; Epoch 2, 2006-2010: 35 348 patients; Epoch 3, 2011-2015: 47 591 patients

Adapted with permission from Shouval R, et al. Lancet Haematol. 2019;6(11):e573-e84.

In a Cochrane meta-analysis of nine randomised controlled trials with 1521 patients, relapse or disease progression was reported for 20%, mortality from relapse 15%, and non-relapse mortality 20%, after a median of two years (22).

In a study of 960 patients transplanted for non-malignant diseases, overall survival of 80-85% and non-relapse mortality of 15% was reported 5 years after transplant. The cumulative incidence of acute GVHD grade III-IV was 9% and the cumulative incidence of chronic GVHD 18% during the first year (23).

Acute myeloid leukemia (AML) is the single most common indication for allogeneic stem cell transplantation. For patients transplanted for AML treatment related mortality is reported to be 15-30% (24). Approximately 30% of patients suffer disease relapse within the first year, 10-36% experience acute GHVD grade III-IV, and 35-51% chronic GVHD (25).

Stem cell donation

Choosing a donor

For a donor to be considered suitable they must meet stringent medical demands in order to tolerate donating with a low risk, they must be immunologically compatible regarding HLA type, and willing to donate (26, 27).

The preferred choice of donor is today usually to find a healthy sibling, as it has been suggested that sibling donations result in less severe GVHD, and perhaps even increased survival compared to unrelated donors (25, 28, 29).

A sibling donor matching the recipient on both alleles of the five most important HLA pairs (HLA-A, -B, -C, -DRB1, and -DQB1), a so called 10/10 match, is usually considered optimal but can only be found in about 30% of all cases (4).

If there is no compatible sibling available, an international search of voluntary unrelated donor or cord blood registries can be performed to find a matching donor. There are currently more than 39 million registered potential donors in different national or regional donor registries (30).

About half of all transplantations are performed with a related donor and half with an unrelated donor, with significant regional differences in the distribution (31). The likelihood of identifying a fully matched unrelated donor is largely influenced by the ethnic origin of the patient, with those of African, Asian or Hispanic descent less likely to find a donor, as a majority of registered voluntary donors are of Western European origin (4)

Over the last ten years, the use of stem cells from haploidentical donors, i.e., a related donor with a 50% HLA match, have gained renewed attention, and the number of such transplants have increased substantially (15). This is made possible mainly through the development of novel treatment protocols, reducing the increased risk of graft rejection and acute GHVD that previously was a limiting factor (32).

International recommendations for evaluating prospective unrelated donors, and criteria for who can be considered as a suitable donor, has existed for at least 25 years, and have been continuously updated (27, 33-36). Unrelated donors are usually restricted to ages 18-60 years. Similar recommendations for related donors are more recent (37). Criteria for permitted comorbidities in related donors have commonly not been as strict as for unrelated donors, and no absolute age limit applied.

Stem cell source

When the first transplantations were performed in the 1950s, stem cells were harvested from deceased adults and infants, from ribs removed during surgery, or by aspiration from the crista iliaca of the hip bone from a living donor (7).

Bone marrow aspiration, usually from the posterior iliac crest during general anaesthesia, was the routine method for harvesting stem cells until the mid-1990s, when stem cell mobilising drug G-CSF was introduced. G-SCF treatment, usually at a standard dose of filgrastim 1 ME/kg/day for 4-5 days prior to apheresis, has been found both to increase the production of haematopoietic stem cells as wells as facilitate their release into the peripheral blood, where they can be collected through an apheresis procedure. After separation of blood stem cells, the majority of mature blood cells are returned to the donor during the apheresis (38).

With apheresis after G-CSF treatment, it is generally possible to obtain and transplant a larger number of stem cells, resulting in a faster engraftment and lower risk of graft failure, but at the expense of an increased risk of chronic GVHD (22, 39). Today approximately 75-80% of all donations are performed with the aid of G-CSF in the Nordic and European countries (15, 40).

Bone marrow aspiration is still used as a stem cell source in about 50% of transplantation for non-malignant diseases, due mainly to a perceived lower risk of GVHD, and in about 10% of transplantations for malignant diseases (31).

A less common, but important, possible source of stem cells is umbilical cord blood. Cord blood can be collected at the time of birth, from the clamped portion of the umbilical cord, and would otherwise be thrown away. After preparation, cord blood cells are frozen and deposited in a public or private cord blood bank until needed. Approximately 35 000 cord blood transplants have been performed, and close to 800 000 cord blood units stored in publicly available cord blood banks (41, 42). The last ten years has seen a decrease in the numbers of cord blood transplant in Europe and the US, but a steady increase in China and other parts of Asia, in part probably explained by the different availability of matched unrelated donors for patients of different ethnic origin. Cord blood transplantation is believed to result in a lower incidence of chronic GVHD, but lower numbers of transplanted cells delay hematopoietic recovery and increases the risk of graft failure (41).

Short term complications after stem cell donation

Several groups have evaluated the short-term side effects (usually meaning within 30 days) experienced by stem cells donors, the larger studies being of unrelated donors from donor registries. The most common side effect, regardless of stem cell source, is pain (40, 43-46). Although bone marrow donors experience a higher degree of pain at the harvest site, peripheral stem cell mobilisation seems to be associated with more pain overall. The duration of symptoms is meanwhile shorter after PBSC donation, with half of PBSC donors completely recovered within a week, compared to less than one in five marrow donors (43). Fatigue and insomnia are other common side effects (43, 45).

Adverse events, other than those commonly expected, e.g., pain and fatigue, have been more common among peripheral blood donors in some studies, in some cases related to the use of venous catheters during harvest (47). Spontaneous splenic rupture is a very rare, but repeatedly reported complication after PBSC donation (48-50). Sickle cell crisis, activation of autoimmune disorders and lung injury are other extremely rare adverse events reported as case reports (51-55).

Serious adverse cardiovascular or thromboembolic events were reported to be more frequent among PBSC donors (10.8/10000) than among bone marrow donors (4.3/10000), in a large European retrospective study (56). In contrast, a large prospective study from the American National Marrow Donor Programme (NMDP) reported significantly more serious adverse events among bone marrow donors than among donors of peripheral blood (57). The discrepancy seems to originate from differences in the definition of "serious adverse events"; the events among marrow donors in the latter study consisted to a large degree of an extra day of hospitalization for expected events such as pain or nausea.

Although most reported adverse events are of moderate severity, fatalities within 30 days of donation have been reported for both bone marrow and peripheral blood donors (47, 51, 58-60).

G-CSF and the risk of cancer

While bone marrow donation is assumed not to increase the risk of malignancy, the use of G-CSF for stem cell mobilisation in PBSC donors has raised some concerns, especially regarding the risk of haematological malignancies (61-63).

In patients with severe congenital neutropenia, a mutated G-CSF receptor has been shown to predispose leukemogenesis (64). In preclinical models on the other hand, G-CSF rather seem to supress leukemogenesis and the leukemic cells (65).

Several studies have looked at whether G-CSF treatment results in lasting genetic or epigenetic changes. Baez et al. found altered gene expression and microRNA expression profiles in peripheral blood cells one year after G-CSF treatment, while Hirsch et al. found no increased risk of aneuploidy, and Leitner et al. found no difference in DNA methylation or DNA methyl transferase activity after G-CSF (66-68).

In patients with aplastic anaemia or severe congenital neutropenia on long-term G-CSF treatment, an increased risk of myelodysplastic syndrome and acute myeloid leukaemia has been reported in observational studies, with rates around 20%, correlating with cumulative doses of G-CSF (69, 70). These findings have not been replicated in randomized trials, and to what extent they are relevant for the short treatment received by healthy donors is doubtful (71).

Several smaller studies and case reports have been published about haematological malignancies in G-CSF treated donors. A larger German retrospective review identified two cases of acute myeloid leukaemia and three cases of Hodgkin's lymphoma, resulting in a statistically significant increased standardised incidence ratios (63). Although several more cases of haematological and/or other malignancies have been identified in a number of large follow up studies of donors, these studies have not found any increase in the cancer incidence (44, 57, 58, 72-83). A common limitation with these studies however, is that follow up time is seldom more than four years; many have collected data retrospectively, and rely on interview or survey data reported by either the transplant centres or by the donors themselves.

Studies of secondary malignancies after different forms of cancer treatment have shown that an increased malignancy rate can persist for up to 30 years after treatment with chemotherapy and/or radiation, with a median time to diagnosis usually in the range of five to 15 years, or somewhat shorter for haematological malignancies (84-88). Although a possible risk of an increased malignancy rate caused by short-term G-CSF treatment of healthy donors could safely be assumed to be lower than after exposure to chemotherapy or radiotherapy, studies with a very long-term follow up are likely to be needed to properly assess the risk of cancer development after donation.

G-CSF and risk of non-malignant diseases

Cardiovascular effects

Myocardial infarctions, stroke and thromboembolic events have all been reported as serious adverse events, among both bone marrow and PBSC donors (73, 77). Among the few studies evaluating the risk of cardiovascular disease after donation, Halter et al. reported an increased rate of mainly cardiovascular serious adverse event in peripheral blood stem cell donors compared with bone marrow donors, while Pulsipher et al. found no difference in the rate of thrombosis (57, 58).

G-CSF has on the other hand also been evaluated in trials as a treatment for both acute myocardial infarction and stroke, hypothesised to exert cardio- and neuroprotective effects by inhibition of apoptosis and inflammation, stimulating angiogenesis and neurogenesis, as well as inducing a regenerative response by stimulation of hematopoietic stem cells (89, 90). Promising experimental data have so far not been replicated in clinical studies, and concerns have been raised about the rise in leucocytosis and acute-phase responses induced by G-CSF, both known to increase the risk of cardiovascular events (91-93). A role of hematopoietic stem cells in the aetiology of atherosclerosis has also gained some attention (94).

G-CSF and autoimmunity

A possible link between G-CSF treatment and autoimmune diseases been suggested by experimental studies, showing G-CSF to induce a "pro-inflammatory" cytokine pattern (95-97). Reports have also been published of single cases of severe autoimmune hyperthyroidism and IgA-nephritis in G-CSF treated donors (52, 53), while the role of endogenous G-CSF in exacerbation of ANCA vasculitis has gotten some attention (98).

