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Autologous Haematopoietic Stem Cell Transplantation

Studies on effectiveness and safety in haematological malignancies and multiple sclerosis

THOMAS SILFVERBERG

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Abstract

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High-dose chemotherapy followed by autologous haematopoietic stem cell trans-plantation (ASCT) is a standard treatment for fit patients with primarily multiple myeloma (MM) and certain lymphomas. The objective of this thesis is to evaluate the effectiveness and safety of ASCT in relation to COVID-19, relapsing-remitting multiple sclerosis (RRMS) and a new conditioning combination for MM, using data from Swedish healthcare registries and electronic medical records in retrospective cohort studies.

In paper I, contraction of COVID-19 occurred in 4.5% of the 442 patients treat-ed with ASCT for haematological malignancy in Sweden in 2020. The COVID-19 mortality rate was 10%. The risk of mortality and need for hospitalisation, oxygen or intensive care was lower in this study compared to previous studies of mainly hospitalised patients.

In paper II, the proportion of the 174 patients treated with treated ASCT for RRMS in Sweden before the year 2020 who maintained no evidence of disease activity (NEDA) after 5 years was 73%. The adverse events were manageable with no treatment-related mortality. These findings support the only randomised con-trolled trial of ASCT for RRMS, suggesting that the results are generalisable to rou-tine healthcare.

In paper III, there were no statistically significant differences between 33 pa-tients conditioned with carmustine, etoposide, cytarabine, and melphalan (BEAM) and 141 with high-dose cyclophosphamide (Cy) at ASCT for RRMS in terms of NEDA including its composites, using data from paper II. Our findings support the use of Cy over BEAM, due to fewer severe adverse events, including febrile neutro-penia, and shorter average hospitalisation.

In paper IV, 43 consecutive patients with relapsed MM following ASCT in first line treatment were treated with a new conditioning combination bortezomib-bendamustine-melphalan (BBM) at ASCT and compared to 43 patients treated with standard high-dose melphalan. A trend of BBM being more effective in all outcomes was seen, most notably in progression-free survival and overall survival, warranting further investigation in larger prospective studies.

In summary, the findings in this thesis provide robust support for the continued use of ASCT for malignant diseases during the COVID-19 pandemic, affirm its therapeutic potential in relapsing-remitting multiple sclerosis, and offer valuable information for optimising conditioning regimens in both multiple sclerosis and re-lapsed multiple myeloma.

Keywords: Hematopoietic Stem Cell Transplantation, Transplantation Autologous, COVID-19, Multiple Sclerosis, Relapsing-Remitting Multiple Sclerosis, Transplantation Condi-tioning, Multiple Myeloma, Cyclophosphamide, BEAM, Melphalan, Bortezomib, Bendamustine

Thomas Silfverberg, Center for Clinical Research Dalarna, Nissersv. 3, Uppsala University, SE-79182 Falun, Sweden. Department of Medical Sciences, Haematology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

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To Jessica, Alfred and Oliver
My rays of light that bring colour to this amazing world.

List of Papers

This thesis is based on the following studies, which are referred to by their Roman numerals.

I. **Silfverberg T**, Wahlin B, Carlson K, Cherif H. (2022) Impact of COVID-19 on patients treated with autologous hematopoietic stem cell transplantation. A retrospective cohort study. *Ups J Med Sci,* Aug 25;127 1(2):3–4

II. **Silfverberg T**, Zjukovskaja C, Ljungman P, Nahimi A, Ahlstrand E, Dreimane A, Einarsdottir S, Fagius J, Iacobaeus E, Hägglund H, Lange N, Lenhoff S, Lycke J, Mellergård J, Piehl F, Svenningsson A, Tolf A, Cherif H, Carlson K, Burman J. (2024) Haematopoietic stem cell transplantation for treatment of relapsing-remitting multiple sclerosis in Sweden. An observational cohort study. *J Neurol Neurosurg Psychiatry*, Jan 11;95(2):125-133

III. **Silfverberg T**, Zjukovskaja C, Noui Y, Carlson K; AutoMS-Swe Investigators; Burman J. (2024) BEAM or cyclophosphamide in autologous haematopoietic stem cell transplantation for relapsing-remitting multiple sclerosis. *Bone Marrow Transplant*, Nov;59(11):1601-1610

IV. **Silfverberg T**, Cherif H, Smitt E, Carlson K. (2025) Bortezomib-bendamustine-melphalan or high-dose melphalan in autologous haematopoietic stem cell transplantation for relapsed multiple myeloma – a single centre retrospective study. *Manuscript*

Contents

Abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
alloSCT	Allogenic Haematopoietic Stem Cell Transplantation
AML	Acute Myeloid Leukaemia
ARDS	Acute Respiratory Distress Syndrome
ASCT	Autologous Haematopoietic Stem Cell Transplantation
ASCT1	Autologous Haematopoietic Stem Cell transplantation in first treatment line (excluding tandem transplantation)
ASCT2	Autologous Haematopoietic Stem Cell Transplantation in second treatment line
ATG	Anti-Thymocyte Globulin
BBM	Bortezomib, Bendamustine, Melphalan
BCL-2	B-Cell Leukaemia/lymphoma protein 2
BEAM	Carmustine, Etoposide, Cytarabine, and Melphalan
BiTE	Bispecific T-Cell Engager
CAR-T	Chimeric Antigen Receptor T-cells
CD	Cluster of Differentiation
CDW	Confirmed Disability Worsening
CIS	Clinically Isolated Syndrome
CML	Chronic Myeloid Leukaemia
CMV	Cytomegalovirus
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Remission
Cy	Cyclophosphamide
DDR	German Democratic Republic
DMT	Disease Modifying Treatment
DNA	DeoxyriboNucleic Acid
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr Virus
EDSS	Expanded Kurtzke Disability Status Scale
G-CSF	Granulocyte Colony-Stimulating Factor
GvHD	Graft-vs-Host Disease
HDM	High-Dose Melphalan

HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLH	Haemophagocytic lymphohistiocytosis
HSC	Haematopoietic Stem Cell
HSCT	Haematopoietic Stem Cell Transplantation
IFM	Intergroupe Francophone du Myélome
IGH	Immunoglobulin Heavy Chain
IMWG	International Myeloma Working Group
IMiD	ImmunoModulatory Drug
KM	Kaplan-Meier
MERS-CoV	Middle East Respiratory Syndrome-related Coronavirus
MHC	Major Histocompatibility Complex
MM	Multiple Myeloma
MDS	MyeloDysplastic Syndrome
MRD	Minimal Residual Disease
mRNA	messenger RiboNucleic Acid
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NEDA	No Evidence of Disease Activity
NF-κB	Nuclear Factor κB
NRM	Non-Relapse Mortality
OS	Overall Survival
p53	Phosphoprotein p53
PFS	Progression-Free Survival
PMAIP1	Phorbol-12-myristate-13-acetate-induced protein 1
PTLD	Post-Transplant Lymphoproliferative Disorder
RCT	Randomised Controlled Trial
RRMS	Relapsing-Remitting Multiple Sclerosis
RT-PCR	Real-Time Polymerase Chain Reaction
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmiNet	Swedish Registry for Communicable Diseases
SMSreg	Swedish MS Registry
TA-GvHD	Transfusion-Associated Graft-versus-Host Disease
TBI	Total Body Irradiation
TNT	Time to Next Treatment
TRM	Treatment-Related Mortality
USA	United States of America
UUH	Uppsala University Hospital
WHO	World Health Organization

Introduction

The bone marrow is in some respects the human body's most vulnerable organ. When chemotherapy started to have its first successes in treating cancers during the 20th century's second half, the bone marrow was the dose-limiting organ. Sometimes referred to as "the red ceiling", the bone marrow restricted how intensive chemotherapy could be given for most cancers. When the concept of haematopoietic stem cell transplantation (HSCT) was conceived, the idea was to enable treatment with higher doses of chemotherapy than what would have been otherwise possible, in order to reach remissions in more cancer patients.

The approach involves administering high-dose chemotherapy to ablate the haematopoiesis of the patient's bone marrow, followed by the reinfusion of stem cells through the bloodstream. These haematopoietic stem cells (HSCs) need to be collected either from a donor (allogeneic) or from the patients themselves (autologous), after having been treated to be mobilized to the donor's bloodstream and then harvested. After the chemotherapy, the HSCs are infused to the recipient, and they find their way back to the bone marrow and restart producing new blood cells. In autologous haematopoietic stem cell transplantation (ASCT) the idea is sometimes to cure the patient, and sometimes to treat the patient to long-term remission. The method has been in clinical use since the 1980's with its largest successes in multiple myeloma (MM) and lymphomas, and in some regards also in chronic myeloid leukaemia (CML). However, since then, its role in treating CML and acute myeloid leukaemia (AML) has been significantly reduced due to the emergence of more effective alternative therapies. Nevertheless, ASCT has found a new and promising role in treating autoimmune diseases such as multiple sclerosis (MS) and selected connective tissue diseases.

The world wars of the 20th century inspired the concepts of chemotherapy and HSC regeneration of the bone marrow. The following scientific and technological advances in biochemistry and medicine were required for the enabling and proliferation of ASCT as a viable therapeutic method. The idea to treat patients with haematological malignancies with chemotherapy approaching the limit for what is tolerated may seem obsolete, but in many ways, to this day, we simply do not know a better way to do it.

The constant challenge of ASCT is to limit the toxicity of the treatment while making it more effective, or at least not compromising the effect. This

thesis aims to describe and manage the toxicities associated with ASCT while optimising its therapeutic effectiveness in the treatment of haematological malignancies and multiple sclerosis.

I regard clinical medicine as a marriage between humanism and science. As a practitioner I meet patients every day, and in each and every meeting I must let humanism shine through everything I say, while science must be the ground on which I stand. To be a part of the worldwide scientific endeavour to improve medical methods and advice is an idea that have always had a special place in my heart.

The field of haematology captured me already in medical school. Maybe it was because of the peculiarities of working with a liquid organ, maybe because it seemed complex and needed approaches from many different medical fields, or maybe because I found the patients to be motivated and openly personal although they were among the most vulnerable that I have ever seen. When I got involved with Jan-Inge Henter's research group, I travelled around Scandinavia to collect data from medical records of children with primary haemophagocytic lymphohistiocytosis (HLH). As I sat alone in deserted small offices in different hospitals, collecting data from the dry and factual entries in the medical records, those very sick children came alive through the words, and I saw what a difference HSCT could do. A few years later, I met Honar Cherif, my main supervisor and we started working on the outlines of this thesis.

Background

Biology

The Bone Marrow

The bone marrow is a semi-liquid organ contained in the large cancellous bones of mammals, terrestrial tetrapods and cetaceans. It constitutes around 5% of the body mass of an adult human-being and consist of one third red marrow, which is the place of haematopoiesis; the production of blood cells, and two thirds yellow marrow which includes adipocytes and supportive stromal cells.[1] The stroma further includes nerves, fibroblasts and blood vessels.

The oldest evidence of bone marrow have recently been found in the lobed-finned fish *Eusthenopteron* that lived in the Devonian period 360-380 million years ago, and was described by researchers from Uppsala University in 2014.[2] It is hypothesized that protecting the haematopoiesis within the bones from the damaging ultraviolet radiation from the sun, was a prerequisite for the subsequent transition from sea to land of animals.[3]

The microcirculation of the bone marrow is termed sinusoids, as the endothelial cells lack connective tissue support and lies in direct contact with the

Photo 1. A 375-million-year-old fossil of *Eusthenopteron foordi* found in the Escuminac Formation, Quebec, Canada as seen in the Royal Tyrrell Museum of Palaeontology, Alberta, Canada.

Photo credit: Bloopityboop[4]

parenchymal cells. The walls of the sinusoids consist of a single layer of endothelial cells, resulting in a high level of permeability.[5] This thin but important bone marrow barrier keep immature blood cells out of the blood circulation, lets mature ones through, provides for the mobilisation and homing of HSCs and explains why haematological malignant cells can move between the bone marrow, lymphoid tissues and the blood circulation.

The Haematopoietic Stem Cell

The HSCs originates from the pluripotent stem cell, which has the ability to form all cell types in the body. It has two distinct characteristics: the ability of self-renewal and differentiation into mature blood cells. The HSC is multipotent, which means that it can differentiate to multiple cell lines. The first step of differentiation is the division to myeloid and lymphoid progenitor cells. These progenitor cells maintain their ability to divide and give rise to many lines of blood cells. The myeloid progenitor cell can differentiate into erythrocytes, platelets and granulocytes, whereas its lymphoid counterpart form B- and T-lymphocytes, natural killer cells and some dendritic cells.

The bone marrow produces approximately 500 billion blood cells per day for an average person in normal conditions.[6] Each such cell division carries the risk of faults being made in the replication of the cell's deoxyribonucleic acid (DNA) molecule, such as new mutations or chromosomal aberrations, which sometimes unluckily pushes the cell towards malignant potential. A certain number of such DNA-replication mistakes in the same cell can give rise to a cancerous cell, with abilities such as replicative immortality, sustained proliferative signalling, evading growth suppression, resisting cell death and invasiveness.[7]

The niches of HSCs and progenitor cells has been found to be close to the endosteum,[8] and around blood vessels.[9] As been touched upon above, the HSCs ability to mobilize from the bone marrow to the blood circulation and find their way back is a key feature for enabling HSCT.

History

The development of ASCT is closely linked to the advances in biochemistry and medicine made in the 20th century in general, and in allogenic haematopoietic stem cell transplantation (alloSCT) in particular. The rationale for developing ASCT was to provide a treatment alternative for patients with acute leukaemia without a compatible donor of haematopoietic stem cells.