A study performed by the National Marrow Donor Program did however not find any increased incidence of autoimmune diseases PBSC donors (57).

Alternatives to G-CSF for stem cell mobilisation

GM-CSF

The cytokine GM-CSF (Granulocyte-macrophage colony stimulating factor) has been used for stem cell mobilisation for over 30 year. It differs from G-CSF in both structure, receptor target as well as target tissue distribution. GM-CSF has been shown to induce lower numbers of haematopoietic stem cell yields than G-CSF (99). Cell grafts obtained after stimulation with GM-CSF differs from that of G-CSF, with lower numbers of T and NK cells, and have been suggested to be linked to lower risk of acute GVHD (100). This possible

advantage has however been considered to be offset by the reduced mobilisation efficacy and toxicity (fever and hypotension) associated with increased doses of GM-CSF, leading to it being used to a much lesser degree than G-CSF (100, 101).

CXCR4-inhibitors

The homing of haematopoietic stem cell to the bone marrow has been shown to depend to an important degree on the interaction between the chemokine receptor CXCR4 and the chemokine SDF-1 (stromal cell-derived factor 1, or CXCL-12) expressed by bone marrow stromal cell (102).

CXCR4-inhibitors were initially developed as a treatment of HIV (Human Immunodeficiency Virus), as CXCR4 is one of several co-receptors used by HIV to infect CD4+ T cells (103). As a side effect in early trials of CXCR4-inhibitors in HIV infected persons, a marked increase in leukocyte counts was noted (103), and later studies confirmed CXCR4-inhibition as a potential target for mobilisation of haematopoietic stem cells in healthy volunteers (104). The CXCR4-inhibitor plerixafor (AMD3100) was approved by the FDA in 2008 and the EMA in 2009 under brand name Mozobil®, for use together with G-CSF in stem cell mobilisation for autologous transplantation, in patients with Multiple Myeloma or Non-Hodgkin Lymphoma.

Successful allogeneic haematopoietic stem cell transplantations have been performed after plerixafor-only mobilisation, with persisting functional grafts (105). In small studies of healthy volunteers, plerixafor have been well tolerated, but apheresis cell yields appear to be lower than after standard regimens of G-CSF (105-107). Adding plerixafor, after failure to obtain adequate cell yield after mobilisation with G-CSF, increases the number of cells collected (108), but also changes the cellular composition of the graft. Numbers of B cells, CD4+ and CD8+ T cells, regulatory T cells, dendritic cells and myeloid-derived suppressor cells are higher after plerixafor (109). If these changes in the grafts cell composition is of any significance to the recipient remains to be evaluated, as well as if there are any medium- to long-term effects on donors. So far, no formal approval has been granted for the use of plerixafor for mobilisation of stem cells in healthy donors.

Several other drugs targeting the CXCR-4 receptor with a possible use in stem cell mobilisation are under development, but have so far not been trialed in humans (110, 111). In a recently published study, a single dose of CXCR2 chemokine receptor-agonist GROß, was shown to be well tolerated in humans as a single agent, but with insufficient stem cell mobilising capacity (112). However, when administered together with plerixafor in mice, stem cell mo-

bilisation levels were similar to standard G-CSF regimens, pointing to a possible new combination of drugs for mobilisation, with the advantage of a single day of administration (112).

Research aims

The overall aim of the doctoral studies is to explore different aspects of the risks associated with donating blood stem cells.

Specific aims:

1. To describe short-term complications from stem cell donation in the Nordic countries, and compare differences depending on stem cell source.

2. To evaluate the implementation of biosimilar G-CSF as a stem cell mobilising agent for stem cell donors, and review its safety.

3. To assess the incidence of malignancies in Swedish peripheral blood stem cell donors compared to the general population, bone marrow donors and their non-donating siblings.

4. To describe potential blood stem cell donors' pre-donation worries and psychological well-being before donation, and investigate possible associations between donor characteristics and psychological well-being.

5. To assess the incidence of cardiovascular diseases in Swedish peripheral blood stem cell donors compared to the general population, bone marrow donors and their non-donating siblings.

Methods

Paper I

Participants

1957 donors included in the Nordic Register of Haematopoietic Stem Cell Donors (NRHSD), donating between 1998 and 2014. Participants were recruited at 10 transplantation centres from Sweden, Denmark, Norway and Finland.

Data collection

Data was collected by transplant physicians or nurses on pre-specified forms at each transplant centres. PBSC donors were assessed during apheresis for bleeding/hematomas or citrate effects, with an additional open text field for "other symptoms." At follow-up, donors were assessed for occurrence of muscle/ skeletal pain, headache, fatigue or other symptoms experienced within the first month after start of G-CSF.

A short questionnaire was completed by donors one month after the donation, containing questions on five topics:

1. Number of days spent in the hospital
2. Number of outpatient visits
3. Number of days on sick leave
4. Time until resuming normal daily activities
5. Would the donor consider donating again

Data analysis

Descriptive statistics and multivariable regression statistics was used for statistical analyses. Chi2-tests were used for comparison of categorical data and Student's t test for continuous data. Multivariable Poisson regression analyses were performed including identified potential covariates, using donation type (BM/PBSC), donor sex (male/female), relationship to recipient (related/unrelated) and age (>50 vs.<50) as variables.

Paper II

Data collection

Literature review

A search for published reports of use of biosimilar filgrastim for stem cell mobilisation in healthy donors was performed, using the database Pubmed.org, the EMA European Public Assessment Reports for each registered biosimilar, as well as the annual meetings abstract books for the European Society for Blood and Marrow Transplantation (EBMT) and the American Society of Hematology (ASH) for the years 2008–2016. Only English-language, peer-reviewed journals were included, alongside abstracts with results not published in manuscript form. Published data for 1287 study participants were included in the analysis.

Survey

A survey was sent to 64 WMDA-associated registries, and completed by 33 registries from Europe, North America, Asia and the Caribbean, South Africa and Israel. The number of transplant and stem cell collection centres associated with each register ranged from one to more than twenty.

Registers were asked to answer questions regarding two topics:

1. What brand of G-CSF was currently being used for unrelated and related donor stem cell mobilisation

2. If they since 2013 had made, or were planning to make, a change of G-CSF brand, and, if so, the reasons for changing

Data analysis

Descriptive statistics were used to report results.

Paper III

Study design

Nationwide register-based cohort study

Data collection

Personal identity number, donation date and stem cell source was collected for 1 576 related first time haematopoietic stem cell donors, donating in 1977–2014. Data was gathered from local transplant centre records from all six Swedish centres for allogeneic stem cell transplantation. Nineteen additional donors were identified but not included in the study, as a correct personal identity

number, donation date or stem cell source could not be correctly identified. Twenty donors with a cancer diagnosis before their donation date were excluded, leaving 1 556 related donors included in the study.

An additional 376 unrelated Swedish donors, donating in 1998–2014, and previously included in the Nordic Register for Haematopoietic Stem cell Donors, were also included in the study (40).

For each PBSC donor, five population based controls with the same year of birth, sex, and county (in Swedish: län) of residence at the end of the year of donation, were drawn at random by Statistics Sweden from the general Swedish population, using the Total Population Register, 5 299 controls in total (113).

The identity of all the PBSC donors' siblings was obtained from the Multi-Generation Register, Statistics Sweden. (114)

A database was created by linking data from four Swedish national population-based registers:

- the Swedish Cancer Register,
- the Swedish Multi-Generation Register,
- the Swedish Patient Register, and
- the Swedish Cause of Death Register,

containing data on all incident cancers for the 1 082 PBSC donors and their 1 115 siblings, 5299 matched controls, and 850 bone marrow donors.

Linkage of data was performed at the Statistics Sweden or the Swedish National Board for Health and Welfare using national identification numbers, which were then removed before delivery of the datasets for statistical analyses.

Data analysis

For data analysis, the statistical software SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA) was used.

Cancer incidences for donors and their comparison groups were modelled through multivariable Cox regression (115), using the SAS procedure PHREG

(116). Sex (male/female), age at donation and relationship to recipient (related/unrelated) were included as potential confounding factors.

Relative risks, compared with controls, bone marrow donors and siblings, were estimated as hazard ratios with 95% CIs and results presented as crude event rates and in models adjusted for potential confounding factors.

Any first-time haematological malignancy, or any cancer, after donation and before December 31 2015, except non-melanoma skin cancer and premalignant lesions (cancer in situ), was counted as an event in the analyses. Data was censored at first event, death or emigration.

Cancer incidence of G-CSF stimulated peripheral blood stem cell donors was compared to population controls, bone marrow donors and siblings using multivariable Cox-regression analysis in statistical programming software SAS.

Paper IV

Study design

Nationwide cross-sectional study.

Data collection

Adult potential haematopoietic stem cells donors were consecutively recruited at the six stem cell transplantation centres in Sweden (Göteborg, Linköping, Lund, Stockholm, Umeå, and Uppsala) from April 2019 to May 2020. Potential donors were defined as individuals being HLA-typed with an HLA-match with the recipient. We defined being an HLA-match as a HLA-typing result compatible with being considered as an HLA-identical, haploidentical or matched registry donor, regardless of the final choice of donor.

Transplant coordinators at each centre identified potential study participants at the time of obtaining results of HLA typing (related donors), or during their medical donor investigation (unrelated donors). A central study coordinator then distributed mail-out questionnaires. Participants were considered to have given written informed consent by answering the questionnaire.

Questionnaires, constructed specifically for the study, included questions about sociodemographic variables, the relation to the recipient, two study specific questions concerning pre-donation worry for the recipient and pre-dona-

tion worry for one-self as a donor, and the validated instruments Hospital Anxiety and Depression Scale (HADS)(117), and the Short Format-12 survey (SF12v2) (118, 119).

Data analysis

The statistical calculations were performed with SPSS 24.0 software (IBM, Chicago, IL, USA)

Descriptive statistics were used to describe the characteristics of the participants and their worries, using independent t-tests or two-sided $\chi 2$-tests depending on the data level. Multivariable linear regression analyses were used to explore the association between pre-donation worry for one-self, pre-donation worry for the recipient, relation to the recipient, gender, age, being a cohabitant, physical health, and three outcome variables; anxiety, depression, and mental health.

Paper V

Study design

Nationwide register-based cohort study

Data collection

The same data set as for the study presented in paper III was used, with linking of data from multiple Swedish national registers performed by Statistics Sweden or the Swedish National Board for Health and Welfare using national identification numbers. The study outcome measure, new diagnoses of cardiovascular disease, was gathered from the Swedish Patient Register.

Data analysis

For data analysis, the statistical software SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA) was used.

Cardiovascular disease incidence rates for donors and their comparison groups were modelled through multivariable Cox regression (115), using the SAS procedure PHREG (116). Age at donation, sex (male/female), and relationship to recipient (related/unrelated) were included as potential confounding factors.

To adjust for potential time trends in diagnosis of cardiovascular disease, and because bone marrow donors were more likely to have donated during the use of ICD-code classification ICD-8 and ICD-9, year of donation was also included as a potential confounding factor in the models comparing disease incidence between PBSC and BM donors.

For each disease category, individuals with a diagnosis of the examined disease prior to the time of donation were excluded from that analysis.

Relative risks, compared with controls, bone marrow donors and siblings, were estimated as hazard ratios with 95% CIs and results presented as crude event rates and in models adjusted for potential confounding factors.

Any first-time cardiovascular diagnosis after donation and before December 31 2015 was counted as an event in the analyses. Data was censored at first event, death or emigration.

Ethical considerations

All studies except for the study presented in paper II have been subject to review by the regional ethics review board in Uppsala and/or Stockholm, number 98-259, 2016/497 and 2018/214. As the study presented in paper II only analysed data that was either; 1: previously published with appropriate ethical approval or 2: did not contain any data involving individual research subjects, it was judged to not require separate review by an ethical review board.

All research subjects in study I and IV had given an informed consent to participate in the studies.

For studies presented in paper III and V, no informed consent was collected. It was considered that it would result in considerable difficulties and financial costs to try to collect informed consent for these studies. The study period of more than 40 years, and that the studies involved large number of individuals, would likely have resulted in a large selective loss of study participants. This would have compromised the scientific quality of the studies, due to reduced statistical power and generalisability of the results. Apart from the potential intrusion on privacy, by accessing data from public health registries, no effects whatsoever were anticipated for the research subjects of these studies, neither harmful nor beneficial. The benefits of performing the study without collecting informed consent were therefore considered to outweigh potential risks.

For study IV, it was considered that the survey might, in some individuals, be considered an intrusion of privacy. The study's aim of improving knowledge about the psychological wellbeing, and thereby possibly help in the improvement of care of potential donors, was considered to outweigh the involved risks.

For all studies, data was analysed in anonymised or pseudonymised form, and presented on an aggregated level, making it impossible to identify individuals from the presented results.

Results

Paper I

Donation of both bone marrow and peripheral blood stem cells was found to be generally well tolerated by related and unrelated donors. A majority, 71%, of donors did not require, or required less than one week of sick leave. Bone marrow donors and related donors were somewhat more likely to require longer sick leave. Compared to unrelated donors, related donors were older, had more comorbidities, and more frequently needed a central venous catheter and/or multiple apheresis.

A majority, >90%, of all donors, experienced some short-term side effects. Bone marrow donors were more likely to experience fatigue while PBSC donors were more likely to suffer from bone/muscle pain and/or headache. The duration of symptoms was longer for bone marrow donors and they reported a longer time to full recovery.

Table 1. Characteristics of peripheral blood stem cell and bone marrow donation procedure.

Characteristics of PBSC donation procedure	**n. (%)**	**Characteristics of BM donation procedure**	**n. (%)**
G-CSF (n=1377)		**Method of anaesthesia (**n=473)	
Filgrastim	1372 (>99%)	General	455 (96%)
Lenograstim	5 (<1%)	Spinal	14 (3%)
		Epidural	4 (1%)
Dose of G-CSF/day (n=1352)		**Duration of BM harvest** (n=459)	
More than 10µg/kg	417 (31%)	Less than 1 hour	73 (16%)
10µg/kg	713 (53%)	1 to 2 hours	346 (75%)
Less than 10µg/kg	222 (16%)	More than 2 hours	40 (9%)
Days of G-CSF (n=1353)		**Site of BM harvest** (n=459)	
4 days or less	549 (41%)	Crista iliaca posterior	450 (98%)
5 days	726 (54%)	Crista iliaca anterior	29 (6%)
6 days	67 (5%)	Sternum	25 (5%)
7 days	11 (1%)		
Days of apheresis (n=1336)		**Volume of harvested BM** (n=464)	
1	816 (61%)	Less than 500 ml	50 (11%)
2	472 (35%)	500 – 1000 ml	215 (46%)
3	48 (4%)	1000 – 1500 ml	144 (31%)
		More than 1500 ml	54 (12%)
Venous access first day of apheresis (n=1336)		**Erythrocyte transfusion** (n=449)	
Central	154 (12%)	Autologous	210 (47%)
Peripheral	1182 (88%)	Allogenic	11 (2%)

Paper II

A worldwide survey of WMDA associated transplant and collection centres for both related and unrelated donors found large differences between centres in the choice of G-CSF drug use, with a majority of centres using originator G-CSF (Neupogen®). Between 2013 and 2017, 20% of surveyed registers had switched to biosimilar filgrastim, with a lower price cited as the main reason for change, while another roughly 20% were currently considering a change.

A review of all identified studies comparing originator G-CSF (Neupogen®) and G-CSF filgrastim biosimilars showed a high degree of similarity in pharmacokinetics and pharmacodynamics between biosimilar drugs and Neupogen, and there were no signs of significant differences regarding short-term side effects or mobilization efficacy.

Paper III

After a median follow up time of 9.8 years, a malignancy had been diagnosed in 5.8% (63) of 1082 PBSC donors.

The incidence rate of six cancer cases per 1 000 person years did not differ from that of age-, sex-, and residence-matched controls, where 282 (5.3%) cancer cases were detected among 5 299 controls, 5.6 cases per 1 000 person-years, hazard ratio 1.03 (95% CI 0.78–1.36, p-value 0.85).

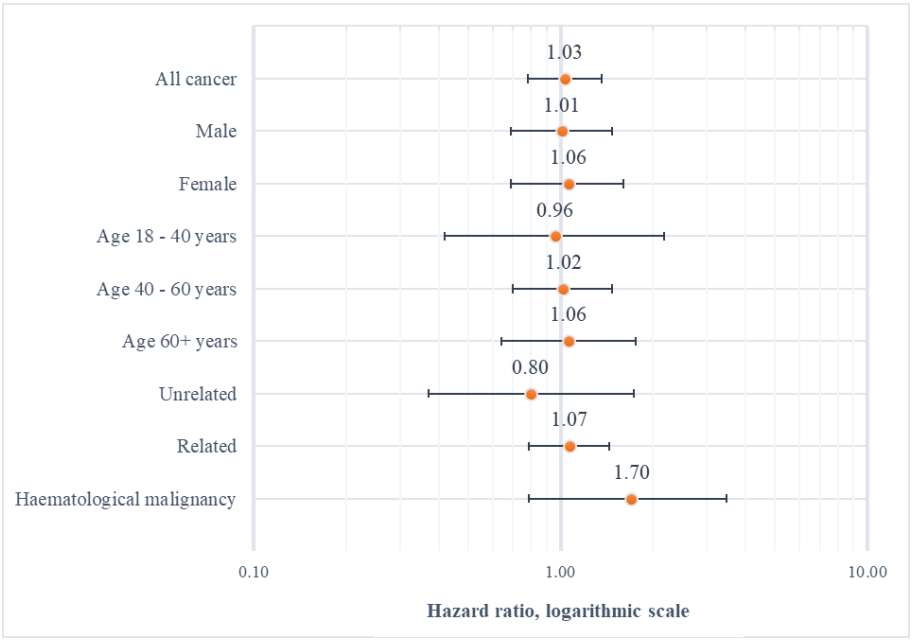

Figure 6. Cancer incidence rate hazard ratios and 95% confidence intervals for peripheral blood stem cell donors, compared with age-, sex- and residency-matched population controls.

Nine PBSC donors (0.83%) were diagnosed with a haematological malignancy during the follow-up period. The resulting haematological malignancy incidence rate of 0.85 cases per 1 000 person-years of follow-up was not significantly different from that in the control group (26 cases (0.51%), incidence rate 0.51 cases per 1 000 person-years, hazard ratio 1.70 (95% CI 0.79–3.64, p-value 0.17).

Paper IV

Out of 210 potential donors surveyed before donation, 21% reported increased anxiety, defined as ≥8 on the HADS-A scale, whereas depressive symptoms as measured by HADS-D were uncommon. General mental health measured by SF-12 was lower than that previously reported for the Swedish population (SF-12 score of 49.5 compared to 52.9).

A lot of worry for one-self pre-donation, lower age and female gender were in multivariable analyses independently associated with a higher level of anxiety. The HADS-A score increased 2.57 points by a lot of worry for one-self; 0.8 points for each 10 years of lower age and 1.18 points by female gender.

Combining these three identified factors, a small group of potential donors were identified that might benefit from a more detailed evaluation of their mental health, and increased support during the donation process. Female potential donors below the median age of the study's participants (<38 years), who expressed a lot of worry for them-self pre-donation, scored substantially higher for anxiety (HADS-A mean score 10.0 vs. 4.8, $p < 0.05$) and lower for mental health (SF-12 MCS mean score 40.5 vs. 49.8, $p < 0.05$) than the rest of the participants.

Paper V

Of 1098 PBSC donors, 5.5%, (n= 60) had a previous diagnosis of cardiovascular disease, mainly hypertension or atrial fibrillation before donation. Of 1038 donors without any cardiovascular disease at the time of donation, a diagnosis of cardiovascular disease was recorded for 16.5% (n=167), during a median follow up of 9.2 years.

The event rate of a new diagnosis of cardiovascular disease was 18.1 cases per 1000 person-years. The event rate in age-, sex-, and residence-matched controls was 19.2 cases per 1000 person-years, with 850 cases detected among 5 299 controls, resulting in a hazard ratio of 0.89 (95% CI 0.75 – 1.06, p-value 0.19).