The Concept of Chemotherapy

The first steps towards treating cancer with chemotherapy were taken in the first decades of the 20th century through letting mice-models with transplanted tumours be exposed to various types of chemicals. This was followed by the discovery in 1919 that exposure to mustard gas, as used in World War I, led to depletion of bone marrow cells resulting in anaemia.[10]

Research from pharmacologists Louis S. Goodman and Alfred Gilman at Yale University in 1942 could prove that intravenous doses of nitrogen mustard, a compound derived from mustard gas, but with a sulphur molecule substituted for nitrogen, led to regression of lymphoma in rodents. The pharmacologists who had done the experiments convinced the thoracic surgeon Gustaf Lindskog to administer nitrogen mustard to a patient with severe airway obstruction due to non-Hodgkin's lymphoma. The patient showed a transient complete regression of the lymphadenopathy.[11-13] Subsequent experiments from a Chicago group led to the development of *mustine*, the prototype alkylating agent.[14]

The Development of Alkylating Agents

In late 1943, a German air raid on the harbour of Bari in Italy during World War II sunk 27 Allied transport ships of which one American vessel carried a secret cargo of mustard gas bombs. The subsequent spill of liquid mustard gas mixed with burning oil from the destroyed ships and was exposed to sailors who had abandoned their ships. Some of the mustard gas evaporated creating a cloud much like what was used in World War I warfare. A day later 628 patients and medical staff showed the first signs of mustard gas poisoning and at least 83 patients eventually died. Observations of the patients revealed that many of them experienced depletion of the bone marrow and lymph nodes.

Photo 2. Burning ships after a German air raid in the harbour of Bari 1943.

Photo credit: Unknown photographer[15]

The experience and publicity from this event together with the experiments from Yale and Chicago resulted in a great interest in finding more agents with cytotoxic properties in the years that followed. Since the 1940's several nitrogen mustard alkylating agents have been developed including melphalan, cyclophosphamide and bendamustine.

Dosing of chemotherapeutic agents

Following animal experiments in the 1930's, where dosing according to body surface area instead of weight had been noted to explain variations in metabolic rates in a various range of animal species, including a few humans, and had a better correlation with blood volume,[16] this concept was proposed for the dosing of chemotherapeutic agents in humans.[17] A retrospective study conducted in the 1950's, reported that the doses of methotrexate and mechlorethamine had large variations depending on the animal size, and for children compared with adults if calculated by body weight, while dosing according to body surface area were almost the same for all species and for humans no matter what age.[18] Despite the lack of validation, body surface area has become the rule for dosing the great majority of chemotherapeutic agents since then.

Haematopoietic Stem Cell Transplantation

The first bone marrow transfusion had been performed already in 1939, when a patient with aplastic anaemia was treated with intravenous injection of allogenic bone marrow cells. There was no apparent positive effect, probably due to immunologic incompatibility.[19] Observations of bone marrow aplasia in patients exposed to the radiation of the atomic bombs that were exploded over Hiroshima and Nagasaki in World War II was the motivation for a race to find methods to restore bone marrow function.

The first breakthrough was made in 1949, when Jacobsen and colleagues reported haematological protection in mice treated with lethal doses of total body irradiation (TBI) when shielding their spleens with lead.[20] Similar results were reported in 1951, if the mice were given intravenous infusion of syngeneic (identical) bone marrow after the TBI,[21] but it was not until the mid-1950's that this protection from irradiation was shown to be due to repopulation of the bone marrow by transplanted donor cells.[22]

Peripheral blood stem cells

In 1958 Bond and colleagues reported the finding of dividing, non-leukemic circulating DNA-synthesizing cells in humans.[23] Evidence that stem cells could migrate from peripheral blood and then repopulate the bone marrow after TBI had been shown in rats in 1956.[24] Further animal experiments demonstrated that circulating stem cells had the ability to reconstitute the

haematopoietic system after myeloablative treatment.[25,26] These findings were required for the development of HSCTs.

Allogenic haematopoietic stem cell transplantation

The first alloSCT performed in a human was done in 1957 at Fred Hutchinson Cancer Research Center in Seattle, United States of America (USA) by a team led by E. Donnall Thomas in a patient with acute leukaemia. The patient was treated with TBI, after which she was infused with her identical twin's bone marrow. Although the patient experienced a successful engraftment and a three-month remission, it was not sufficient to cure the disease. This first procedure was conducted at a very early stage, before there was adequate understanding of several essential factors required for successful HSCTs.

One such factor was the 1958 report from van Rood and colleagues, describing that about a third of all pregnant women formed antibodies against human leukocyte antigens (HLAs),[27] which are proteins on the surface of cells that let the immune system distinguish self from non-self. In the years that followed, the HLA could be further described and its application started to be evident in HSCTs, such as to cause graft rejection.[28] Practically it was not until Terasaki and colleagues in 1963 presented a technique for testing the HLA subtypes that HLA-testing could reach clinical use.[29] HLA is the name of the major histocompatibility complex (MHC) found in humans; in animals it is referred to as MHC, and in humans HLA. With the knowledge of HLA and MHC, alloSCT took a big step to becoming practically feasible.

Another immunological challenge, and opportunity, was described in 1956, in mice with a reaction, later to be named graft-versus-host disease (GvHD), could result in the eradication of leukaemic cells.[30] In 1965 Mathé and colleagues coined the term graft-versus-leukaemia effect after describing the successful engraftment of marrow function in a patient with acute leukaemia treated with allogenic stem cells. The patient subsequently died due to GvHD.[31] The role of matching for MHC was shown in experiments of littermate dogs in 1968. Dog siblings with matched MHC-donors had significantly better outcome,[32] and developed GvHD later than mismatched littermates.[33] Several studies to find suitable immunosuppressive agents to counteract GvHD were performed in canines, eventually identifying the antimetabolite methotrexate as such an agent.[34] Methotrexate was first used clinically in 1969, and was later combined with calcineurin inhibitors such as cyclosporine and tacrolimus showing strong synergistic effects.[35] They remain the most commonly used drugs for preventing GvHD to this day. In 1974, the first use of T-cell depleting treatment with anti-thymocyte globulin (ATG) for the prevention of acute GvHD was reported.[36]

In 1969, high-dose cyclophosphamide was successfully used as an alternative to TBI for engraftment of allogenic bone marrow.[37] The challenge had been to use a cytotoxic compound powerful enough to prevent graft rejection, and cyclophosphamide was found to do just that.

All alloSCTs in the first ten years failed to be curative, as the understanding of histocompatibility matching, conditioning regimens and GvHD-prevention was inadequate. Of the first 200 patients, transplanted between 1957 and 1967, all 200 died. In 125 cases the death was due to graft failure, and 47 due to GvHD. Other causes of death were infections and relapse of the underlying malignancy.[38]

The first successful alloSCTs were performed in patients with primary immune deficiency disorders and were reported in 1968, although the greatest need were among patients with haematological malignancies and severe aplastic anaemia.[39-41] It was not until advances were made in supportive care, most notably in prevention and treatment of infections and transfusion support, that the first survivors of alloSCT were seen in patients with malignancy, reported by Thomas *et al* in two landmark papers in 1975.[42,43] The first successful alloSCT performed with stem cells from an unrelated donor was done in 1979.[44]

In the years following 1975 the method became more successful, and in the end of the 1970's Thomas *et al* reported a cure rate of 50% in acute myeloid leukaemia patients.[45] The lack of alternative treatment options for patients that lacked a matched donor of haematopoietic stem cells motivated the development of ASCT, but that required new insights in biochemistry and new medical technologies.

Autologous Haematopoietic Stem Cell Transplantation

The concept of transplantable haematological stem cells from peripheral blood was introduced in the early 1960's,[46] when the first experiments to recover bone marrow function in large animals with autologous and allogenic HSCs from peripheral blood was performed.[47-49] In 1971 the collection of peripheral stem cells through apheresis was demonstrated in humans,[50] but the problem was that the amount of HSCs in peripheral blood was very low. Several clinical attempts to transplant HSCs from peripheral blood in the following ten years were unsuccessful, probably due to low stem cells yields.[51,52]

Stem cell mobilisation

The first progress was made when non-myelotoxic chemotherapy and myelosuppression was reported to be able to increase stem cell concentrations in the apheresis products.[53] This method was one step in the right direction, but still the process of apheresis lasted several days and included handling of large volume of apheresis products limited the potential use of ASCT.

The next key obstacle was overcome with the use of cryopreservation of leukapheresis products, such as HSCs, with liquid nitrogen was successful in the latter part of the 1970's.[54,55] In this way, it was possible to store the stem cells for a long time, and to recover a majority of the cells when thawing them.

Photo 3. L'Hôpital Saint-Antoine, Paris, France.

Photo credit: Piero d'Houin[56]

It was not until the development of haematopoietic growth factors during the 1980's, namely granulocyte colony-stimulating factor (G-CSF), was reported to be able to mobilise haematopoietic stem cells to peripheral blood that saw ASCT becoming an established treatment in routine health care.[57-59] It simply made the process of stem cell mobilisation more practical and stem cell harvesting more reliable.

The first attempts

The first ASCT was performed at L'Hôpital Saint-Antoine in Paris 1976 in a 28-year-old patient with relapsed AML with stem cells collected from his bone marrow during the first complete remission (CR). The patient achieved a second CR of short duration.[60] A second patient with AML treated by the same team experienced a CR of four years after the ASCT.

The first ASCTs with cryopreserved stem cells were performed at the National Institutes of Health Clinical Center in Bethesda, USA in a case series of 12 patients with malignant lymphoma reported by Frederick Appelbaum in 1978. The ASCT-treated patients had shorter duration of neutropenia and less febrile neutropenia than 10 patients who were not treated with ASCT, but only high doses of chemotherapy.[61]

The first clinical ASCTs with peripheral blood was performed in 1981 in London and Baltimore in patients with CML. Although haematopoietic recovery was achieved, the patients did not obtain long-term engraftment.[62,63] The first successful ASCT with peripheral stem cells was performed in a patient with Burkitt's lymphoma in Heidelberg in 1985, treated with TBI and high-dose cyclophosphamide and support of thawed cryopreserved peripheral stem cells.[64] The patient had received seven successive leukapheresis, and had rapid engraftment after 9 days. This first case was followed by several more in the years that followed and included patients with non-Hodgkin's lymphoma and AML.[65-68] This procedure is very much like what is still used today.

ASCT for solid tumours

The concept of ASCT influenced treatment of cancers other than in the haematological sphere, because it enabled higher doses of chemotherapy to be administered to the patients. Several preclinical reports suggested a log-linear correlation between dose and response for several alkylating agents.[69] Furthermore, there was a widespread belief that high myeloablative doses of cytotoxic drugs would overcome resistance. Anthracyclines were not suitable for drug escalation because of their cardiac toxicities, but alkylators were. Beginning in late 1970's and twenty years on, high dose chemotherapy with support of ASCT was investigated in the therapy of many solid cancers including breast cancer, lung cancer, ovarian cancer, neuroblastoma, glioma, soft tissue sarcoma, Ewing's sarcoma and many more.[70] The best-known and most widely used example was the case of breast cancer.

During the 1980's, breast cancer patients started to be treated with ASCT in order to reach higher rates of cure through more intensive treatment. In 1988, a review of 172 patients from 27 trials, suggested that the method could produce remissions in patients with advanced breast cancer that were unresponsive to conventional therapy.[71] From this point, ASCT became widely incorporated in breast cancer care, though the evidence for its effectiveness was questionable. The Blue Shield Association, an association of independent community-based insurance companies, raised concerns about the method, because of the high costs and the associated toxicities, especially because of the large number of potentially eligible patients with this common form of cancer. In 1995, a South African randomised controlled trial (RCT) reported positive results adding to the use of the treatment,[72] a trial that has later been confirmed to be the result of scientific fraud.[73] In May 1999, three RCTs reported no advantage in overall survival (OS) respectively.[74-76] These trials would effectively end the use of ASCT for breast cancer. At that time, more than 30.000 breast cancer patients had been treated, with a method increasing their suffering while rarely adding to the effect.[77] There are several underlying causes for this error including enthusiasm for new treatment methods, patient demand, media reporting, economic interests, and legislative and administrative mandates.

To this day, the only non-haematological solid tumours for which high-dose chemotherapy with ASCT support is in use is for germ cell cancer, unless in highly specialised cases.

Infectious complications

The advances in the prevention and treatment of infections following HSCT developed during the 1970's to 1990's. In the 1970's barrier care including air filters was developed and antibiotics were used to decrease the microbial burden of the gastrointestinal tract before HSCT. In the early 1980's acyclovir was reported to prevent herpes virus infection/reactivation, primarily reactivation of varicella zoster virus causing shingles.[78] Oral fluoroquinolones was demonstrated to prevent bacterial infection in recipients of HSCTs in the late 1980's.[79,80] It was shown to be effective in the neutropenic phase following ASCT.[81] It was not until the 1990's that saw the introduction of monitoring for cytomegalovirus (CMV) reactivation,[82] and the use of fluconazole to prevent invasive yeast infection.[83]

In the late 1980's sulfamethoxazole in combination with trimethoprim for *Pneumocystis jirovecii* was introduced.[84] *P. jiroveci* can cause a feared pneumonia that often is fatal, and the risk is higher the more immunocompromised the patients are, especially if they have received T-cell depleting treatments including high-dose corticosteroids. Trimethoprim-sulfamethoxazole is the first choice for preventing *P jiroveci*, as it is more effective than the alternatives; aerosolized pentamidine, oral dapsone, or oral atovaquone.[85,86] Prophylaxis for *P. jiroveci* is given for three months and herpes viruses for up to a year following ASCT.[87,88]

Although growth factors such as G-CSF was proved to reduce the duration of neutropenia following ASCT in the 1990's,[89,90] and potentially the risk of infection, further studies have failed to show a mortality advantage.[91,92] The use of G-CSF following ASCT is widely used, but scientifically it remains somewhat controversial.