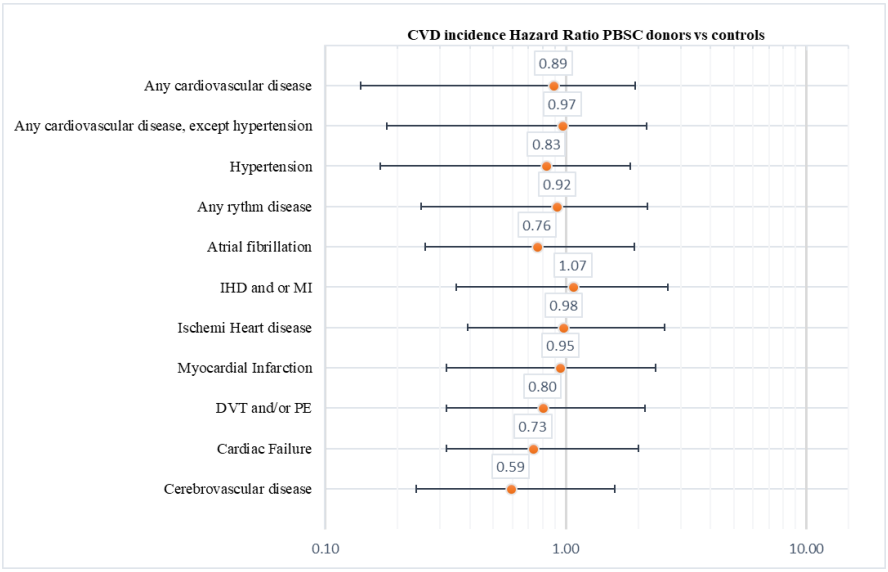

Figure 7. Cardiovascular disease incidence rate hazard ratios and 95% confidence intervals, for peripheral blood stem cell donors compared with age-, sex- and residency-matched population controls.

Mortality from any cause was 2.9% for donors (32 of 1098) compared to 4.4% for population controls (240 of 5495), hazard ratio 0.65 (95% CI 0.45–0.94, p-value 0.02) in a model adjusting for sex and age at donation.

Discussion

The care for haematopoietic stem cell donors and the criteria for selecting appropriate donors need to be continually evaluated, to serve the dual purpose of ensuring the safety and wellbeing of the donor as well as the highest possible chance of a successful transplantation.

Short-term risks and donor characteristics

When the initiative was taken to gather information from the Nordic countries about donor characteristics, short-term side effects and the results of stem cell harvesting in the NRHSD, few publications existed in this area from the Nordic setting (120, 121). Although much knowledge has been gained and published since, the data from the NRHSD presented as part of paper I is the first large study focusing on haematopoietic stem cell donors in the Nordic countries, with almost 2000 included donors.

Our study found that most donors experienced only limited side effects from donation, with shorter symptom duration for PBSC donors than for BM donors, consistent with results from the large US National Marrow Donor Program for unrelated donors (43, 122). Only one percent of PBSC donors reported symptoms lasting more than one week, while 36% of BM donors did, and 8 % of BM donors had persisting symptoms after four weeks. This was also reflected in 59 % of BM donors reporting being on sick-leave more than one week compared to 20% of PBSC donors, in an analysis restricted to donors of working age (18-65 years).

We also found several important differences between related and unrelated donors, both in donor characteristics and regarding the donation procedure. Related donors were older, with a mean age of 44.6 years compared to 36.6 years for unrelated donors, and comorbidities such as hypertension, cardiovascular disease and diabetes were more common in related donors. A previous malignancy (15 cases), thromboembolic event (6 cases), or myocardial infarction (6 cases) was only reported for related donors.

Related PBSC donors were also almost twice as likely (45% vs 27%) to need multiple days of apheresis or need a central venous catheter during apheresis (13% vs 8%).

One could assume this would put related donors at a higher risk of side effects, but except for more related donors experiencing fatigue after BM donation, we found no differences in reported side effects between related and unrelated donors. Findings in other studies comparing related and unrelated donors have not been uniform, but an increased risk of more serious adverse events have been reported for related donors (58), or for related donors who did not fulfil criteria applied to unrelated donors (79).

Long-term health risks after G-CSF and PBSC donation

G-CSF exerts its effects mainly through the transmembrane G-CSF receptor, found on cells at various stages of haematopoiesis but also on non-haematopoietic cells (123, 124). The concern for long-term increased risks of cancer or cardiovascular disease after PBSC donation rest mainly on theoretical reasoning and case reports (58, 61, 62), although an increased incidence rate of AML and Hodgkin lymphoma was reported in a retrospective single centre study of >8000 German donors. This finding has however not been reproduced in numerous other studies, reporting no increase in cancer incidence (61, 75, 76, 79, 125).

Cardiovascular events after PBSC donation have also been described in several studies, finding no differences in cardiovascular disease incidence between PBSC donors and BM donors (56, 125), or compared to the general population (126). Previous studies generally have been limited by a short follow-up time, often less than 4 years, and large loss to follow-up, possibly affecting their results.

In two studies of cancer and cardiovascular disease incidence presented in paper III and V, we used Swedish national population based registers to calculate disease incidence rates after PBSC donation. These registers allowed us to compare disease incidence rates both to those of the general population, the donors' siblings and to bone marrow donors, with a long-term follow up and low loss to follow up.

We found no difference in the total cancer incidence of PBSC donors, and a low incidence rate of haematological malignancies, not significantly higher than that of matched population controls. Similarly, the overall risk for cardiovascular disease was not increased after PBSC donation. In the study of cardiovascular disease risk, all-cause mortality was lower for PBSC than for

matched population controls, possibly due to unaccounted-for differences in pre-existing comorbidities, sociodemographic or lifestyle factors.

The results are reassuring, although limitations in study size (Sweden has a population of about 10 million) prevented us to adequately evaluate potential effects on the incidence of individual haematological malignancies.

Psychological aspects of becoming a stem cell donor

The physical risks that stem cell donors are subject to, with common symptoms such as fatigue, headache, bone pain, muscle pain and nausea, have been well described by others and by our group (56, 122, 125, 127-130).

Less research exist regarding the psychological aspects of becoming a donor, but qualitative (131-139) and small quantitative studies (129, 140-142) have shown donors to report increased stress, as well as feelings of loneliness and abandonment.

In a survey of 210 adult potential stem cell donors from all six Swedish haematopoietic stem cell transplantation centres, we found mental health to be lower than that previously reported for the general Swedish population (SF-12 mental health score of 49,5 compared to 52,9). A 3-point lower SF12 mental health score was previously shown to increase the risk of clinical depression by 40%, warranting further studies of how to best identify those donors most at-risk (118).

In our study, lower age, female gender, and a high level of worry for one self pre-donation were all found to be associated with a lower mental health score, and also with higher levels of anxiety. This finding might possibly aid in identifying a group of potential donors with increased vulnerability and need for additional support throughout the donation process.

Conclusions

The studies included in this thesis have aimed to increase the knowledge about different aspects of risks inherent to becoming a blood stem cell donor.

I. Data from the Nordic Register for Haematopoietic Stem cell Donors confirm that haematopoietic stem cell donation is generally safe in the short term, and associated with only transient side effects in a majority of donors. The nature of side effects differ between bone marrow donors and donors of peripheral blood stem cells, and bone marrow donors usually need longer time to full recovery.

II. A worldwide survey by the World Marrow Donor Association, show that an increasing number of transplant and collection centres have implemented the use biosimilar filgrastim for stem cell mobilisation. The so far published experiences from almost 10 years of using biosimilar filgrastim for this purpose are remarkably small, but show no sign of substantial differences regarding donor safety, mobilisation efficacy or transplant results.

III. A register-based study of 1082 Swedish PBSC donors does not show an increased incidence of haematological malignancies or overall cancer incidence, after a median follow up time of 9.8 years.

IV. The psychological aspects of becoming a stem cell donor have so far not received as much attention as the physical risks. A national survey of potential stem cell donors finds increased anxiety levels and a lower mental wellbeing in a proportion of donors. Younger female donors with high levels of pre-donation worries are identified as a group that might benefit from more support during the donation process.

V. A register-based study of 1098 Swedish PBSC donors does not show an increased incidence of cardiovascular disease, after a median follow up time of 9.2 years.

Future perspectives

Allogeneic stem cell transplantation has evolved during the last 70 years from a highly experimental scientific idea, to a clinical treatment that, although complicated and with known serious risks for the recipient, can be considered standard of care for selected groups of patients. As the number of transplantations performed each year has continually increased over the last 30 years, so has the number of stem cell donors needed.

Several important changes in the management of prospective donors have developed over the years, such as international guidelines describing updated donor eligibility criteria for related and unrelated donors, the introduction of G-CSF for stem cell mobilisation and the increasing number of unrelated and haploidentical donors. There is still a need for increased knowledge about how to further minimise risks for donors, and how to best offer support to those donors most in need, throughout all parts of the donation process.

Stem cell mobilising drugs beside G-CSF, especially plerixafor that in recent years seem to have gained an increased use, as well as other novel drugs being developed, will need to be thoroughly evaluated. Systematic studies of both short- and long-term consequences for donors, using large national registers or multi-national cooperation, will continue to be important tools to evaluate potential rare side effects.

Impact of new treatments on the number of allogeneic stem cell transplantations

As allogeneic stem cell transplantation continues to be a treatment associated with significant risks for treatment related morbidity and mortality for patients, there is a continuous effort of finding less toxic treatment alternatives. The emergence of new treatment alternatives could influence both which patients, and the number of patients, that are selected for allogeneic stem cells transplantations in the coming decades, and thereby the number of donors needed.

Among the treatments having so far perhaps gained the greatest attention, are CAR-T cell therapy, immune check-point inhibitors (ICIs), bispecific antibodies and antibody-drug conjugates, further described below. There is also a vast number of other therapies under development that could affect the future need for allogeneic stem cell transplantation (143).

CAR-T cells

CAR-T cells are T cells, engineered ex-vivo to target an antigen present on tumour cells, figure 8[ii].

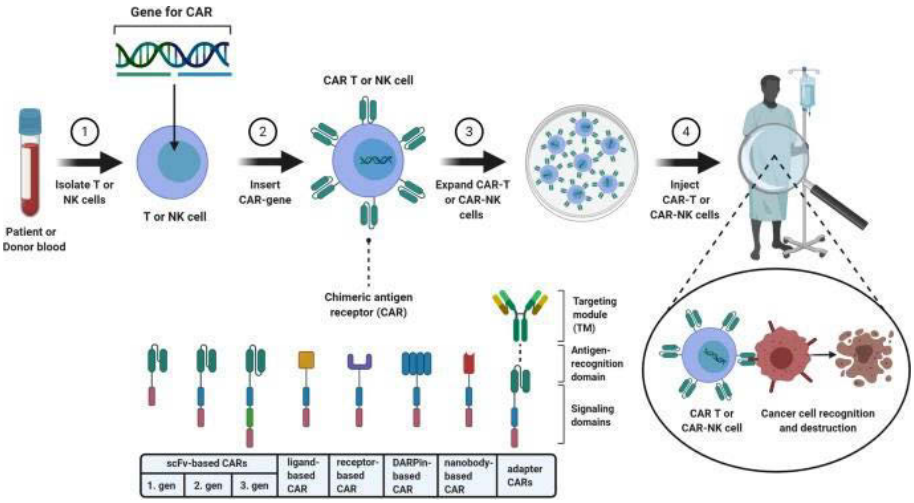

Figure 8[iii]. **1**: T (or NK) cells are isolated from the patient's blood. **2**: Cells are modified to express chimeric antigen receptors (CARs) recognising tumour antigens. **3**: CAR-T cells are expanded until sufficient cell numbers are attained. **4**: Cells are injected into the patient's body.

Promising results in the treatment of relapsed/refractory diffuse large B-cell lymphoma and acute B lymphoblastic leukemia have led to the approval of CD19-targeted CAR-T-cell therapies by FDA and EMA, at least in some cases replacing allogeneic stem cell transplantation as a preferred therapy (144, 145). The number of current clinical trials involving CAR-T cell therapies has been estimated to exceed 500 globally, in different stages of clinical trials (146).

[ii] Albinger, N. et al, Gene Ther 28, 513–527 (2021),
Reprinted with permission, http://creativecommons.org/licenses/by/4.0/. .

Immune check-point inhibitors

Downregulation of the immune systems response to tumour cells is an important mechanism for some tumour cells' survival. By blocking key inhibitory immune checkpoints, ICIs can help restore the immune systems cancer cell-killing capacity (147).

Currently approved ICIs act on one of the inhibitory checkpoints CTLA-4 (cytotoxic T lymphocyte-associated molecule-4), PD-1 (programmed cell death receptor-1), or PD-L1 (programmed cell death ligand-1), but drugs acting on numerous other immune checkpoints are under development (148).

Except for the treatment of Hodgkin's lymphoma, ICI treatment has been successful mainly in solid tumours, thereby currently not affecting the need for allogeneic stem cell transplantation, but with the intense development of new drugs taking place this could change in the future.

Bi-specific antibodies

Bi-specific antibodies are molecules with two different antibody-based antigen-binding sites and can be synthesised in many different forms (149). Their mechanism of action in cancer treatment is mainly through binding and activation of immune cells to tumour cells, or by simultaneously targeting multiple levels of cell signalling, with a large number of antibodies in development (150). The first bispecific antibody to be approved for cancer treatment, blinatumomab, targets CD19 and CD3 antigens. CD19 is expressed mainly on B-cells, and CD3 is part of the T-cell receptor. Blinatumomab treatment of heavily pre-treated adult patients with relapsed or refractory ALL result in significantly higher remission rates, event free and overall survival compared to standard chemotherapy, although no difference is seen in the proportion of patients later undergoing allogeneic stem cell transplantation (151).

Antibody-drug conjugates

Antibody-drug conjugates are molecules linking a tumour-targeting antibody to a cytotoxic drug. While the first antibody drug conjugates were approved more than 20 years ago, the rapid development of new antibodies has in the last 10 years led to renewed interest. Several new drugs for the treatment of both haematological malignancies and solid tumours have been approved, among them Brentuximab vedotin for treatment of relapsed/refractory Hodgkin's lymphoma and Trastuzumab emtansine for treatment of HER2 positive breast cancer (152, 153).

Are new treatments leading to fewer allogeneic transplants?

Although there has been a steady upward trend in the yearly number of allogeneic stem cell transplants for the last 30 years, for the last three years reported

from the EBMT (2016-2019) the numbers have levelled of (15), while the numbers seem to continue to increase in the US (154).

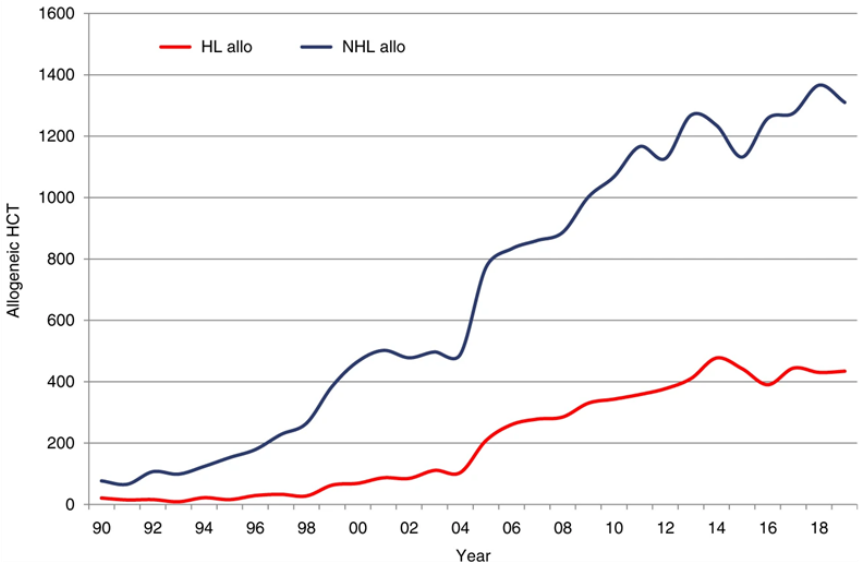

Figure 9[iii]. Allogeneic stem cell transplants for Hodgkin (HL) and non-Hodgkin lymphoma (NHL), from 1990-2019, EBMT associated countries

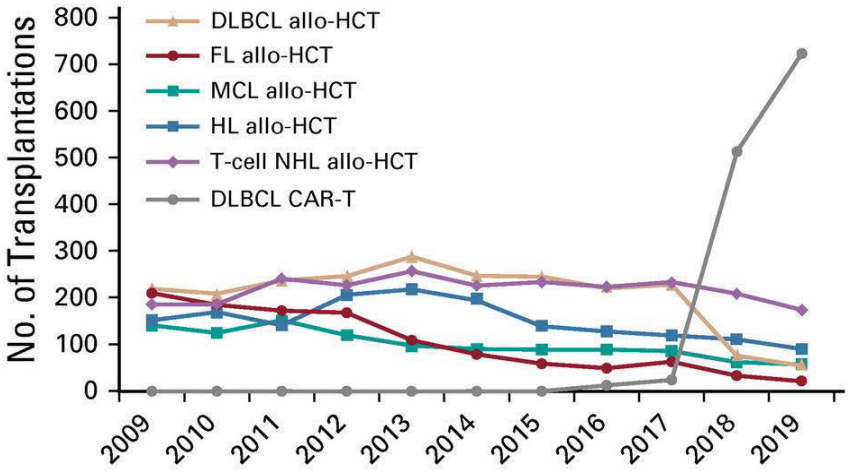

Figure 10[iv]. Allogeneic stem cell transplants for lymphomas, and CAR-T treatments for DLBCL, 2009 to 2019, United States.

DLBCL=Diffuse large B cell lymphoma; FL=follicular lymphoma; MCL=Mantle cell lymphoma; HL=Hodgkin's lymphoma; NHL= non-Hodgkin lymphoma; CAR-T=Chimeric antigen receptor T-cells

In the case of allogeneic stem cell transplantation as a treatment of lymphoma, there has in recent years been an overall stagnation or even a slight decline in the yearly numbers, figure 9[iii] and 10[iv], (15, 155).

In the US a dramatic decrease in the number of patients transplanted for DLBCL have been noted and coincide with an increase of the number of DLBCL patients treated with CAR-T, figure 10, (155). Whether this is a permanent trend or the number of transplants will rebound remains to be seen.

For at least the near future, allogeneic transplantation will remain an important treatment option for a large number of patients, and related and unrelated haematopoietic stem cell donors will continue to play a vital part in the treatment of these patients.

[iii] Reprinted with permission, http://creativecommons.org/licenses/by/4.0/
Published in: Passweg, J.R., Baldomero, H., Chabannon, C. et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplant 56, 1651–1664 (2021)
[iv] Reprinted with permission
Published in: Nirav N. Shah; Mehdi Hamadani; Journal of Clinical Oncology 2021 39487-498.

Acknowledgements

My main supervisor, *Hans Hägglund*, for introducing me to research and teaching me the value of collaboration and looking beyond imaginary boundaries to answer the research question at hand.

My co-supervisor, *Gunnar Larfors*, for always kindly answering endless questions on how to handle day to day research problems, large and small, and sharing your expertise in epidemiology and statistical programming.

All co-authors; T*orstein Egeland, Anne Fischer-Nielsen, Eva Haastrup, Jörg Halter, Dag Heldal, Maija Itälä-Remes, Jan-Erik Johansson, Marjut Kauppila, Annika Kisch, Johanna Lagnebjörk, Riita Niittyvuopio, Ulla Axdorph Nygell, Jeanette Winterling, Stig Lennhof, Per Ljungman, Anna Sandstedt, Bronwen E Shaw, Jeff Szer, and Ann E Woolfrey*, for sharing with me your globally acquired knowledge about science and stem cell transplantation, and for valuable feedback on the manuscripts.

All current and former colleagues at the Department for Blood and Tumour Diseases, Uppsala University Hospital; for the daily cups of coffee and discussions, a dedication to achieving the best possible care for each patient, and for an atmosphere appreciative of the value of combining research with clinical work.

All study participants who have contributed to the research projects presented in this thesis. Without your participation, there would have been nothing!

Current research collaborators, *Gunilla Enblad, Beatrice Ginman, Ingrid Glimelius, and Daniel Molin,* for your scientific enthusiasm, inspiring me to continue research after the dissertation.