Further advances included reducing infections in recipients of ASCT by hospital room design, equipment and maintenance. Patients should ideally be isolated in a well-sealed single occupancy room where the ventilation has at least 12 exchanges per hour, central or point-of use HEPA-filters, consistent positive airflow including monitoring, and self-closing doors.[93] Cleaning should be done minimally once per day with special attention to dust control. Barrier precautions including hand hygiene, personal protective equipment (e.g. gloves, masks, eye or face protection and gowns) during activities or procedures close to the patient should be worn. The patients should take daily showers and brush their teeth with a soft regular toothbrush. Health care workers should avoid treating patients when they have potentially transmissible infections. Intravascular catheters should be cleaned and maintained ambitiously.[94]

Supportive care

Many patients who undergo ASCT need transfusion of erythrocytes or platelets. As all ASCT-patients are immunocompromised after the high-dose chemotherapy, there is a risk of engraftment of donor lymphocytes through such transfusions. These fully capable lymphocytes can cause transfusion-associated graft-versus-host disease (TA-GvHD) which include fever, skin rash, diarrhoea, hepatic dysfunction, and bone marrow aplasia and can be fatal.[95] TA-GvHD can be prevented by irradiating the blood products given to ASCT-patients with gamma- or X-ray radiation.[96]

Chemotherapy induced nausea and vomiting affect most ASCT patients to some extent and is the reason why all patients are given prophylactic anti-emetic treatment. Grading of emetic risk of individual chemotherapeutic agents could be used to adapt the anti-emetic prophylaxis given to patients. Using medications from several different drug classes should be considered including 5-hydroxytryptamine receptor antagonists, neurokinin 1 receptor antagonists, glucocorticoids, and atypical antipsychotics (olanzapine). Other potentially useful drug classes include benzodiazepines, antihistamines and typical antipsychotics (haloperidol).[97]

Oral mucositis is one of the most common toxicities of high-dose chemotherapy. As the mucous membranes in the body have a high cell turnover, they also represent an area of high risk for toxicity as chemotherapeutic agents affect all dividing cells. Oral mucositis usually presents in the first week following conditioning with a typical duration of one to two weeks.[98] Severe forms of the condition need to be treated with parenteral nutrition and/or narcotic analgesia. Preventive measures include oral cryotherapy, for chemotherapeutic agents with short half-life, primarily melphalan. Patients chew ice briefly prior, during and after the infusion of the chemotherapy to cause vasoconstriction and reducing the blood flow to the oral cavity, thereby reducing the local dose.[99,100] Other effective treatments, with a practical limitation due to high cost, are low-level laser therapy,[101] intraoral photo-biomodulation, and the recombinant human keratinocyte growth factor agent palifermin.[102]

Current Use

ASCT is currently in use for multiple myeloma and plasma cell disorders, B- and T-cell lymphomas including Hodgkin's lymphoma, amyloidosis and testicular germ cell cancer (Table 1). It is not curative for acute leukaemia, why the use in AML and acute lymphocytic leukaemia is limited.

In the global perspective, ASCTs had been performed and reported in 85 countries until the end of 2016, and 741.670 patients had been treated globally.[103] Up to the year 2014, ASCTs were only performed in countries larger than 700 km², with more than 300,000 inhabitants, and a gross national income

Table 1. European indications for ASCT in adults

Disease	Condition	Response	Status	Evidence[α]
Haematological diseases				
Acute myeloid leukaemia	Favourable/intermediate risk. MRD-	CR1-2	CO	I
	Acute promyelocyte leukaemia	CR2	SoC	II
Acute lymphoid leukaemia	Standard risk, MRD-	CR1	CO	III
Myelodysplastic syndrome	Intermediate risk[β]		CO	II
Large B-cell lymphoma	Chemo-sensitive late relapse	≥CR2	SoC	II
	Primary CNS lymphoma		SoC	II
	Intermediate/high risk	CR1	CO	I
	Chemo-sensitive early relapse	≥CR2	CO	I
Follicular lymphoma	Chemo-sensitive relapse	≥CR2	SoC	I
	Transformed to aggressive lymphoma	≥CR2	CO	III
Mantle cell lymphoma		CR1	SoC	I
	No prior ASCT	CR/PR >1	CO	II
Waldenström's lymphoma	Chemo-sensitive relapse	≥CR2	CO	II
Peripheral T-cell lymphoma		CR1	CO	II
	Chemo-sensitive relapse	≥CR2	CO	II
Hodgkin's lymphoma	Chemo-sensitive relapse, no prior ASCT		SoC	I
	Refractory/relapse after ASCT		CO	III
Multiple myeloma	Upfront		SoC	I
	Chemo-sensitive relapse, prior ASCT		SoC	II
Amyloidosis			CO	II
Other diseases				
Germ cell tumours	Primary refractory, second or further relapse		SoC	II
Medulloblastoma	Post-surgery, high risk/recurrent disease		CO	III
Ewing's sarcoma	Locally advanced/metastatic, chemo-sensitive		CO	II
Breast cancer	Adjuvant high risk, selected patients		CO	I
	Metastatic, chemo-sensitive		CO	II
Multiple sclerosis	Highly active RRMS failing DMT		SoC	I
	Progressive MS with active inflammation		CO	II
Systemic sclerosis			SoC	I
Systemic lupus erythematosus			CO	II
Crohn's disease			CO	II
Rheumatoid arthritis, Juvenile idiopathic arthritis			CO	II
Vasculitis ANCA+, Takayasu			CO	II
Polymyositis/Dermatomyositis			CO	II
Autoimmune cytopenia			CO	II
Neuromyelitis Optica			CO	II
CIDP, myasthenia gravis, Stiff person syndrome			CO	II
Refractory coeliac disease			CO	II

Indications for ASCT in Europe as proposed by Snowden *et al* (2022) Bone Marrow Transplant.[104]
[α]Evidence grade - Grade I - Evidence from at least one well-executed randomised trial. Grade II - Evidence from at least one well-designed clinical trial without randomisation; cohort or case-controlled analytic studies, multiple time-series studies; or dramatic results from uncontrolled experiments. Grade III - Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees. [β]Without additional factors including >5% marrow blasts, poor karyotype, profound cytopenia (i.e., Hb <80 g/L, ANC <0.8 × 10^9/L, platelets <50 × 10^9/L), or severe bone marrow fibrosis.
Abbreviations: ANCA - Anti-neutrophil cytoplasm antibodies, CIDP - Chronic inflammatory demyelinating polyneuropathy, CNS – Central Nervous System, CO – Clinical option, CR – complete remission, DMT – Disease Modifying Treatment, MRD – Minimal Residual Disease, PR – partial remission, RRMS - relapsing-remitting multiple sclerosis, SoC – Standard of Care.

per person of US$1260 or higher,[105] thus making the method out of reach for patients in many parts of the world.

Procedure

ASCT is a multistep procedure consisting of stem cell mobilisation, harvest and cryopreservation, conditioning to ablate the bone marrow and reinfusion of the stem cells to the patient. After the ASCT follows a time of supportive care, most often in-patient care, for approximately two weeks. Here follows a description of the procedure used in Sweden and thus in each individual study of this thesis. The procedure described corresponds well to what most international centres performs.

Mobilisation

HSCs are most often mobilised using a combination of cyclophosphamide 2 g/m^2 and G-CSF 5 micrograms/kg subcutaneously starting on day 5 or 6 until stem cell harvest. Recent guidelines, not affecting any of the studies in this thesis, omit cyclophosphamide for stem cell mobilisation in multiple myeloma.[106]

Harvest

HSCs are harvested by apheresis of peripheral blood. A minimal yield of 2.0 $\times 10^6$ $CD34^+$ cells/kg is required for each ASCT. For patients with multiple myeloma the minimum required harvest of 4.0 $\times 10^6$ $CD34^+$ cells/kg is collected as current guidelines recommends a second ASCT in relapse if the patient is still eligible. The stem cells are cryopreserved in liquid nitrogen and stored in at least -80°C, with no *ex-vivo* manipulation.

Conditioning

Agents used for conditioning varies according to underlying disease and comorbidities. A minimum wash-out time of 24-48 hours from the last administered chemotherapy before the reinfusion of the autologous stem cells is used to prevent the stem cells from being exposed to the cytotoxic compounds.

Neutropenic phase

During the neutropenic period, that begins a few days after the infusion of the conditioning and continues until the neutrophils rise to 0.5 $x10^9/L$ or higher, the patients are very vulnerable for infections. Many suffer from toxicities from the high doses of chemotherapy, including symptoms from mucous membranes such as nausea, diarrhoea and mucositis, alopecia and cytopenia.

Supportive care

Oral fluoroquinolones are used to prevent bacterial infection during the neutropenic phase.[81,107] In Sweden, the drug of choice is ciprofloxacin, due to the

relatively low local rates of bacterial resistance against fluoroquinolones. Prophylaxis against herpes simplex virus and *P. jirovecii* is prescribed for a minimum of 3 months following ASCT. During the neutropenic period, oral fluconazole is used to prevent yeast infections, in essence *Candida* species, in mucous membranes and systemically.[108,109] Monitoring for reactivation of CMV and Epstein-Barr virus (EBV) is not generally performed for patients with malignant disease, unless treated with T-cell depletion such as ATG, e.g. MS-patients, during induction or conditioning. Such patients carry a greater risk for EBV-related post-transplant lymphoproliferative disease (PTLD). Since 2017, pegylated G-CSF administered on day +5 is used to shorten the duration of the neutropenia at Uppsala University Hospital (UUH). If there is need for transfusions, the blood products are filtered and irradiated until the lymphocyte count exceeds 1.0 $x10^9$/L, to prevent TA-GvHD.

Eligibility

Before ASCT all patients go through a pre-transplantation eligibility evaluation that include clinical evaluation, laboratory tests, serology for infectious status (hepatitis, human immunodeficiency virus (HIV), CMV and EBV), cardiac and pulmonary evaluation and performance status. Exact criteria vary between different centres, but in general, eligibility criteria include age (ASCT rarely performed above 75 years of age), performance status (Eastern Cooperative Oncology Group performance status 2 or lower), absence of substantial disease of the heart, liver or lungs, uncontrolled active infections and signs of myelodysplastic syndrome (MDS) on bone marrow examination.

Toxicity

Several factors affect the risk of complications and death following ASCT. Such factors include prior cancer therapies, status of underlying disease at the time of transplantation, comorbidities including impaired renal function, conditioning regimen and duration of cytopenias.[110-112]

The toxicity varies depending on underlying disease and conditioning protocol. General toxicities include transient alopecia, haematological cytopenia and amenorrhea. Fertility is at risk following ASCT.[113]

For multiple myeloma, the treatment-related mortality (TRM) rate following ASCT is reported to be less than 1%.[114,115] The most common adverse events (AEs) in myeloma patients are mucositis, nausea, vomiting, anorexia and myelosuppression.[114,116]

ASCT for lymphoma has been reported to have a TRM rate of 2.5% to 11%.[117-120] A Swedish retrospective study of 433 lymphoma patients from 1994 to 2016 reported a non-relapse mortality (NRM) rate of 5.5% after 100 days following ASCT. The major causes of death were infections (58%), of which sepsis occurred in half of all NRM cases, and organ failure (13%).[121]

Other AEs included mucositis, enterocolitis/diarrhoea and cardiovascular toxicity including syncope and arrhythmias in elderly patients.[122]

The TRM rate following ASCT for multiple sclerosis has been estimated to be 0.2–0.3%.[88,123,124]

Infectious complications remain a large proportion of morbidity in ASCT because of the immunosuppression caused by high-dose chemotherapy. In the neutropenic phase after ASCT the risk is substantial for bacterial, yeast and herpes simplex infections and infections of respiratory viruses. In the time following engraftment, bacterial infections and respiratory viruses remains common, whereas reactivation of CMV and varicella zoster are getting more frequent, as well as opportunistic microbes such as *Pneumocystis jirovecii* that takes time to develop.

Long-term toxicities include secondary malignancies and organ dysfunction. Haematological malignancies are the most common, where therapy-related MDS and AML have been reported to occur in 5-15% of ASCT-patients after 2-5 years.[125] Multiple chromosomal aberrations are common in secondary myeloid malignancies including monosomy 5q and 7q as well as balanced translocations to 11q23.[125] Risk factors were cumulative doses of alkylating agents and conditioning regimens containing TBI.[126,127]

Secondary solid cancers take time to develop and is an area which has been insufficiently studied in ASCT. If extrapolating the results from studies of HSCTs, which mainly would constitute alloSCTs but also some ASCTs, the increased risk of secondary cancers appears late, generally after at least 3-5 years. AlloSCT is quite different from ASCT as long-term immunosuppression, chronic inflammation including GvHD are all risk factors for cancer development. For all HSCTs, there is an increased risk for cancer of the bones, central nervous system (CNS), connective tissue, oesophagus, liver, oral cavity, pharynx, salivary gland and thyroid as well as melanoma. The cumulative incidence was 8.3 times higher in HSCT-treated patients compared to the general population after 10 or more years.[128,129]

Late therapy-related causes of mortality include 2-3% cardiac toxicity and 2% pulmonary complications.[130] Other long-term toxicities include a risk of amenorrhea, infertility and premature menopause. It has been estimated that 80% of HSCT-treated patients are at risk of primary or secondary amenorrhoea that may result in infertility.[113] A meta-analysis of female patients in reproductive age reported a pregnancy rate of 25% following ASCT.[131] Among women of reproductive age, 15-44 years, haematological malignancies comprise 17% of all cancers.[132]

Most patients recover from ASCT and regain or improve their quality of life after the treatment. The median duration to recover has been reported to be 3 months, but may be longer.[133] A few patients experiences long-term symptoms which negatively affect their quality of life several years after ASCT, such as fatigue, asthenia, and neuropathic pain.[134]

COVID-19

Every new widespread communicable pathogen with a risk of mortality requires thorough evaluation for patients undergoing ASCT. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in the Chinese city of Wuhan in late 2019 and caused a respiratory disease named Coronavirus Disease 2019 (COVID-19). The virus was isolated and described in January 2020 and was found to be a beta-coronavirus.[135] The primary way of transmission through droplets and very small particles caused a worldwide pandemic during the spring of 2020 resulting in lockdowns and curfews in many countries.

Common symptoms of COVID-19 include rhinorrhoea, headache, sore throat and cough. Other symptoms are fever, myalgia and anosmia or other smell abnormalities. The most common causes of death in COVID-patients were acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure. Common complications were venous thromboembolism and renal failure.[136] Diagnostic tests were either nucleic acid amplification tests including real-time polymerase chain reaction (RT-PCR) or antigen-based tests. Vaccines were developed in collaborations between governments and pharmaceutical companies in record time, including two first in class messenger ribonucleic acid (mRNA) vaccines, Comirnaty© and Spikewax© that was approved in the USA and Europe in December 2020.