My loving family, *Elisabet, Fredrik, Klara and Eskil,* for always reminding me of the true meaning of life.

References

1. Storb R, Thomas ED. Allogeneic Bone-Marrow Transplantation. Immunological Reviews. 1983;71(1):77-102.
2. Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2020;7(2):e157-e67.
3. Nowak J. Role of HLA in hematopoietic SCT. Bone Marrow Transplant. 2008;42 Suppl 2:S71-6.
4. Tiercy J-M. How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica. 2016;101(6):680-7.
5. Táin Bó Cúalnge, the Book of Leinster CELT, the Corpus of Electronic Texts [Available from: https://celt.ucc.ie/published/T301035/text032.html.
6. Osgood EE, Riddle MC, Mathews TJ. APLASTIC ANEMIA TREATED WITH DAILY TRANSFUSIONS AND INTRAVENOUS MARROW; CASE REPORT. Annals of Internal Medicine. 1939;13(2):357-67.
7. Thomas ED, Lochte HL, Lu WC, Ferrebee JW. Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy. New England Journal of Medicine. 1957;257(11):491-6.
8. Thomas ED, Ferrebee JW. Transplanation of marrow and whole organs: experiences and comments. Can Med Assoc J. 1962;86(10):435-44.
9. Barnes DWH, Loutit JF, Micklem HS. "SECONDARY DISEASE" OF RADIATION CHIMERAS: A SYNDROME DUE TO LYMPHOID APLASIA. Annals of the New York Academy of Sciences. 1962;99(3):374-85.
10. Billingham RE. The biology of graft-versus-host reactions. Harvey Lect. 1966;62:21-78.
11. Klein J, Sato A. The HLA system. First of two parts. N Engl J Med. 2000;343(10):702-9.
12. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. Nat Rev Cancer. 2021;21(5):298-312.
13. Thomas ED, Buckner CD, Banaji M, Clift RA, Fefer A, Flournoy N, et al. One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood. 1977;49(4):511-33.
14. Hansen JA, Clift RA, Thomas ED, Buckner CD, Storb R, Giblett ER. Transplantation of marrow from an unrelated donor to a patient with acute leukemia. N Engl J Med. 1980;303(10):565-7.
15. Passweg JR, Baldomero H, Chabannon C, Basak GW, de la Cámara R, Corbacioglu S, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplant. 2021;56(7):1651-64.

16. Phelan R, Arora, M., Chen, M. Current use and outcome of hematopoietic stem cell transplantation CIBMTR US summary slides. 2020.
17. Dickinson AM, Norden J, Li S, Hromadnikova I, Schmid C, Schmetzer H, et al. Graft-versus-Leukemia Effect Following Hematopoietic Stem Cell Transplantation for Leukemia. Front Immunol. 2017;8:496.
18. Gratwohl A, Brand R, Apperley J, Biezen Av A, Bandini G, Devergie A, et al. Graft-versus-host disease and outcome in HLA-identical sibling transplantations for chronic myeloid leukemia. Blood. 2002;100(12):3877-86.
19. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-61.
20. Shouval R, Fein JA, Labopin M, Kröger N, Duarte RF, Bader P, et al. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. Lancet Haematol. 2019;6(11):e573-e84.
21. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced Mortality after Allogeneic Hematopoietic-Cell Transplantation. New England Journal of Medicine. 2010;363(22):2091-101.
22. Holtick U, Albrecht M, Chemnitz JM, Theurich S, Skoetz N, Scheid C, et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. Cochrane Database of Systematic Reviews. 2014(4).
23. Umeda K, Imai K, Yanagimachi M, Yabe H, Kobayashi M, Takahashi Y, et al. Impact of graft-versus-host disease on the clinical outcome of allogeneic hematopoietic stem cell transplantation for non-malignant diseases. Int J Hematol. 2020;111(6):869-76.
24. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, et al. Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission: Systematic Review and Meta-analysis of Prospective Clinical Trials. JAMA. 2009;301(22):2349-61.
25. Saber W, Opie S, Rizzo JD, Zhang MJ, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. Blood. 2012;119(17):3908-16.
26. Worel N, Buser A, Greinix HT, Hagglund H, Navarro W, Pulsipher MA, et al. Suitability Criteria for Adult Related Donors: A Consensus Statement from the Worldwide Network for Blood and Marrow Transplantation Standing Committee on Donor Issues. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015;21(12):2052-60.
27. WMDA. Donor medical suitability recommendations [cited 2022. Available from: https://share.wmda.info/display/DMSR/WMDA+Donor+Medical+Suitability+Recommendations+Main+page.
28. Yakoub-Agha I, Mesnil F, Kuentz M, Boiron JM, Ifrah N, Milpied N, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(36):5695-702.

29. Kim HJ, Kim SY, Lee MH, Min WS. Peripheral blood stem cell transplantation from human leukocyte antigen-matched sibling donors and unrelated donors in acute myeloid leukemia patients. Acta haematologica. 2013;130(3):206-16.
30. WMDA. WMDA Global Trends Report 2020. 2021.
31. Passweg JR, Baldomero H, Chabannon C, Basak GW, de la Cámara R, Corbacioglu S, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplantation. 2021;56(7):1651-64.
32. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(6):641-50.
33. Cleaver SA, Warren P, Kern M, Hurley CK, Raffoux C, Keller J, et al. Donor work-up and transport of bone marrow--recommendations and requirements for a standardized practice throughout the world from the Donor Registries and Quality Assurance Working Groups of the World Marrow Donor Association (WMDA). Bone Marrow Transplant. 1997;20(8):621-9.
34. Hurley CK, Raffoux C. World Marrow Donor Association: international standards for unrelated hematopoietic stem cell donor registries. Bone Marrow Transplant. 2004;34(2):103-10.
35. Sacchi N, Costeas P, Hartwell L, Hurley CK, Raffoux C, Rosenmayr A, et al. Haematopoietic stem cell donor registries: World Marrow Donor Association recommendations for evaluation of donor health. Bone Marrow Transplant. 2008;42(1):9-14.
36. Lown RN, Philippe J, Navarro W, van Walraven SM, Philips-Johnson L, Fechter M, et al. Unrelated adult stem cell donor medical suitability: recommendations from the World Marrow Donor Association Clinical Working Group Committee. Bone Marrow Transplant. 2014;49(7):880-6.
37. van Walraven SM, Nicoloso-de Faveri G, Axdorph-Nygell UAI, Douglas KW, Jones DA, Lee SJ, et al. Family donor care management: principles and recommendations. Bone Marrow Transplant. 2010;45(8):1269-73.
38. Dreger P, Haferlach T, Eckstein V, Jacobs S, Suttorp M, Löffler H, et al. G-CSF-mobilized peripheral blood progenitor cells for allogeneic transplantation: safety, kinetics of mobilization, and composition of the graft. Br J Haematol. 1994;87(3):609-13.
39. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, et al. Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors. New England Journal of Medicine. 2012;367(16):1487-96.
40. Pahnke S, Larfors G, Axdorph-Nygell U, Fischer-Nielsen A, Haastrup E, Heldal D, et al. Short-term side effects and attitudes towards second donation: A comparison of related and unrelated haematopoietic stem cell donors. J Clin Apher. 2017.
41. Zhu X, Tang B, Sun Z. Umbilical cord blood transplantation: Still growing and improving. Stem cells translational medicine. 2021;10 Suppl 2(Suppl 2):S62-s74.
42. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. Blood. 2013;122(4):491-8.
43. Pulsipher MA, Chitphakdithai P, Logan BR, Shaw BE, Wingard JR, Lazarus HM, et al. Acute toxicities of unrelated bone marrow versus peripheral blood

stem cell donation: results of a prospective trial from the National Marrow Donor Program. Blood. 2013;121(1):197-206.
44. Hölig K. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. Blood. 2009;114(18):3757-63.
45. Miller JP. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. Biology of blood and marrow transplantation. 2008;14(9 suppl):29-36.
46. Pulsipher MA, Chitphakdithai P, Miller JP, Logan BR, King RJ, Rizzo JD, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. Blood. 2009;113(15):3604-11.
47. Anderlini P, Rizzo JD, Nugent ML, Schmitz N, Champlin RE, Horowitz MM. Peripheral blood stem cell donation: an analysis from the International Bone Marrow Transplant Registry (IBMTR) and European Group for Blood and Marrow Transplant (EBMT) databases. Bone Marrow Transplant. 2001;27(7):689-92.
48. Moalic V. Mobilization and collection of peripheral blood stem cells in healthy donors: risks, adverse events and follow-up. Pathologie-biologie. 2013;61(2):70-4.
49. Akyol G, Pala C, Yildirim A, Keklika M, Demir K, Dortdudak S, et al. A rare but severe complication of filgrastim in a healthy donor: splenic rupture. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2014;50(1):53-5.
50. Falzetti F, Aversa F, Minelli O, Tabilio A. Spontaneous rupture of spleen during peripheral blood stem-cell mobilisation in a healthy donor. Lancet. 1999;353(9152):555.
51. Adler BK, Salzman DE, Carabasi MH, Vaughan WP, Reddy VV, Prchal JT. Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. Blood. 2001;97(10):3313-4.
52. Kroschinsky F, Hundertmark J, Mauersberger S, Hermes M, Poppe-Thiede K, Rutt C, et al. Severe autoimmune hyperthyroidism after donation of growth factor-primed allogeneic peripheral blood progenitor cells. Haematologica. 2004;89(4):Ecr05.
53. Funakoshi Y, Nazneen A, Nakashima Y, Nakashima K, Okada M, Taguchi T, et al. Possible involvement of G-CSF in IgA nephropathy developing in an allogeneic peripheral blood SCT donor. Bone Marrow Transplant. 2010;45(9):1477-8.
54. de Azevedo AM, Goldberg Tabak D. Life-threatening capillary leak syndrome after G-CSF mobilization and collection of peripheral blood progenitor cells for allogeneic transplantation. Bone Marrow Transplant. 2001;28(3):311-2.
55. Wetzko K, Blechschmidt M, Holig K, Poppe-Thiede K, Ganepola S, Fischbach R, et al. Pulmonary adverse events in unrelated donors of peripheral blood stem cells. Transfusion medicine (Oxford, England). 2013;23(1):69-71.
56. Halter J, Kodera Y, Ispizua AU, Greinix HT, Schmitz N, Favre G, et al. Severe events in donors after allogeneic hematopoietic stem cell donation. Haematologica. 2009;94(1):94-101.
57. Pulsipher MA. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. Blood. 2014;123(23):3655-63.
58. Halter J. Severe events in donors after allogeneic hematopoietic stem cell donation. Haematologica (Roma). 2009;94(1):94-101.

59. Halter JP, van Walraven SM, Worel N, Bengtsson M, Hagglund H, Nicoloso de Faveri G, et al. Allogeneic hematopoietic stem cell donation-standardized assessment of donor outcome data: a consensus statement from the Worldwide Network for Blood and Marrow Transplantation (WBMT). Bone Marrow Transplant. 2013;48(2):220-5.
60. Imataki O, Uchida S, Yokokura S, Uemura M, Matsushita K, Kadowaki N. Bone Marrow and Peripheral Blood: Which Is Safe? Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22(12):2283-4.
61. Martino M, Fedele R, Massara E, Recchia AG, Irrera G, Morabito F. Long-term safety of granulocyte colony-stimulating factor in normal donors: is it all clear? Expert opinion on biological therapy. 2012;12(5):609-21.
62. Bennett CL. Haematological malignancies developing in previously healthy individuals who received haematopoietic growth factors: report from the Research on Adverse Drug Events and Reports (RADAR) project. British journal of haematology. 2006;135(5):642-50.
63. Hölig K. G-CSF in Healthy Allogeneic Stem Cell Donors. Transfusion medicine and hemotherapy. 2013;40(4):225-35.
64. Germeshausen M, Ballmaier M, Welte K. Incidence of CSF3R mutations in severe congenital neutropenia and relevance for leukemogenesis: Results of a long-term survey. Blood. 2007;109(1):93-9.
65. Metcalf D. The Charlotte Friend Memorial Lecture. The role of hematopoietic growth factors in the development and suppression of myeloid leukemias. Leukemia. 1997;11(10):1599-604.
66. Baez A, Martin-Antonio B, Piruat JI, Prats C, Alvarez-Laderas I, Barbado MV, et al. Granulocyte colony-stimulating factor produces long-term changes in gene and microRNA expression profiles in CD34+ cells from healthy donors. Haematologica. 2014;99(2):243-51.
67. Hirsch B, Oseth L, Cain M, Trader E, Pulkrabek S, Lindgren B, et al. Effects of granulocyte-colony stimulating factor on chromosome aneuploidy and replication asynchrony in healthy peripheral blood stem cell donors. Blood. 2011;118(9):2602-8.
68. Leitner GC, Faschingbauer M, Wenda S, Weigel G, Fischer G. Administration of recombinant human granulocyte-colony-stimulating factor does not induce long-lasting detectable epigenetic alterations in healthy donors. Transfusion. 2014;54(12):3121-6.
69. Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B, et al. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood. 2006;107(12):4628-35.
70. Ohara A, Kojima S, Hamajima N, Tsuchida M, Imashuku S, Ohta S, et al. Myelodysplastic syndrome and acute myelogenous leukemia as a late clonal complication in children with acquired aplastic anemia. Blood. 1997;90(3):1009-13.
71. Gurion R, Gafter-Gvili A, Paul M, Vidal L, Ben-Bassat I, Yeshurun M, et al. Hematopoietic growth factors in aplastic anemia patients treated with immunosuppressive therapy-systematic review and meta-analysis. Haematologica. 2009;94(5):712-9.
72. Pulsipher MA. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. Blood. 2009;113(15):3604-11.

73. Cavallaro AM, Lilleby K, Majolino I, Storb R, Appelbaum FR, Rowley SD, et al. Three to six year follow-up of normal donors who received recombinant human granulocyte colony-stimulating factor. Bone Marrow Transplant. 2000;25(1):85-9.
74. Anderlini P, Chan FA, Champlin RE, Korbling M, Strom SS. Long-term follow-up of normal peripheral blood progenitor cell donors treated with filgrastim: no evidence of increased risk of leukemia development. Bone Marrow Transplant. 2002;30(10):661-3.
75. Tassi C, Tazzari PL, Bonifazi F, Giudice V, Nannetti A, Ricci F, et al. Short- and long-term haematological surveillance of healthy donors of allogeneic peripheral haematopoietic progenitors mobilized with G-CSF: a single institution prospective study. Bone Marrow Transplant. 2005;36(4):289-94.
76. Rubia Jd. Follow-up of healthy donors receiving granulocyte colony-stimulating factor for peripheral blood progenitor cell mobilization and collection. Results of the Spanish Donor Registry. Haematologica (Roma). 2008;93(5):735-40.
77. Martino M, Console G, Dattola A, Callea I, Messina G, Moscato T, et al. Short and long-term safety of lenograstim administration in healthy peripheral haematopoietic progenitor cell donors: a single centre experience. Bone Marrow Transplant. 2009;44(3):163-8.
78. Jeger A. Tumor incidence in related hematopoietic stem cell donors. Bone marrow transplantation (Basingstoke). 2011;46(9):1240-4.
79. Kodera Y. PBSC collection from family donors in Japan: a prospective survey. Bone marrow transplantation (Basingstoke). 2014;49(2):195-200.
80. Schmidt AH, Mengling T, Pingel J, Rall G, Ehninger G. Follow-up of 12,559 Unrelated Donors of Peripheral Blood Stem Cells or Bone Marrow. Blood. 2010;116(21):365-.
81. Wiersum-Osselton JC, van Walraven SM, Bank I, Lenselink AM, Fibbe WE, van der Bom JG, et al. Clinical outcomes after peripheral blood stem cell donation by related donors: a Dutch single-center cohort study. Transfusion. 2013;53(1):96-103.
82. Mueller MM, Bialleck H, Bomke B, Brauninger S, Varga C, Seidl C, et al. Safety and efficacy of healthy volunteer stem cell mobilization with filgrastim G-CSF and mobilized stem cell apheresis: results of a prospective longitudinal 5-year follow-up study. Vox Sang. 2013;104(1):46-54.
83. Confer DL, Miller JP. Long-term safety of filgrastim (rhG-CSF) administration. Br J Haematol. 2007;137(1):77-8; author reply 9-80.
84. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second Malignant Neoplasms in Five-Year Survivors of Childhood Cancer: Childhood Cancer Survivor Study. JNCI: Journal of the National Cancer Institute. 2001;93(8):618-29.
85. Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, Storm H, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(12):1489-97.
86. Praga C, Bergh J, Bliss J, Bonneterre J, Cesana B, Coombes RC, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(18):4179-91.

87. Curtis RE, Boice JD, Jr., Stovall M, Bernstein L, Greenberg RS, Flannery JT, et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med. 1992;326(26):1745-51.
88. Hasenclever D, Sextro M. Safety of AlloPBPCT donors: biometrical considerations on monitoring long term risks. Bone Marrow Transplant. 1996;17 Suppl 2:S28-30.
89. Huang X, Liu Y, Bai S, Peng L, Zhang B, Lu H. Granulocyte colony stimulating factor therapy for stroke: A pairwise meta-analysis of randomized controlled trial. PloS one. 2017;12(4):e0175774.
90. Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F, et al. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci U S A. 2001;98(18):10344-9.
91. Bath PM, Sprigg N, England T. Colony stimulating factors (including erythropoietin, granulocyte colony stimulating factor and analogues) for stroke. The Cochrane database of systematic reviews. 2013(6):Cd005207.
92. Moazzami K, Roohi A, Moazzami B. Granulocyte colony stimulating factor therapy for acute myocardial infarction. The Cochrane database of systematic reviews. 2013(5):Cd008844.
93. Ringelstein EB, Thijs V, Norrving B, Chamorro A, Aichner F, Grond M, et al. Granulocyte colony-stimulating factor in patients with acute ischemic stroke: results of the AX200 for Ischemic Stroke trial. Stroke. 2013;44(10):2681-7.
94. Lang JK, Cimato TR. Cholesterol and hematopoietic stem cells: inflammatory mediators of atherosclerosis. Stem cells translational medicine. 2014;3(5):549-52.
95. Hartung T, Docke WD, Gantner F, Krieger G, Sauer A, Stevens P, et al. Effect of granulocyte colony-stimulating factor treatment on ex vivo blood cytokine response in human volunteers. Blood. 1995;85(9):2482-9.
96. Pollmacher T, Korth C, Mullington J, Schreiber W, Sauer J, Vedder H, et al. Effects of granulocyte colony-stimulating factor on plasma cytokine and cytokine receptor levels and on the in vivo host response to endotoxin in healthy men. Blood. 1996;87(3):900-5.
97. Anderlini P, Przepiorka D, Champlin R, Korbling M. Biologic and clinical effects of granulocyte colony-stimulating factor in normal individuals. Blood. 1996;88(8):2819-25.
98. Freeley SJ, Coughlan AM, Popat RJ, Dunn-Walters DK, Robson MG. Granulocyte colony stimulating factor exacerbates antineutrophil cytoplasmic antibody vasculitis. Annals of the rheumatic diseases. 2013;72(6):1053-8.
99. Lane TA, Law P, Maruyama M, Young D, Burgess J, Mullen M, et al. Harvesting and enrichment of hematopoietic progenitor cells mobilized into the peripheral blood of normal donors by granulocyte-macrophage colony-stimulating factor (GM-CSF) or G-CSF: potential role in allogeneic marrow transplantation. Blood. 1995;85(1):275-82.
100. Devine SM, Brown RA, Mathews V, Trinkaus K, Khoury H, Adkins D, et al. Reduced risk of acute GVHD following mobilization of HLA-identical sibling donors with GM-CSF alone. Bone Marrow Transplant. 2005;36(6):531-8.
101. Cashen AF, Lazarus HM, Devine SM. Mobilizing stem cells from normal donors: is it possible to improve upon G-CSF? Bone Marrow Transplant. 2007;39(10):577-88.
102. Lapidot T, Kollet O. The essential roles of the chemokine SDF-1 and its receptor CXCR4 in human stem cell homing and repopulation of transplanted immune-deficient NOD/SCID and NOD/SCID/B2m(null) mice. Leukemia. 2002;16(10):1992-2003.