Treatment of COVID-19 was initially limited to supportive measures such as high-flow oxygen and respirator treatment and preventing thrombosis with low-molecular-weight heparin. Convalescent plasma treatment was one of the most widely used therapies for COVID-19 in 2020 despite limited effectiveness data. It was later confirmed that convalescent plasma did not improve OS or decrease the risk of respirator treatment.[137] Dexamethasone was reported to improve survival in hospitalised patients in the summer of 2020,[138,139] which led to rapid spread of its use worldwide. The first direct antiviral treatment that was approved for COVID-19 was remdesivir. The drug had been developed for treatment of Ebola,[140] and although limited effectiveness it was introduced as a therapeutic option for severe COVID-19.[141]

The Pandemic

Societies all over the world suffered from economic recession, lockdowns, supply shortages, restrictions of business and travel, mask mandates, quarantines and closings of educational institutions and public areas, which were unprecedented in the modern world. The demands of health care systems were stretched, especially to provide intensive care for critically ill and maintaining normal standards of care when many health care workers were quarantined, and transmission control was key. There was a shortage of test material for SARS-CoV-2 from the outbreak until early June 2020 (in Europe). As of governmental

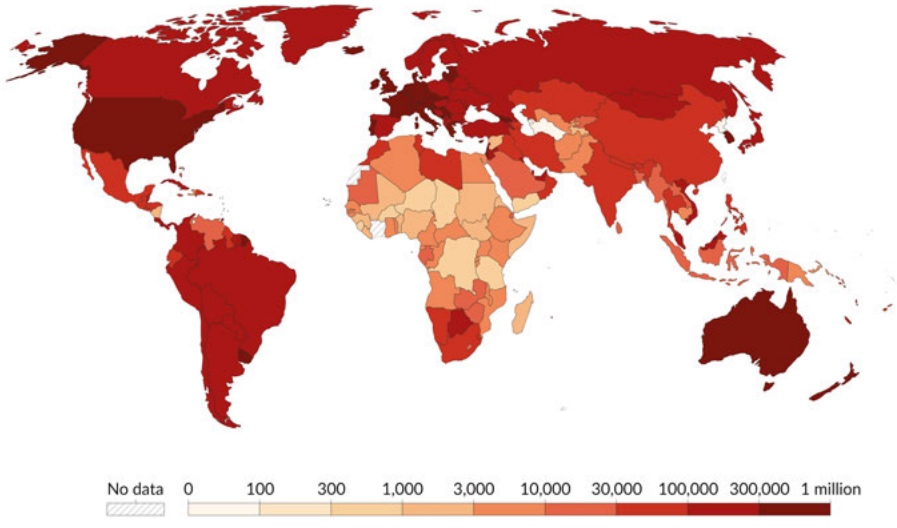

Figure 1. Cumulative confirmed cases of COVID-19 per million inhabitants 25 June 2025.

Credit: Our World in Data. Data source: World Health Organization (2025); population based on various sources (2024).[142]

restrictions, Sweden was an exception in that there were no mandatory lockdowns or curfews. The country rather relied on voluntary compliance for transmission control, through recommendations including self-isolation for patients with mild symptoms or non-infected vulnerable people.

The spread of SARS-CoV-2 occurred in waves, when cases rose markedly. Two distinct waves has been described for much of the world, including Europe.[143] Five new variants of concern has emerged since the original Wuhan-strain of SARS-CoV-2 including the alpha-, beta-, gamma-, delta- and omicron-variants. They all have different clinical features, transmissibility and sensitivity to medicine and vaccine protection. The omicron variant is the only one still to be of international interest in early 2025, but it does not fulfil criteria to be classified as a variant of concern.[144]

The World Health Organization (WHO) declared the COVID-19 pandemic to be over on the 5th of May 2023.[145] Official reports from governments in 229 nations and territories, which effectively ended in April 2024, summoned the global deaths of COVID-19 to 7,010,681,[146] but the WHO estimated excess deaths globally to 14.9 million in 2020 and 2021.[147]

COVID-19 and ASCT

As infections are the major cause of short term TRM following ASCT,[121] physicians in haematological transplantation clinics hesitated to perform ASCT in the spring and summer of 2020. The reason for concern was, apart from the

uncontrolled spread of COVID-19 stretching the health care resources, that the direct mortality in respiratory viral infections after ASCT had previously been reported to be 10-17%.[148,149] Furthermore, lymphocytopenia was found in a majority of infected SARS-CoV-2 patients,[150] which in turn increases the risk for mortality.[149] There had been two previous epidemics of beta-coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2004-2006 and Middle East respiratory syndrome-related coronavirus (MERS-CoV) since 2012, which caused mortality rates of 10%,[151] and 34% respectively in the general population.[152]

The first scientific reports of COVID-19 in patients with haematological malignancies or who were immunocompromised showed high mortality rates. A small study from two haematological wards in hospitals in Wuhan reported a 62% mortality rate in patients and none among health care workers.[153] Another study of cancer patients from 14 hospitals in Wuhan reported in April 2020 a 33% mortality rate in haematological cancer patients.[154] Studies from August 2020 had larger cohorts, consisting of almost exclusively hospitalised patients. An Italian multicentre retrospective cohort study reported 37% mortality rate among haematological cancer patients,[155] and a Spanish counterpart reported 31%.[156] In a meta-analysis using data up to Aug 2020 published in December 2020 presented a mortality rate of 34%.[157]

The European Society for Blood and Marrow Transplantation (EBMT) published guidelines on the management of HSCT-patients in May 2020. The authors recognised the difficulties in presenting guidelines on which patients that should deferred or delayed from transplantation.[158] Effectively, many ASCTs were postponed during the first half of 2020, and patients with non-malignant indication for ASCT were deferred. The patients were tested for SARS-CoV-2 before and at admission, and if positive, the ASCT was delayed for a minimum of two weeks.

Many of the early, rapidly conducted trials and studies, identified patients from a few hospitals and did not include outpatients. The high demand for scientific reports together with the lack of knowledge led reputable scientific journals to publish papers that painted an alarming picture of the situation. The initial lack of a comprehensive overview of the risks that COVID-19 poses to ASCT-patients motivated paper I in this thesis, as it would provide haematologists and transplantationists with valuable information in their risk-benefit assessment. Our aim was to describe how COVID-19 affects patients with haematological malignancies treated with ASCT.

Multiple Sclerosis

MS is the most common immune-mediated inflammatory demyelinating disease of the CNS and also the leading cause of permanent neurological disability in young adults second to trauma.[159] It is estimated that 2.8 million people live with MS worldwide and it affects women twice as often as men.[160]

Causes and risk factors

Even if the specific causes of MS remain unknown,[161,162] it is considered to be environmental factors influencing individuals with genetic susceptibility that explains most cases of the disease.[163] The most well-established environmental risk factors are infection with EBV during adolescence or early adulthood, tobacco exposure, lack of sun exposure, low vitamin D-levels and obesity during adolescence.[164] EBV-infection is the most robust of these risk factors, as close to 100% of MS-patients are seropositive for EBV,[165] and may be regarded as a prerequisite for developing MS,[166] although a direct causal relationship has not yet been established.

Familial occurrence constitutes about 13% of all cases of MS.[167] The risk of developing MS is 2.3-3% if you have a sibling with the disease, 1.7-6% with a dizygotic twin and 15-35% with a monozygotic twin.[168,169] The genetic susceptibility is not limited to a single gene, as the disease is polygenic where no gene is in itself disease-causing. Over 200 such genetic risk variants have been identified.[170] Certain polymorphisms in the genes for HLA class I and II are associated with the highest risk for developing MS.[164]

Pathophysiology

The most widely accepted theory postulates that MS begins as an autoimmune inflammatory disorder mediated by lymphocytes causing demyelination and axonal degeneration.[171,172]

The main pathological characteristic of MS is focal plaques (lesions), most commonly found around post-capillary venules, caused by demyelination. A prerequisite for such lesions are defects in the blood-brain barrier, likely caused by a combination of pro-inflammatory cytokines and chemokines.[173,174] Macrophages, B- and T-lymphocytes migrate through the activated blood-brain barrier and into the CNS where they cause inflammation and demyelination, followed by loss of oligodendrocytes, axonal degeneration and reactive gliosis.[175,176] Historically, T-lymphocytes have been considered to be the most important cell in the inflammatory cascade of MS, but with the emergence and efficiency of anti-CD20-directed therapies, that view has somewhat changed. Although no antibody has been shown to cause MS, patients with MS has an increased level of immunoglobulins within the CNS, corresponding to oligoclonal bands in cerebrospinal fluid, compared to healthy individuals. There is little or no change in the levels of the immuno-

globulin profile with clinically successful treatment with anti-CD20 antibodies, suggesting that the role of B-lymphocytes in MS is not dependent on cerebrospinal fluid immunoglobulin levels.[177,178]

In later stages of MS, secondary progressive MS, the active inflammatory components are less conspicuous. Instead more diffuse infiltration of pro-inflammatory cells and activated microglia in both white and grey matter is frequent.[163,168,179] Grey matter involvement increases with time and is commonly seen in progressive MS. Remyelination is generally limited, but is very heterogeneous, explaining why clinical improvement can occur after relapses. Axonal injuries, and any corresponding disability, is considered permanent.[163]

Symptoms, phenotypes and disease course

The typical presentation occurs in a young adult that experience an episode of dysfunction in the CNS, usually denominated bout, attack or relapse. The symptoms will reflect one or many focal inflammatory demyelinating lesions at specific locations. A single first such episode is called clinically isolated syndrome (CIS). To make the diagnosis, a demonstration of dissemination in time and space is usually required. Magnetic resonance imaging (MRI) or analysis of the cerebrospinal fluid can be used to support the diagnosis.[180] Patients lacking symptoms of MS, but in whom incidental findings of demyelinating-appearing white matter lesions in the CNS on neuro-imaging is referred as radiologically isolated syndrome,[181] and has been shown to predispose for a first clinical attack of 34% within 5 years and 51% after 10 years.[182,183]

As the symptoms of MS depends on where in the CNS the inflammatory lesion is situated, the symptoms are heterogeneous and there are no clinical findings unique to MS. Symptoms suggestive of MS include optic neuritis with unilateral vision loss, internuclear ophthalmoplegia causing diplopia (double vision), Lhermitte's sign and heat sensitivity.[184] The most common symptoms of MS include sensory loss/aberrations in limbs or one side of the face, visual loss or loss of colour vision, motor weakness, gait disturbance, balance or bladder problems, limb ataxia, vertigo and pain.[185]

MS is categorized into subtypes depending on the clinical activity and progression of the disease, which usually changes over time.[186] Relapsing-remitting MS (RRMS) is the most common type of MS, especially in young patients, characterized by reoccurring clinical relapses. RRMS can over time morph into secondary progressive MS, usually after two decades after onset in patients without disease-modifying treatment (DMT).[187] Secondary progressive MS is characterized by gradual worsening of disabilities, but occasional relapses, minor remissions, and plateaus can occur. The third type of MS is called primary progressive MS. It represents about 10% of patients, and is characterized by progressive accumulation of disability from disease onset.[188] Acute relapses, short-term minor remissions, and limited plateaus can occur.

The clinical disease course is highly variable. With the expanded Kurtzke disability status scale (EDSS) it is possible to systematically assess and evaluate disability over time, based on classic neurological examination and asessment of several functional systems including; pyrimidal, cerebellar, brain stem, sensory, bowel and bladder, visual, mental and other functions (Table 2).[189]

Table 2. Expanded Kurtzke Disability Status Scale

Points	Explanation
0	Normal neurologic exam without clinical disability
1.0-1.5	Abnormal neurological exam without clinical disability
2.0-2.5	Minimal disability but fully ambulatory
3.0-3.5	Moderate disability but fully ambulatory
4.0-4.5	Fully ambulatory for 300-500 metres, can work a full day
5.0-5.5	Fully ambulatory for 100-200 meters, disability impair full day activities
6.0-6.5	Material assistance needed to walk
7.0-7.5	Inability to walk more than a few steps to 5 metres
8.0	Restricted to bed or chair
8.5	Restricted to bed, retains some self-care functions
9.0	Confide to bed, can eat and communicate
9.5	No ability to communicate or eat
10	Death

The Expanded Disability Status scale for MS as proposed by Kurtzke *et al* 1983.[189]

Treatment

Acute exacerbations of MS are treated with high-dose glucocorticoids, most commonly daily injections of intravenous methylprednisolone 1000 mg for five days. If the patients respond poorly to glucocorticoid treatment, plasma exchange is an alternative.[190] Exacerbation therapy does not reduce the risk of developing new relapses or affect long-term disability, but aims to decrease the time to recovery. Most patients diagnosed with RRMS should be offered DMTs to diminish the risk of subsequent exacerbations.[191,192] During the last twenty years, a number of novel therapies have been introduced for the treatment of MS, including monoclonal antibodies, oral agents, injections therapies and immune modulating agents (Table 3). Drugs are classed as either high efficiency or moderate efficiency according to the systematization of the Association of British Neurologists, defined as their ability to reduce the annualised relapse rate substantially more than 50%.[193] The currently most used DMT for newly diagnosed RRMS in Sweden is rituximab.[194]

In scientific trials and studies on MS, there are two key outcome measures that need to be explained. Confirmed disability worsening (CDW) is defined as an increase in EDSS score (i.e. disability) of one point (1.5 points if baseline

EDSS score was 0, and 0.5 points if baseline EDSS score was >5.5 points)confirmed by equal or higher EDSS scores over at least 6 months.[195] The second measure is No Evidence of Disease Activity (NEDA), conceptualized for MS by Havrdova and colleagues, which is a composite measure that includes freedom from clinical relapse, freedom from new or enlarged gadolinium-enhanced MRI lesions,[196,197] and freedom from CDW.[198,199]

Table 3. Disease modifying therapies for relapsing/remitting multiple sclerosis

Agent	Brand name	High efficiency[α]	Approval
Monoclonal antibodies			
Alemtuzumab (antiCD52)	Lemtrada®	yes[β]	2014
Natalizumab (antiCD49d)	Tysabri®, Tyruko®	yes[β]	2004, 2023
Ocrelizumab (antiCD20)	Ocrevus®	yes[δ]	2017
Ofatumumab (antiCD20)	Kesimpta®	yes[δ]	2020
Rituximab (antiCD20)	MabThera®	yes[δ]	-
Ublituximab (antiCD20)	Briumvi®	-	2022
Oral agents			
Fumarates			
Dimetylfumarate	Tecfidera®	no[β]	2013
Diroximel fumarate	Vumerity®	no[ζ]	2019
Monomethyl fumarate	Bafiertam®	no[ζ]	2020
S1PR			
Fingolimod	Gilenya®	no[β]	2010
Siponimod	Mayzent®	no[ζ]	2019
Ozanimod	Zeposia®	no[γ]	2020
Ponesimod	Ponvory®	no[ζ]	2021
Pyrimidine synthesis inhibitors			
Teriflunomide	Aubagio®	no[β]	2012
Purine nucleoside analogs			
Cladribin	Mavenclad®	yes[γ]	2019
Injection therapies			
Interferon 1α	Avonex®, Rebif®	no[β]	1996, 2002
Interferon 1β	Betaseron®, Extavia®	no[β]	1993, 2009
Peginterferon 1α	Plegridy®	no[β]	2014
Glatiramer acetate	Copaxone®	no[β]	1997
Immune modulating agents			
Azathioprin	Imurel®	-	-
Cyclophosphamide	Sendoxan®	-	-
Glucorticoids	Prednisone®	-	-
Intravenous immune globulin	various	-	-
Mitoxantrone	Novantrone®	yes[δ]	2000
ASCT		yes[ε]	2016[η]

[α]According to the Association of British Neurologists; ability to reduce the annualised relapse rate substantially more than 50%. [β]According to Scolding N, *et al.* 2015.[193] [γ]According to Samjoo IA, *et al* 2021.[200] [δ]According to He A, et al 2020.[201] [ε]According to Miller AE, *et al* 2021.[202] [ζ]According to Atlas of MS.[203] [η]Approved on Swedish national level
Abbreviations: ASCT - Autologous haematopoietic stem cell transplantation, CD – Cluster of Differentiation. S1PR - Sphingosine 1-phosphate receptor modulators

ASCT for Multiple Sclerosis

In the 1990's the idea to use the immunosuppressive effects of ASCT for other diseases grew from theory to practise. Encouraging results from animal experiments,[204,205] and positive case reports of patients with haematological disease and coincidental autoimmune disease treated with ASCT or alloSCT,[206,207] paved the way for the use of ASCT in aggressive autoimmune disease by the late 1990s.[208] The rationale of using ASCT in this context is to reset the immune system by eliminating autoreactive lymphocytes, in order to induce long-term remission.[209] This has recently been supported by a study showing loss of memory T-cells following ASCT and replacement of the T-cell repertoire.[210]

The first ASCTs for the treatment of MS was performed in 1995 in Thessaloniki in Greece and Northwestern University, Chicago, in the USA.[211,212] In Greece, 15 patients with progressive MS and EDSS 5-7.5 were included in a phase I/II trial and mobilized with cyclophosphamide 4 g/m^2 and G-CSF. They were treated with the conditioning regimen carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by ASCT and ATG given on day +1 and +2. Allergic AEs occurred in 93% of patients, and infections in 87%. During the 6-18 months of follow-up, seven improved in EDSS.[211] In Chicago, three patients with progressive MS and EDSS score of 8.0, were treated with cyclophosphamide 120 mg/kg, TBI and 4000 mg of methylprednisolone. The study reported modest improvements in neurological disability in all three patients.[212] The effectiveness and safety of ASCT for MS have improved since then, primarily due to better patient selection, increased centre experience and improved conditioning regimens.[213]

In the early years, ASCT was primarily used in patients with progressive MS and high burden of disability.[214] This approach has somewhat shifted towards treating patients in the earlier stages of MS, as a consequence of reports showing better effectiveness early in the disease course in patients with active inflammation with a relapsing-remitting disease course.[215-217] About two thirds of patients have been reported to keep NEDA after 5 years following ASCT.[217,218] Many patients even improves in neurological disability following the treatment, primarily in RRMS.[215,216,219,220]

There has been a fast development of new DMTs for RRMS in the last 20 years, but for most of them, the clinical experience is less than 10 years. How to treat MS most effectively remains uncertain, and a single approach is unlikely to suit all patients. ASCT's effectiveness in suppressing disease activity, including its effect on neurological disability, motivates treatment of selected patients despite the associated toxicities. American guidelines have proposed, that ASCT should be considered for patients who demonstrate substantial breakthrough disease activity (new inflammatory CNS lesions and/or clinical relapses) despite treatment with high-efficiency DMT or have contraindications to high-efficiency DMTs and are younger than 50 years, with disease

duration less than 10 years.[202,221,222] Similar criteria have recently been endorsed in Europe,[223] but also includes EDSS values <6.0, unless caused by a recent relapse in MS which would suggest an acute inflammatory activity rather than chronic neurodegenerative processes. Parameters that indicate disease aggressiveness include frequent relapses, incomplete recovery from relapses, high frequency of new MRI lesions, and rapid accumulation of disability.[223]

Effectiveness of ASCT

ASCT is considered a high-efficiency treatment for RRMS.[202] As is the case for all DMTs for MS, the evidence base is stronger for RRMS compared to progressive MS and consequently ASCT is mainly used for RRMS in most centres.[88,124,224,225] In the only RCT of ASCT for MS, the outcome was excellent with only 3 out of 55 patients exhibiting progression of the disease at the end of the study and more than half of all patients improved in disability compared to at baseline.[218] Disability improvement on group-level is not limited to the immediate period following ASCT, but continue over the years following the treatment. In a retrospective study of 414 RRMS patients, the mean EDSS decreased from 3.87 at ASCT to 2.19 at five years.[124] It is estimated that two thirds of all patients maintain NEDA five years after the ASCT.[214,226]

The Swedish Board of Health and Welfare approved ASCT for MS in 2016, but in most countries, it has not yet been integrated into clinical guidelines. The outcome of ASCT for RRMS in broader use outside clinical trials remains undetermined.

Toxicity of ASCT

The most common AEs of ASCT are related to the immunosuppressive effect of the treatment and include febrile neutropenia, sepsis and reactivation of viral agents.[214] Toxicities specific for MS-patients include limb spasticity, reduced mobility, frequent urinary tract infections and Uhthoff phenomenon,[227] which is a temporary (usually less than 24 hours), worsening of neurological function in response to increased core body temperature.

Long-term side effects are secondary autoimmune disease, primarily thyroiditis and immunological thrombocytopenia, affecting 3.6-6.4% of MS-patients, but also a few cases of acquired haemophilia, Crohn's disease and alopecia areata have been reported.[123,228-231] A moderately elevated risk of infections up to one year after the procedure has been reported, primarily in reactivations of viruses.[231] Reports on secondary malignancies are contradictory. One study reported secondary malignancies to occur in 3.2% in a cohort of 281 patients reported to the EBMT, including 1.1% risk of MDS.[123] In a Swedish study of 139 patients, there were no case of invasive cancer, and only one case of basal cell carcinoma.[231]

The prevalence of EBV is almost 100% in patients with MS and prior EBV exposure appears to be necessary to develop MS.[232] Early studies reported high frequencies of EBV reactivations following ASCT, and even cases of fatal EBV-related post-transplantation lymphoproliferative disease.[233,234] These findings raised concerns about EBV reactivations in ASCT for MS, and monitoring of virus levels in blood is recommended.[223]

Acute toxicities remain the principal barrier to wider use of ASCT to treat MS. As of July 2019, the EBMT registry had recorded 1,446 patients treated with ASCT for MS in Europe since 1995.[88] A possible explanation for the relatively low number, apart from the psychological aspect of treating patients without a malignancy with chemotherapy, could be early reports of high TRM and acute toxicities. Over time, the high effectiveness in suppressing disease activity of especially RRMS has become more evident but reports of outcome are largely limited to patients treated within the setting of clinical trials. Whether these efficacy and safety outcomes generalise to routine care remained uncertain and provided the rationale for paper II of this thesis.

Conditioning Regimens

Early trials of ASCT for MS utilized high-intensity conditioning regimens, such as high-dose busulfan or TBI, which were associated with high toxicity and treatment-related mortality.[209] Busulfan was associated with potentially serious AEs including veno-occlusive disease.[235] TBI has proven to be associated with even more toxicity, including infections, secondary malignancies and deterioration of neurological disability.[88] In the following years, conditioning protocols were de-escalated and safety has improved significantly. Different modifications of intermediate intensity protocols were tried, and it was the myeloablative BEAM- and the immunoablative (non-myeloablative) high-dose cyclophosphamide-protocol that soon became the most widely used.[88] Both are typically combined with T-cell depleting serotherapy, primarily ATG. Proper depletion of the T-cell population is thought to be needed to suppress disease activity, as MS is an inflammatory disease where both B- and T-cells are involved, in contrast to the malignant diseases normally treated with ASCT.

BEAM

Use of the BEAM conditioning-protocol was first reported in 1986 and consists of carmustine, etoposide, cytarabine, and melphalan.[236] It was soon a success as it used readily available and well-known drugs, was shown to be highly effective in lymphomas,[237,238] and had acceptable non-haematological toxicities such as oral mucositis, nausea, diarrhoea and hepato- and nephrotoxicity.[238] There has been concerns that carmustine component of the BEAM protocol has been associated with pulmonary toxicity.[130,239] Furthermore, there

has been reports that melphalan is associated with higher frequency of secondary malignancies compared to other alkylating agents.[240,241] It has been the standard conditioning regimen for Hodgkin and non-Hodgkin lymphoma for 40 years.[238,242,243] BEAM has been used for ASCT for MS since more than 20 years and is one of two regimens that are recommended in the latest European guidelines.[88]

The BEAM protocol takes 7 days to administer and include carmustine 300 mg/m^2 on day -7, etoposide 100 mg/m2 twice daily on day -6 to -3 (in total 800 mg/m2), cytarabine arabinoside 800 mg/m2 continuous infusion day -6 to -3, melphalan 140 mg/m2 on day -2, and ATG from rabbit 5 mg/kg on day +1 to +2 (in total 10 mg/kg). Minimum washout time of 48 hours is implemented before reinfusion of the harvested stem cells.

High-dose Cyclophosphamide

Cyclophosphamide was developed in Germany in the 1950's and was the first nitrogen mustard formulated as a prodrug, i.e. an inactive compound that is activated in vivo.[244] This property resulted in better tolerance and a wider therapeutic range. Cyclophosphamide was soon found to be potently immunosuppressive, though it spared stem cells and was not myeloablative.[245] It was deemed excellent for aplastic anaemia, but unsuitable for conditioning patients with acute leukaemia.[246] In the 1990's cyclophosphamide was shown to be even more immunosuppressive when it was combined with ATG.[247] At the same time cyclophosphamide became the most widely used mobilisation regimen for peripheral stem cell harvest in combination with G-CSF.[248,249] Its use in non-malignant alloSCT motivated the use of cyclophosphamide in autoimmune disease. The most widely used protocol uses 200 mg of cyclophosphamide/kg, in contrast to 120 mg/kg that is classified as low intensity and seems less effective in suppressing relapses in MS.[250]

Common toxicities of cyclophosphamide include haemorrhagic cystitis and it has a dose-related association with acute cardiotoxicity,[251] that may result in acute heart failure in rare cases,[252] but it is unclear whether it corresponds to a long-term risk.[253]

Haemorrhagic cystitis was recognised as a serious AE following high-dose cyclophosphamide soon after the introduction to clinical use in the 1950's, and affected 10-40% the patients.[254] It is mediated by a metabolite of cyclophosphamide, acrolein, that damages the bladder mucosa and causes local haemorrhages in the bladder. To prevent haemorrhagic cystitis the use of hyperhydration and uromitexan as it detoxifies the acrolein is recommended.[255]

The high-dose cyclophosphamide protocol used in conditioning for ASCT for RRMS takes 5 days to administer and include cyclophosphamide 50 mg/kg on day -5 to -2 (in total 200 mg/kg) and rabbit ATG, 0.5 mg/kg day -5, 1 mg/kg day -4 and 1.5 mg/kg day -3 to -1 (in total 6 mg/kg). Additionally, 1000 mg IV methylprednisolone is administered day -5 to -1 (total 5000 mg) including

tapering for seven days from 30 mg/day on day 0. Hyperhydration and uromitexan (2-mercaptoethanesulfonic acid, often referred to as mesna) is administered day -5 to -2 to prevent haemorrhagic cystitis. Minimum washout time is 24 hours before reinfusion of the stem cells.

BEAM vs High-dose Cyclophosphamide

Until recently there was only one published retrospective study, of primarily patients with progressive MS, which compares BEAM and high-dose cyclophosphamide in MS. The study reports comparable event-free survival between the cohorts, but noted more severe AEs, longer hospitalisation and three deaths in the BEAM-treated patients.[256] A retrospective registry study, that was only published as an abstract, could not find any differences in effectiveness and safety.[257] A recent Danish retrospective study of 32 RRMS-patients, reported higher toxicity with BEAM when compared to high-dose cyclophosphamide, but no difference in effectiveness.[258]

Which of the regimens that is to be preferred in MS remains unclear. As stipulated by the United States National Multiple Sclerosis Society, research is needed to establish standards for conditioning regimens in ASCT.[202] This was the motivation for paper III of this thesis.