103. Hendrix CW, Flexner C, MacFarland RT, Giandomenico C, Fuchs EJ, Redpath E, et al. Pharmacokinetics and safety of AMD-3100, a novel antagonist of the CXCR-4 chemokine receptor, in human volunteers. Antimicrobial agents and chemotherapy. 2000;44(6):1667-73.
104. Broxmeyer HE, Orschell CM, Clapp DW, Hangoc G, Cooper S, Plett PA, et al. Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist. The Journal of experimental medicine. 2005;201(8):1307-18.
105. Devine SM, Vij R, Rettig M, Todt L, McGlauchlen K, Fisher N, et al. Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction. Blood. 2008;112(4):990-8.
106. Takahashi Y, Tawab A, Kurlander R, Elshal M, Bolan C, Read EJ, et al. AMD3100 Mobilized Apheresis Products Are Rich in T-Cells That Do Not Undergo a Th-2 Type Cytokine Polarization: Implications for Allografting. Blood. 2005;106(11):296-.
107. Lemery SJ, Hsieh MM, Smith A, Rao S, Khuu HM, Theresa D, et al. A pilot study evaluating the safety and CD34+ cell mobilizing activity of escalating doses of plerixafor in healthy volunteers. Br J Haematol. 2011;153(1):66-75.
108. Cid J, Monsalvo S, Castillo C, Pascual C, Moreno-Jiménez G, López-Parra M, et al. Addition of plerixafor to G-CSF in poor mobilizing healthy related donors overcame mobilization failure: An observational case series on behalf of the Grupo Español de Trasplante Hematopoyético (GETH). Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2021;60(2):103052.
109. Teipel R, Oelschlägel U, Wetzko K, Schmiedgen M, Kramer M, Rücker-Braun E, et al. Differences in Cellular Composition of Peripheral Blood Stem Cell Grafts from Healthy Stem Cell Donors Mobilized with Either Granulocyte Colony-Stimulating Factor (G-CSF) Alone or G-CSF and Plerixafor. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2018;24(11):2171-7.
110. Wu CH, Chang CP, Song JS, Jan JJ, Chou MC, Wu SH, et al. Discovery of novel stem cell mobilizers that target the CXCR4 receptor. ChemMedChem. 2012;7(2):209-12.
111. Zachariassen ZG, Karlshøj S, Haug BE, Rosenkilde MM, Våbenø J. Probing the Molecular Interactions between CXC Chemokine Receptor 4 (CXCR4) and an Arginine-Based Tripeptidomimetic Antagonist (KRH-1636). J Med Chem. 2015;58(20):8141-53.
112. Hoggatt J, Singh P, Tate TA, Chou BK, Datari SR, Fukuda S, et al. Rapid Mobilization Reveals a Highly Engraftable Hematopoietic Stem Cell. Cell. 2018;172(1-2):191-204.e10.
113. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.
114. Multi-generation register 2009 - A description of contents and quality. . In: Sweden S, editor. Örebro2010.
115. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society: Series B (Methodological). 1972;34(2):187-202.
116. SAS_Institute_Inc. PHREG procedure: SAS Institute Inc; 2021 [cited 2021 May 12]. Available from: https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.4/statug/statug_phreg_references.htm#statug_phregcox_d72.

117. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
118. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.
119. Maruish MEE. User's manual for the SF-12v2 Health Survey. 3 ed. Lincoln, editor: RI: QualityMetric Incorporated.; 2012.
120. Höglund M, Smedmyr B, Simonsson B, Tötterman T, Bengtsson M. Dose-dependent mobilisation of haematopoietic progenitor cells in healthy volunteers receiving glycosylated rHuG-CSF. Bone Marrow Transplant. 1996;18(1):19-27.
121. Theilgaard-Mönch K, Raaschou-Jensen K, Andersen H, Russell CA, Vindeløv L, Jacobsen N, et al. Single leukapheresis products collected from healthy donors after the administration of granulocyte colony-stimulating factor contain ten-fold higher numbers of long-term reconstituting hematopoietic progenitor cells than conventional bone marrow allografts. Bone Marrow Transplant. 1999;23(3):243-9.
122. Miller JP, Perry EH, Price TH, Bolan CD, Jr., Karanes C, Boyd TM, et al. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(9 Suppl):29-36.
123. van de Geijn GJ, Aarts LH, Erkeland SJ, Prasher JM, Touw IP. Granulocyte colony-stimulating factor and its receptor in normal hematopoietic cell development and myeloid disease. Rev Physiol Biochem Pharmacol. 2003;149:53-71.
124. Touw IP, Geijn G-JMvd. Granulocyte colony-stimulating factor and its receptor in normal myeloid cell development, leukemia and related blood cell disorders. Frontiers in Bioscience-Landmark. 2007;12(3):800-15.
125. Pulsipher MA, Chitphakdithai P, Logan BR, Navarro WH, Levine JE, Miller JP, et al. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. Blood. 2014;123(23):3655-63.
126. Martino M, Bonizzoni E, Moscato T, Recchia AG, Fedele R, Gallo GA, et al. Mobilization of hematopoietic stem cells with lenograstim in healthy donors: efficacy and safety analysis according to donor age. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015;21(5):881-8.
127. Holig K, Kramer M, Kroschinsky F, Bornhauser M, Mengling T, Schmidt AH, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. Blood. 2009;114(18):3757-63.
128. Pruszczyk K, Skwierawska K, Krol M, Moskowicz A, Jablonski D, Torosian T, et al. Bone marrow harvest from unrelated donors-up-to-date methodology. Eur J Haematol. 2017;99(4):357-65.
129. Rowley SD, Donaldson G, Lilleby K, Bensinger WI, Appelbaum FR. Experiences of donors enrolled in a randomized study of allogeneic bone marrow or peripheral blood stem cell transplantation. Blood. 2001;97(9):2541-8.
130. Siddiq S, Pamphilon D, Brunskill S, Doree C, Hyde C, Stanworth S. Bone marrow harvest versus peripheral stem cell collection for haemopoietic stem cell donation in healthy donors. The Cochrane database of systematic reviews. 2009(1):Cd006406.

131. Christopher KA. The experience of donating bone marrow to a relative. Oncol Nurs Forum. 2000;27(4):693-700.
132. Kisch A, Bolmsjo I, Lenhoff S, Bengtsson M. Being a haematopoietic stem cell donor for a sick sibling: Adult donors' experiences prior to donation. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2015;19(5):529-35.
133. Kisch AM, Forsberg A. The Core of Sibling Stem Cell Donation - A Grounded Theory Study. Open Nurs J. 2017;11:73-83.
134. Munzenberger N, Fortanier C, Macquart-Moulin G, Faucher C, Novakovitch G, Maraninchi D, et al. Psychosocial aspects of haematopoietic stem cell donation for allogeneic transplantation: how family donors cope with this experience. Psycho-oncology. 1999;8(1):55-63.
135. Pillay B, Lee SJ, Katona L, De Bono S, Warren N, Fletcher J, et al. The psychosocial impact of haematopoietic SCT on sibling donors. Bone Marrow Transplant. 2012;47(10):1361-5.
136. Williams S, Green R, Morrison A, Watson D, Buchanan S. The psychosocial aspects of donating blood stem cells: the sibling donor perspective. J Clin Apher. 2003;18(1):1-9.
137. Billen A, Madrigal JA, Scior K, Shaw BE, Strydom A. Donation of peripheral blood stem cells to unrelated strangers: A thematic analysis. PLoS One. 2017;12(10):e0186438.
138. Holroyd E, Molassiotis A. Hong Kong Chinese perceptions of the experience of unrelated bone marrow donation. Soc Sci Med. 2000;51(1):29-40.
139. Wanner M, Bochert S, Schreyer IM, Rall G, Rutt C, Schmidt AH. Losing the genetic twin: donor grief after unsuccessful unrelated stem cell transplantation. BMC Health Serv Res. 2009;9:2.
140. Billen A, Madrigal JA, Strydom A, Szydlo RM, Switzer GE, Shaw BE. Predonation health-related quality of life scores predict time to recovery in hematopoietic stem cell donors. Biol Blood Marrow Transplant. 2015;21(2):350-6.
141. Bredeson C, Leger C, Couban S, Simpson D, Huebsch L, Walker I, et al. An evaluation of the donor experience in the canadian multicenter randomized trial of bone marrow versus peripheral blood allografting. Biol Blood Marrow Transplant. 2004;10(6):405-14.
142. Fortanier C, Kuentz M, Sutton L, Milpied N, Michalet M, Macquart-Moulin G, et al. Healthy sibling donor anxiety and pain during bone marrow or peripheral blood stem cell harvesting for allogeneic transplantation: results of a randomised study. Bone Marrow Transplant. 2002;29(2):145-9.
143. Xin Yu J, Hubbard-Lucey VM, Tang J. Immuno-oncology drug development goes global. Nature Reviews Drug Discovery. 2019;18:899-900.
144. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. New England Journal of Medicine. 2018;379(1):64-73.
145. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-48.
146. Albinger N, Hartmann J, Ullrich E. Current status and perspective of CAR-T and CAR-NK cell therapy trials in Germany. Gene Therapy. 2021;28(9):513-27.
147. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer. 2012;12(4):252-64.
148. Marin-Acevedo JA, Kimbrough EO, Lou Y. Next generation of immune checkpoint inhibitors and beyond. J Hematol Oncol. 2021;14(1):45.

149. Brinkmann U, Kontermann RE. The making of bispecific antibodies. MAbs. 2017;9(2):182-212.
150. Duell J, Lammers PE, Djuretic I, Chunyk AG, Alekar S, Jacobs I, et al. Bispecific Antibodies in the Treatment of Hematologic Malignancies. Clinical pharmacology and therapeutics. 2019;106(4):781-91.
151. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med. 2017;376(9):836-47.
152. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(18):2183-9.
153. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.
154. CIBMTR. HRSA Transplant Activity Report 2015-2019 [Available from: http://bloodcell.transplant.hrsa.gov/research/transplant_data/transplant_activity_report/index.html.
155. Shah NN, Hamadani M. Is There Still a Role for Allogeneic Transplantation in the Management of Lymphoma? Journal of Clinical Oncology. 2021;39(5):487-98.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1832

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-471647

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2022