Multiple Myeloma

Multiple myeloma (MM) is an chronic haematological lymphoid malignancy that originates from plasma cells in the bone marrow and accounts for about 10% of all haematological cancers, and 1% of all cancers in general.[259] The malignant plasma cells are typically found in the bone marrow, but can sometimes be detected in peripheral blood and extramedullary tissues. The principal function of plasma cells is to produce immunoglobulins (antibodies). The malignant plasma cells in MM usually secrete monoclonal immunoglobulin proteins (commonly referred to as M-protein or paraprotein) and represents the most common disease marker for MM. In around 20% of the patients, the immunoglobulins are defective to such an extent that the secreted protein only consists of the light chain of the immunoglobulin protein, referred to as free light chains in serum or Bence Jones proteinuria when found in urine. There are rare cases where the myeloma cells does not secrete any detectable immunoglobulin proteins at all, referred to as non-secretory myeloma.[260] MM is more common with increased age and about 33% more common in men compared to women.[261]

The causal aetiology of MM has not been established, but there are associations between age, sex, prior autoimmune disease,[262] family history of monoclonal gammopathy,[263] or occupational exposure to chemicals such as benzene and pesticides.[264,265] Acquired immunodeficiency syndrome (AIDS) have

been reported to have a 12-fold increased risk for developing MM.[266] Additionally, familial clusters of MM have been described for about 100 years.[267]

Multiple genetic aberrations are needed to develop MM. Such genetic events are highly heterogeneous, although translocations of the immunoglobulin heavy chain (IGH) locus in chromosome 14, resulting in strong enhancers controlling oncogenes, or hyperdipliody of odd-numbered chromosomes is considered necessary for disease initiation.[268] Secondary genetic events which has been translated into poor prognosis include deletion of the short arm of chromosome 17, referred to as del(17p), and amplification of chromosome 1q.[269,270] Most secondary genetic aberrations are selected through survival pressure caused by myeloma treatment,[271] corresponding in the disease becoming more and more genetically complex and more therapy-resistant for each treatment cycle given. The tumour microenvironment is altered and essential for the plasma cells in MM as well as in other malignancies. The microenvironment surrounding the myeloma cells promotes tumour growth, immune evasion and drug resistance, and include supportive stromal cells, endothelial cells, osteoblasts and osteoclasts, various immune cells and mesenchymal stromal cells.[272,273]

The clinical presentation of MM include bone pain and fractures from osteolytic lesions, and can be found in >80% of patients at diagnosis.[260] Renal insufficiency is found in almost 40% of patients at diagnosis,[274] many times caused by the precipitation of toxic free light-chains.[275] Laboratory findings include anaemia, hypercalcaemia, thrombocytopenia, leukopenia, and haemostatic abnormalities.[276] Extramedullary disease, where foci of plasma cells are able to infiltrate and grow outside of the microenvironment of the bone marrow, is a sign of aggressiveness and poor prognosis.[277]

Diagnostic criteria for MM include clonal plasma cells in the bone marrow of at least 10% and one or more myeloma defining events including hypercalcaemia, renal insufficiency, anaemia and osteolytic bone lesions. Myeloma-defining biomarkers include clonal plasma cells of ≥60% in the bone marrow, involved-uninvolved serum free light chain ratio of ≥100 and more than one focal lesion of at least 5 mm on MRI.[278] In order to initiate treatment, the same criteria needs to be fulfilled.

Risk stratification for MM-patients are based on serum levels of β_2-microglobulin (a component of MHC class I molecules), albumin and lactate dehydrogenase, as well as cytogenetic aberrations, primarily del(17p), but also gain or amplification of chromosome 1q.[279,280] The former international staging system risk classification also included translocation 4;14 and 14;16 as prognostic risk factors.[281]

The purpose of treating MM is to obtain control of the disease and to limit, and preferably reverse, any associated complications. The optimal goal is to reach minimal residual disease (MRD) negativity, which has been reported to strongly predict progression-free survival (PFS) and OS.[282] The current recommendations are to base induction treatment on three or four different

agents. Eligible patients are recommended consolidation therapy with ASCT in first line of treatment. Patients with high-risk cytogenetics who does not achieve CR after induction therapy are recommended tandem (double) ASCTs as part of the first line treatment.[283-285] Maintenance therapy with low intensity treatment after ASCT is recommended for high-risk patients until disease progression or at least 2 years.[286]

After first line treatment, with or without consolidation or maintenance therapy, usually follows a period of watchful waiting until the disease show signs of progression. The exact time of when to restart treatment is debated and can vary according to national and local tradition and individual physicians. At the latest, reinitiation of treatment is mandated with any new myeloma defining events, such as described above. ASCT is indicated in the relapsed setting if the remission after the first ASCT was long enough. The recommended time until first relapse to be eligible for a second ASCT varies between a minimum of 18-36 months.[287-289] A maximum of two ASCTs are performed per patient, unless the patient were treated with tandem transplantation in the first treatment line, for whom three ASCTs can be performed if the duration of response was long enough.

A New Therapeutic Landscape

In the last 25 years a number of new therapies for MM have been introduced, including immunomodulatory drugs (IMiDs), proteasome inhibitors, monoclonal anti-CD38 antibodies, chimeric antigen receptor T-cell (CAR-T) therapy and bispecific T-cell engagers (BiTE).[290] These new drugs in combination with new technologies for diagnosis, risk and response assessment as well as new treatment strategies, most importantly the triplet- or quadruplet-drug combinations for induction therapy, as well as the introduction of maintenance therapy, has corresponded to a doubling in survival for MM-patients.[291,292] The management of patients with MM, with more individualised approaches in terms of therapeutic choices, but also potentially the use of response depth with MRD to control both treatment and duration of treatment is likely to be integrated into guidelines as the scientific evidence base grows. With these new ways of treating MM, ASCT is challenged as a standard of care for all sufficiently young fit patients in the first lines of treatment.

Melphalan

Melphalan was synthesized in 1953 through exchange of a phenylalanine-group for a methyl-group on nitrogen mustard. Due to its broad antitumor activity, it has been used in the treatment of not only acute leukaemia, lymphoma and MM, but in ovarian cancer and neuroblastoma as well.[293] The first use of melphalan in MM was reported in case series of six patients in 1958.[294] Mel-

phalan was found to have low extramedullary toxicity,[295] which in combination with effective bone marrow ablation and potent immunosuppressive effect paved the way for its use in bone marrow transplantations. Additionally, melphalan was effective enough to be used as single agent for ablation of the bone marrow.[296]

The dose limiting toxicity of melphalan is bone marrow suppression,[90] but in the context of HSCT it is rather mucositis.[297] As mentioned previously, the mucosal toxicity can be decreased through cryotherapy with oral ice administration causing decreased blood flow through vasoconstriction.[298] Other common side effects include nausea, diarrhoea, vomiting and anorexia, in the sense of loss of appetite. If using melphalan with ASCT, febrile neutropenia and septicaemia are common side effects during the neutropenic period.

The long-term complications of melphalan in the context of ASCT is a 10-fold increased risk in MDS and AML when compared to non-melphalan-based ASCT.[299]

High-dose Melphalan and ASCT

The first report of high-dose melphalan (HDM) for MM came from the Royal Marsden Hospital in Sutton, United Kingdom in 1983 when a 34-year-old patient with plasma cell leukaemia was treated with melphalan 140 mg/m^2 to CR. Of their first 9 patients treated, 4 achieved CR, but the time until neutrophil recovery was long, 20-56 days.[300] In 1986, a study of 58 patients treated with melphalan 140 mg/m^2 reported severe myelosuppression and a median time to leukocyte recovery of 28 days in previously untreated patients, and 42 days in refractory patients.[301] In 1986, an MD Anderson study of refractory MM-patients where 16 patients received 80-100 mg/m^2 melphalan without ASCT, and seven patients were given 140 mg/m^2 and ASCT. The aim was to minimize the time of neutropenia, in order to decrease complications and mortality. The study reported faster and more reliable leukocyte recovery and less TRM in the patients with ASCT despite higher dose of melphalan.[302] HDM supported by ASCT has been an integrated part of the management of MM for fit patients since the 1990's, and as standard of care since the turn of the century.[303-305]

Treating MM-patients with HDM was associated with higher rates of CR and improved OS compared to conventional therapy.[303,306] In a randomized trial comparing early ASCT with ASCT performed after relapse showed similar OS but early ASCT was associated with shorter duration of chemotherapy and better quality of life.[307] The rationale of using HDM with ASCT was further motivated by a report from Child and colleagues who could show an advantage of CR, PFS and OS when melphalan 200 mg/m^2 was used at ASCT compared to standard chemotherapy.[308] In contrast, several subsequent studies failed to show a significant advantage of HDM with ASCT over chemotherapy alone.[309-311]

ASCT improves OS by approximately 12 months compared to induction treatment alone.[303,305,308,312] OS has been reported to be significantly better after ASCT compared to alloSCT for MM.[313] A meta-analysis from 2007 reported significant advantage for ASCT in PFS, but not in OS.[314] The Determination trial reported better median PFS following ASCT compared to bortezomib, lenalidomide and dexamethasone without ASCT (67.5 months vs 46.2 months).[315] Recently, HDM with ASCT has been reported to double the number of patients with MRD negativity, the deepest therapeutic response, in the context of novel agent induction therapy.[316]

There are not any prospective comparative studies to rely on; hence, emerging questions have arisen in the scientific community regarding whether HDM with ASCT will maintain its position in treating newly diagnosed MM in a time marked by recent advances in treatment effectiveness, safety and monitoring.[292]

Other Conditioning Regimens

Many different variations of conditioning regimens in ASCT has been tried, including cyclophosphamide,[317] etoposide,[318] and busulphan and thiotepa,[319] without any beneficial effect. To combine melphalan with TBI,[320] idarubicin and cyclophosphamide,[321] topotecan and cyclophosphamide,[322] carmustine,[323] arsenic trioxide,[324] or busulphan did not improve outcome.[325-327] Recently, carfilzomib was added to HDM and reported 16% cardiac toxicity without any clear advantage in efficacy.[328]

The use of HDM with ASCT remains the gold standard for treating MM after induction therapy according to international guidelines.[288,290,329,330] The current protocol is to use melphalan 200 mg/m^2, except in patients with renal impairment or age above 70 for whom 140 mg/m^2 is recommended if the patient is otherwise eligible for transplantation.[288]

Bortezomib

Bortezomib is a first-in-class proteasome inhibitor, which has become a cornerstone in the treatment of MM since its introduction. The compound was first synthesized in 1994, but it was not until 2003 that it was approved for MM.[331] In the original phase II study that the approval was based on, patients more than doubled the time to next treatment (TNT) compared to other available treatments.

Cells are dependent on regulating the protein environment both externally and within the cell. Tightly regulated protein degradation is essential for cellular functions and survival. There are two main pathways for protein degradation in mammalian cells: lysosomal degradation and the ubiquitin-proteasome pathway. Malignant cells are more dependent on the latter and often include aberrant proteasome function.[332] Bortezomib directly and reversibly

inhibits the 26S subunit of the proteasome,[333] with a lasting effect of approximately 72 hours.[334] Bortezomib exerts its effect on malignant cells in several ways, firstly it inhibits the nuclear factor κB (NF-κB) pathway,[335] a pathway that several malignant cell types rely on. Secondly, it cleaves and phosphorylates the B-cell leukaemia/lymphoma 2-protein (BCL-2), a protein that regulates apoptosis.[336] Thirdly, bortezomib upregulates Phorbol-12-myristate-13-acetate-induced protein-1 (PMAIP1, sometimes referred to as NOXA), a mediator of phosphoprotein p53-dependent apoptosis.[337,338] Furthermore, bortezomib potentially blocks the p53 degradation,[339] a critical tumour suppressor protein that prevents the development of cancers in the mammalian body. Bortezomib has been found to activate pro-apoptotic caspases,[340] which could be another mechanism of action for the compound. In addition to all these cellular effects, bortezomib also generates radical oxygen species, which could induce cell death,[341] and inhibit angiogenesis.[342]

Adverse events include thrombocytopenia, fatigue, peripheral neuropathy, and neutropenia.[331] The main off-target effects, that limit the use of bortezomib is peripheral neuropathy and renal dysfunction. Peripheral neuropathy affects up to 40% of patients treated with bortezomib,[343] is dose-dependent, and mostly reversible within six months if the treatment is discontinued.[344] Renal impairment following bortezomib is rare, but cases of thrombotic microangiopathy and acute interstitial nephritis have been reported.[345,346]

Proteasome inhibitors constitute a central part of modern treatment of MM. They are used in many induction combinations and has been seen to have beneficial effects when combined with alkylating agents including melphalan.[347,348] There are two more proteasome inhibitors that has achieved approval for MM since the introduction of bortezomib; carfilzomib approved in 2012 and ixazomib approved in 2015. Current guidelines recommend the use of bortezomib in primary induction treatment as well as in relapsed patients with MM. Bortezomib is recommended with dexamethasone and in combination with cyclophosphamide, daratumumab, elotuzumab, lenalidomide, melphalan, pomalidomide, selinexor, and/or thalidomide.[349,350]

Bendamustine

Bendamustine hydrochloride was developed in the German Democratic Republic (DDR) in 1963 and is an alkylating agent with antimetabolite properties.[351] It was tested in a variety of malignancies, but the first objective response was seen in 1969 in patients with MM.[352] The use of the drug was restricted to the DDR until after the reunification of Germany in 1989, where it was used for a variety of malignancies including MM, chronic lymphocytic leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, and lung cancer.[353] The availability of validated medical research results from trials in the DDR is limited. Several studies were performed from early 2000's until 2012, es-

tablishing bendamustine as an effective treatment option in the setting of relapsed/refractory MM especially for elderly patients.[354-357] Bendamustine in combination with prednisone, was approved for first-line treatment of MM in patients ineligible for ASCT and with clinically relevant neuropathy, thus making the clinical use of thalidomide and bortezomib in combination with bendamustine unfavourable.[358,359]

Bendamustine deregulates DNA-repair genes, activates proapoptotic genes, and induces more DNA double-strand breaks compared to other alkylating agents.[360,361] Furthermore, it has been reported to have activity in p53-deficient cell lines resistant to standard therapy.[362] Bendamustine has been reported to overcome melphalan-resistance in myeloma cell-lines by inducing cell death through mitotic catastrophe.[363]

The most common toxicities of bendamustine include haematological cytopenia, and gastrointestinal disturbances including nausea, mucositis and vomiting.[364]

The use of bendamustine in MM is currently limited and is primarily an option in later treatment lines, especially for elderly patients that are refractory to many other therapeutic groups.

Bortezomib, Bendamustine and Melphalan in ASCT

When novel agents, including old drugs with new indications become establish for a certain disease, it is motivated to explore in which ways to use them best. There are a few studies that has investigated using either bortezomib or bendamustine in combination with melphalan in conditioning treatment before ASCT for MM. In France, the Intergroupe Francophone du Myélome (IFM) working group has investigated the addition of bortezomib to HDM in ASCT in both a phase 2 and phase 3 study, showing no improvement in rates of CR, but importantly no increase in toxicity.[365,366] Another phase II trial compared bortezomib and HDM in relapsed MM after HDM and ASCT in first line treatment, showing no difference in TNT or PFS.[367] It is generally accepted that TNT and PFS is shorter in relapsed MM than in first line therapy.

Bendamustine has been shown to be effective and well tolerated in combination with the proteasome inhibitor bortezomib and dexamethasone in relapsed/refractory MM.[368] In 2013, a phase I trial evaluating the combination bendamustine and HDM conditioning with ASCT reported no increase in toxicity using escalating doses of bendamustine in combination with HDM. The overall response rate was 80%, including 45% of the patients obtaining CR.[369] A phase II study from 2019 investigated the efficacy and safety of bendamustine in combination with HDM and ASCT for MM-patients, and reported a CR rate of 51% and a median PFS of 45 months in relapsed/refractory patients and slightly better in newly diagnosed patients.[370]

Neither bortezomib nor bendamustine showed any significant increase in toxicity when combined with HDM. The promising findings in the reports

mentioned above motivated a change in conditioning protocol for patients illegible for a second ASCT after relapse of MM at UUH. Patients were treated with the combination bortezomib, bendamustine and melphalan (BBM) between 1 Nov 2011 and 31 Oct 2018. Experiences of the combination of these agents in conditioning for ASCT have not been published before. The motivation for paper IV in this thesis was to evaluate the results of this approach to treat MM and compare it to standard HDM.

Rationale

To conclude, the rationale of this thesis was to, through real-world data, address the lack of comprehensive overview of the impacts of COVID-19 in patients recently treated with ASCT, whether the efficacy and safety of ASCT from the only fully published randomized controlled trial in multiple sclerosis would stand in routine health care while addressing the unanswered question of which conditioning regimen is to prefer. And finally, to investigate whether it is possible to ameliorate conditioning therapy with high-dose melphalan by combining it with two approved and readily available drugs, bortezomib and bendamustine, for multiple myeloma.

Objectives

The overall objective of this thesis is to evaluate the effectiveness and safety of ASCT with a particular focus on its application in multiple myeloma and multiple sclerosis and examining infection as the leading cause of treatment-related morbidity in the context of the COVID-19 pandemic.

The objectives of each study were:

I. to assess the impact of COVID-19 on patients with haematological malignancies treated with ASCT.
II. to evaluate the effectiveness and safety of ASCT for relapsing-remitting multiple sclerosis when implemented within routine clinical care.
III. to compare the effectiveness and safety of the two most commonly used conditioning protocols, BEAM and high-dose cyclophosphamide, in the treatment of relapsing-remitting multiple sclerosis.
IV. to evaluate the effectiveness and safety of bortezomib-bendamustine-melphalan conditioning regimen and compare it with high-dose melphalan in patients with relapsed multiple myeloma.

Patients and Methods

Data Sources

Sweden has seven university hospitals that carry out all ASCTs nationwide. Patients are referred to these centres by regional or local hospitals based on well-defined geographical catchment areas (regions). Nearly all neurological and haematological specialised care is publicly funded, and equal access to all aspects of health care is guaranteed by law.

There are few categories of patients in modern health care who are as thoroughly and systematically managed and supervised as patients treated with HSCTs. Patients included in the studies of this thesis were identified using the local EBMT registries at each transplantation centre. For paper IV, the local registry of UUH was used to identify all patients. In addition, the Swedish MS registry (SMSreg) was used to identify patients for paper II and III.

The EBMT registry was introduced in 1974 and collects data on HSCTs and advanced cellular therapies such as CAR-T therapies in Europe. The registry contains, as of 2024, more than 850 000 patients treated with HSCT. To keep full EBMT membership status, the member countries must report all consecutive HSCTs performed each year, thus ensuring a high coverage of the registry data.

In order to obtain data for paper I on which patients that had tested positive for SARS-Cov-2 we used data from The Public Health Agency of Sweden (PHAS). PHAS has the national responsibility to monitor and control communicable diseases and collects clinical data in the Swedish Registry for Communicable Disease (SmiNet). The PHAS used several different surveillance systems to monitor the spread of SARS-CoV-2 in the years following February 2020, including mandatory reporting under the Communicable Diseases Act from clinical physicians and laboratories. The coverage of this database is estimated to be very high, close to 100%.[371] Study I linked the patients identified through the local EBMT registries with SARS-CoV-2 positive patients in SmiNet.

SMSreg is a nationwide registry that has been prospectively collecting data on diagnosis, clinical relapses, radiology, treatment and many other clinical aspects of multiple sclerosis since the mid 1990's. The registry is well-maintained and a useful tool for the treating doctor in the clinical setting with a specific patient, as the data is individualised and transparent. The coverage is estimated to be excellent, and for patients that have received advanced therapy

such as ASCT, close to (if not) 100%.[372] The SMSreg was used to extract effectiveness data for paper II and III.

In all four studies, clinical safety data were collected from electronic patient records and for study I and IV all effectiveness data as well.

Methods

Paper I is a retrospective observational cohort study of all patients treated with ASCT for haematological malignancy in Sweden from 1 January 2020 until 31 December 2020. Patients identified through the local EBMT registers were linked with SARS-CoV-2 positive patients in SmiNet. Patients who were treated with ASCT and tested positive for SARS-CoV-2 from start of conditioning until 31 March 2021 were included in the study. Clinical data were obtained from systematic analysis of electronic patient records. Mortality data were gathered at time of identification and/or at the time of clinical data collection. The primary endpoints were OS at 30 and 90 days following a positive test for SARS-CoV-2, and COVID-19-related mortality. The WHO's definition of COVID-19 related mortality was used in this study, which was defined as a death resulting from a confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease (e.g. trauma), with no period of complete recovery from COVID-19 between illness and the time of death. Secondary endpoints included level of supportive care needed, occurrence of COVID-19 related complications and risk factors for severe outcome. An ad-hoc analysis was performed, with publicly available data from SmiNet of the incidence of COVID-19 in the general population, comparing it to the study cohort.

Paper II and III are both retrospective nationwide multicentre cohort studies using prospectively collected data of all patients with RRMS treated with

Table 4. Study design and methodology of studies I-IV

Study	I	II	III	IV
Design	Retrospective observational cohort study	Retrospective observational cohort study	Retrospective observational cohort study	Retrospective observational cohort study
Diagnosis	All haematological malignancies	RRMS	RRMS	Multiple myeloma
Location	National	National	National	Uppsala (single centre)
Study period	Jan 2020 - Mar 2021	2004-2023	2004-2023	2006-2025
Data sources	SmiNet, medical records	SMSreg, medical records	SMSreg, medical records	Medical records
Population	n=20	n=174	n=174	n=86
Excluded	n=0	n=42	n=42	n=46
Endpoints	Mortality, need for oxygen/intensive care	NEDA, ARR, change in EDSS, TRM, AEs	NEDA, ARR, change in EDSS, TRM, AEs	TNT, PFS, OS, TRM, AEs

Abbreviations: AEs – adverse events, ARR – Annualised relapse rate, EDSS - Expanded Kurtzke Disability Status Scale, NEDA – No evidence of disease activity, OS – overall survival, PFS - progression-free survival, RRMS – relapsing-remitting multiple sclerosis, SmiNet – Swedish Registry for Communicable Diseases, SMSreg – Swedish Multiple Sclerosis Registry, TNT – time to next treatment, TRM – Treatment related mortality.

ASCT in Sweden before 2020. Effectiveness data were extracted from the SMSreg and safety data from electronic patient records. A neurologist at each transplantation centre retrospectively scrutinized the disease course and outcome data in the SMSreg with electronic patient records to validate the quality of the data. A haematologist collected safety data by systematically analysing medical records from the time of stem cell mobilisation to day +100 following ASCT. All severe AEs, defined as AE of grade 3 or higher, were documented in accordance with United States National Cancer Institute's common terminology criteria for adverse events (CTCAE) v5.0. Cytopenia and transient alopecia and amenorrhea were expected during the first weeks after ASCT and were not included in the analysis. Patients who were assessed to have developed progressive MS at the time of ASCT or did not meet the criteria for minimal data were excluded. The minimal dataset included data on disease course at the time of ASCT, date of ASCT, type of conditioning regimen, and at least one follow-up visit (unless early death before first follow-up visit) including clinical assessment with EDSS and neuroradiology assessment with MRI. The primary endpoint was the Kaplan-Meier (KM) estimate of NEDA at 5 years and treatment related mortality. Secondary endpoints were NEDA at 10 years, PFS, relapse-free survival, MRI event-free survival, confirmed disability worsening at 3, 5 and 10 years. In addition, secondary endpoints were also the annualised relapse rate (ARR) after ASCT, the EDSS change between baseline and follow-up at 1, 2 and 3 years, and the proportion of patients with clinical improvement.

Paper III is a retrospective national multicentre cohort study using the data collected for paper II in order to compare the two most widely used conditioning regimens in ASCT for RRMS; BEAM and high-dose cyclophosphamide (Cy), both used in combination with T-cell depleting therapy in the form of ATG. The comparison included the endpoints listed in the last section.

Paper IV is a retrospective single centre cohort study comparing the conditioning regimen BBM to standard HDM in MM-patients that had relapsed after first line treatment including a single ASCT. Patients treated with ASCT in first relapse at UUH were given BBM between 1 Nov 2011 and 31 Oct 2018. Before and after this period patients received standard HDM. We compared the cohort receiving BBM with two cohorts of patients that were treated with HDM, half of whom were treated before the BBM-period and half after. Patients were excluded if they had a tandem ASCT as part of the first line treatment, had the second ASCT later than in second treatment line or if they did not meet the minimal data requirements which included date of ASCT in the first (ASCT1) and the second line (ASCT2), date of start of induction treatment for relapsed myeloma prior to ASCT2, medical records from hospitalisation for ASCT2, at least one follow-up visit (unless early death before first follow-up visit), date of progression and first treatment of relapsed MM after ASCT2 (Table 5). We used the International Myeloma Working Group (IMWG) definitions of diagnosis and response for MM.[278,373]

Table 5. Endpoints for study IV

Primary endpoint	KM-estimated relative difference in median TNT between ASCT2 and ASCT1
Secondary endpoints	KM-estimated relative difference in median PFS after ASCT1 and ASCT2
	KM-estimated median TNT after ASCT2
	KM-estimated median PFS after ASCT2
	KM-estimated median OS after ASCT2
	Average TNT after ASCT2 compared to ASCT1 for each individual patient
	Median difference of TNT between ASCT1 and ASCT2 for each individual patient.
	Depth of best response after ASCT2
	Average duration of neutropenia at ASCT2
	Average time until engraftment at ASCT2
	Average duration of hospitalisation after stem cell infusion at ASCT2
	Frequency of severe adverse events
	Treatment-related mortality rate

All severe AEs were collected until day +100 after ASCT2 according to CTCAE v5.0
Abbreviations: ASCT1 – autologous haematopoietic stem cell transplantation in treatment line 1, ASCT2 – autologous haematopoietic stem cell transplantation in treatment line 2, KM – Kaplan-Meier, OS – overall survival, PFS – progression-free survival, TNT – time to next treatment

Ethical Considerations

The papers described in this thesis all complies with the Declaration of Helsinki. Every patient involved in the individual studies gave their written consent, permitting their data to be reported to the EBMT registry. As all studies in this thesis were retrospective, we asked to abstain from acquiring specific written consent from the study participants in the applications for ethical approval. The main reason was in all cases that it would substantially lower the scientific quality of the data. It would be a great challenge to find and acquire such consent from patients and relatives after many years and when many patients had passed away. To minimize the risk of loss of personal integrity for each study participant in this thesis, data identification, collection, analysis and storage of any personal data has adhered to the standards of Uppsala University. Such measures included pseudo-anonymisation of all entered data, keeping the case report form code-secured and stored within a safe locked room and keeping correspondence with personal data limited to a minimum and through secured file sharing options. All data has been presented on group level except for isolated cases of mortality, where we assessed that it was more important to describe the circumstances (diagnosis, complications and time since ASCT) for the readers of the published articles to attain a deeper comprehension of the causes of mortality.

For paper I, approval from the Ethical Review Authority in Sweden was granted (with reference number 2020-01781) on 23 April 2020, with amendment on 3 August 2020 (reference number 2020-03433).

For paper II and III, the Ethical Review Authority in Sweden granted approval for the study on April 14, 2021 (with reference number 2021-01530).

Although participation in national quality registries like SMSreg is obligatory for Swedish citizens receiving publicly funded health care, patients retain the option to opt out of research conducted using data from these registers. We have not included any patient who executed such a will.

For paper IV, approval from the Swedish Ethical Review Authority was obtained on Sep 12, 2023 (with reference number 2023-04134-01).

Statistical Analysis

In all four papers, descriptive statistics were used, and data were summarised using frequencies for categorical variables, medians (interquartile range) for discrete variables and time data, unless inappropriate due to rare events, and means (standard deviations (±SD)) for continuous variables. Frequencies were presented with a 95% confidence interval. In all papers, a two-tailed p value <0.05 was considered statistically significant.

In paper I, proportions were expressed with a 95% confidence interval (CI, Wilson Score) and incidences with 95% CI (Miettinen's (1974d) modification of the Mid-P exact test) in OpenEpi, version 3.

In paper II, statistical analysis was performed with R version 3.5.3, using the packages ggplot2, survival, fBasics, ggpubr, moments, survminer, plotrix, grid, gridExtra, lattice, and devtools. The Mann Whitney test was used to determine statistically significant differences between two groups, Fisher's exact test was used to determine statistically significant differences between proportions, and the Wilcoxon signed rank test was used to determine statistically significant differences between two time points. Survival was estimated using KM plots (95% CI).

In paper III, statistical analysis was performed with R version 4.2.3, using the packages ggplot2, survival, fBasics, ggpubr, moments, survimner, plotrix, grid, gridExtra, cowplot, tidyverse and devtools. To determine statistically significant differences between two time points, the Wilcoxon signed rank test was used. Differences in time to progression, relapse, confirmed disability worsening, new MRI event or death were estimated using the log-rank test in KM plots. Unpaired Student's t-tests were used to determine statistical significance for means and proportions of normal distribution.

In paper IV, statistical analysis was performed with R version 4.4.3, using the packages ggplot2, survival, survimner, tidyverse, gtsummary and devtools. To determine statistically significant differences between proportions, Fisher's exact test was used. Differences in TNT, PFS and OS were estimated using the log-rank test in KM plots. Unpaired Student's t-test was used to determine statistical significance for means and proportions of normal distribution. Two-sample z-test was used to determine statistical significance for sample proportions. Uni- and multivariable linear regression analyses were performed to estimate the effects of key confounding variables.

Results and Discussion

Paper I

Results

We identified 442 unique patients who had undergone at least one ASCT in Sweden in 2020. Out of these, 20 patients (4.5%) subsequently tested positive for SARS-CoV-2 before the end of March 2021. The cases were evenly distributed according to geographical location, diagnosis motivating ASCT and time since ASCT. The median age was 60 years (range 40-70). The median time from ASCT to positive test for SARS-CoV-2 was 5.6 (0.6-11.6) months. None of the patients had been vaccinated for SARS-CoV-2 at time of infection. Symptoms of disease included fever, cough and in one case headache. Four patients in this study received glucocorticoids as treatment for COVID-19, one received remdesivir and one received convalescent plasma.

For three patients, the only information available in the study was diagnosis, date of ASCT and mortality data, due to difficulties in clearing permission to obtain other clinical data. Two thirds (11 of 17, 65%) of the patients did not need hospitalisation. The remaining six patients (35%) were admitted to hospital out of which four (24%) needed oxygen and two (12%) were admitted for intensive care. Both patients receiving intensive care died due to COVID-19. One more patient died, but that patient tested positive for SARS-CoV-2 as an in-patient with relapsed mantle cell lymphoma in a terminal state. The cause of death was deemed as relapse unrelated to COVID-19. Thus, the COVID-19 related mortality in the study was 10% (CI 2.79-30.1%) and the overall mortality rate was 15%. The absolute risk of mortality due to COVID-19 for all patients treated with ASCT in Sweden 2020 was 0.45% (CI 0.12-1.63%).

Discussion

First of all, it is important to point out that this study was conducted in a cohort of patients that were not vaccinated, did not have access to several of the disease modifying COVID-19 treatments that were later developed (only one patient was treated with remdesivir) and the variants of SARS-CoV-2 were the original Wuhan strain and from December 2020 the alpha-variant.

The risk of COVID-19 related mortality in haematological patients treated with ASCT seemed lower in this study compared to the 31-37% reported in previous studies.[155-157] This pattern was similar for patients in need for oxygen, and intensive care. A reason for this is that our study included non-hospitalised patients, thus patients who only developed mild COVID-19. The risk of severe COVID-19 or death was substantially higher in patients treated with ASCT compared to the general population (Table 6).

The average monthly incidence of COVID-19 after ASCT in this cohort was comparable with that of the general population in the same time period; 0.54% (CI 0.38-0.82) compared to 0.572% (CI 0.571-0.573), suggesting that the susceptibility to be infected with SARS-CoV-2 is not increased after ASCT, although behaviour including exposure to infected people and probability of performing a test would have differed in the populations.

Table 6. Level of care and death in ASCT-patients vs the general population

Age group, years	**Cases**	**Hospitalisation**, n (%)	**ICU,** n (%)	**Death,** n (%)
40-49				
Sweden	148 656	5 817 (3.91)	614 (0.41)	90 (0.06)
Study cohort	5	1 (20)	0	0
50-59				
Sweden	133 053	9 468 (7.13)	1 383 (1.04)	329 (0.25)
Study cohort	2	1 (50)	0	0[α]
60-69				
Sweden	69 354	10 582 (15.26)	1 890 (2.73)	854 (1.23)
Study cohort[β]	10	4 (40)	2 (20)	3 (27)[γ]
Total (40-69)				
Sweden	351 063	25 885 (7.37) (CI 7.29-7.46)	3 887 (1.11) (CI 1.07-1.14)	1 273 (0.36) (CI 0.34-0.38)
Study cohort	17	6 (35) (CI 17.3-58.7)	2 (12) (CI 3.29-34.3)	3 (15) (CI 5.24-36.0)[δ]

Risk of hospitalisation, need for intensive care and death following infection with SARS-CoV-2 in the Swedish general population and the study cohort of patients treated with ASCT for haematological malignancy. The percentages shown are compared with the total number of cases for the row. Data from the Public Health Agency of Sweden. [α]Mortality data available for four patients in the 50–59 cohort. [β]One patient was 70 years and 1 month at time of infection. [γ]Mortality data available for 11 patients in the 60–69 years cohort. [δ]Mortality data available for all 20 patients. Abbreviations: ICU – Intensive care unit
With permission from Upsala Journal of Medical Sciences, Silfverberg et al (2022).[374]

Limitations

The principal limitation of this study was the low number of patients who contracted SARS-CoV-2. For that reason, we could not provide a meaningful discussion on association between risk factors, complications and outcome of COVID-19. The statistical uncertainty of the presented endpoints is large, making any advanced conclusions from this study impossible to make.

In the spring of 2020, two factors limit the conclusion of this study. Firstly, there was a shortness of available PCR-tests for SARS-CoV-2, which corresponds to a likely underestimation of the number of individuals who contracted SARS-CoV-2 during that time, although patients treated with ASCT

and with haematological disease were likely to be prioritized for testing. Secondly, there was a reluctance to treat patients with ASCT, as it was very difficult to estimate the risk of COVID-19 in a time of uncontrolled spread of the pandemic. The scale of this hesitation is not known but is likely to have been rather small.

All comparisons with the general population were done ad hoc, and should be interpreted with care, although the coverage of the data from SmiNet is thought to be excellent. There are several parameters influencing the risk of contracting SARS-CoV-2 that this study cannot cover, including level of self-isolation, use of protective barriers, and level of local community spread.

Paper II

Results

We identified 216 patients treated with ASCT for RRMS in Sweden before 2020 that met the inclusion criteria. There were 42 patients who fulfilled at least one exclusion criteria; 30 had progressive MS at ASCT and 12 did not meet the criteria for the minimal dataset. The first patient was treated in 2004. Median age at ASCT was 31 years and the median follow-up time was 5.5 years. The KM estimate of maintaining NEDA at 5 years was 73% (95% CI: 66–81%) and 65% (95% CI: 57–75%) at 10 years (Figure 2). There was no treatment-related mortality. After a median of 2.9 years, 20 patients (11%) received other DMT. There were 10 patients who transitioned from RRMS to progressive MS after a median of 4.1 years. The ARR was 1.7 in the year prior to ASCT and 0.035 during the follow-up period, $p<0.0001$. Of the 149 patients with any degree of disability at baseline (EDSS ≥2), 80 (54%) had improved in disability, 55 (37%) were stable, and 14 (9%) had deteriorated at last follow-up (Figure 3). The median EDSS was significantly lower at last follow-up compared to baseline before ASCT, 2 vs 3.5, $p<0.0001$.

The mean number of severe AEs per patient was 1.7 for grade 3 events and 0.06 for grade 4 events. Five patients were admitted for intensive care, with a median and maximum duration of 2 days. Febrile neutropenia was the most frequently observed severe AE linked to ASCT, affecting 125 patients (72%). There were no cases of CMV- or EBV-related disease, invasive or systemic fungal infection, haemorrhagic cystitis or fatal COVID-19. One patient died during the follow-up period, more than six years after ASCT due to suicide and was determined unrelated to the ASCT.

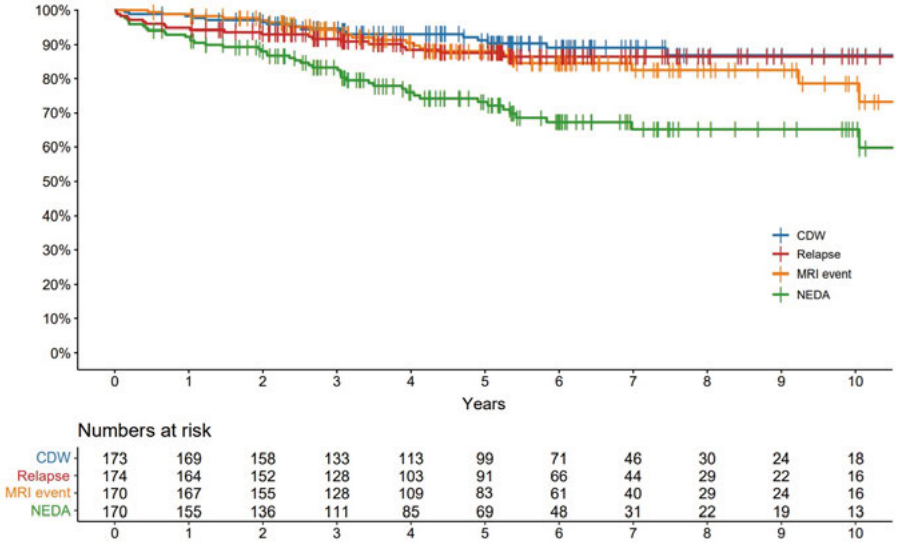

Figure 2. Kaplan-Meier estimation of the probability of maintaining no evidence of disease activity (NEDA), including its composites freedom from new or enlarged MRI events, freedom from clinical relapses, and freedom from confirmed disability worsening (CDW).

With permission from Journal of Neurology, Neurosurgery and Psychiatry, Silfverberg et al (2024).[375]

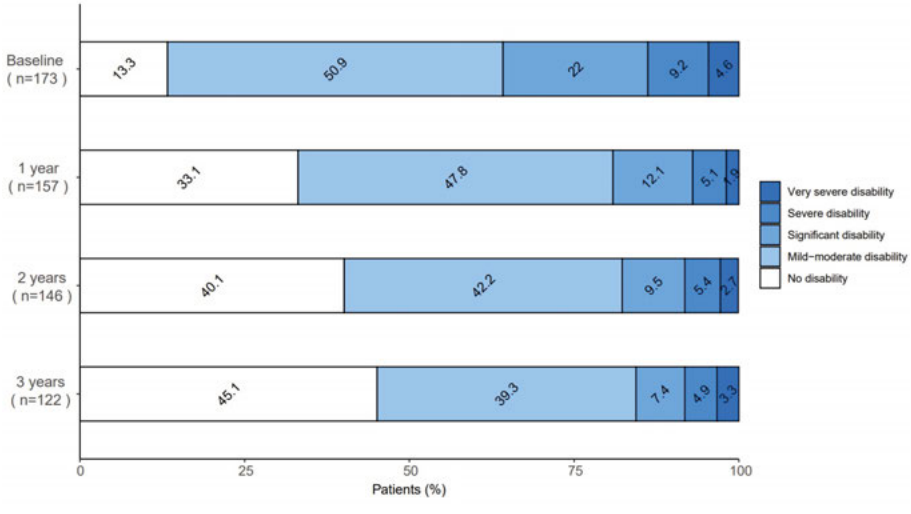

Figure 3. Change in the proportions of patients with different levels of disability over time. Disability was defined using the Kurtzke Expanded Disability Status Scale (EDSS) from baseline and until three years after ASCT. Definition of disability levels was: no disability as EDSS 0–1.5, mild-moderate disability as EDSS 2–3.5, significant disability as EDSS 4–5.5, severe disability as EDSS 6–6.5, and very severe disability as EDSS 7–9.5.

With permission from Journal of Neurology, Neurosurgery and Psychiatry, Silfverberg *et al* (2024).[375]

Discussion

In this study, two thirds of the patients with RRMS had not experienced any sign of the disease ten years after the ASCT, which is a rather outstanding result in terms of treatment for RRMS. The effect of the ASCT in RRMS is durable, which was measured in several ways in this study; a low number of patients needing other DMTs, low frequency of conversion to progressive MS, and 88% of the patients did not experience any confirmed disability worsening. More than half of the patients improved in their neurological disability, which is rarely the case in RRMS. The ARR was 2.1% of the rate before the ASCT, thus fulfilling the criteria of high efficiency (<50%) by an extensive margin. The adverse events were manageable and there was no treatment-related mortality. The findings confirm the only randomised controlled trial on ASCT for MS published to this date,[218] which suggests that the results are generalisable to routine health care.

The thorough analysis of safety data allows for a detailed description of severe AEs. Notably, the frequency of febrile neutropenia was higher in this study compared to most previous studies, which could be explained partly by the definition of fever, or even the use of oral ciprofloxacin used as prophylaxis in Sweden instead of intravenous antibiotics. On the other hand, previous reports have indicated a high prevalence of EBV and CMV reactivation following ASCT,[233,234] but in our cohort the levels of reactivation were low, only one patient being treated with rituximab for EBV reactivation. Five patients received oral treatment for CMV reactivation and only one needed intravenous treatment.

Limitations

The main limitation of paper II is the lack of a control group as the study was observational and retrospective. Identifying a control group was deemed unfeasible considering obvious problems with selection bias, as many of the patients treated with ASCT would have had a more inflammatory and aggressive presentation compared to others, especially in the beginning of the study period. The lack of control group limits the comparison with any other treatments for RRMS, and similarly the effect size of any regression to the mean.

As this was a retrospective study, there is a risk of missing data, especially concerning safety as the data was collected from medical records. To ensure the accuracy of the effectiveness data, an on-site neurologist cross-verified the data from SMSreg with the medical records. The risk of missing data was the rationale to only describe severe AEs, essentially graded as 3 or higher according to CTCAE v5.0, as non-severe AEs would have a greater risk of not being mentioned in the medical records.

Paper III

Results

Of the 174 RRMS identified for paper II, 33 patients were treated with BEAM and 141 with Cy. The rates of NEDA at 5 years were comparable, 81% for BEAM vs 71% for Cy, p=0.29. There was no treatment-related mortality in either group. There was no statistically significant difference in between the cohorts in terms of freedom of MRI events freedom from clinical relapses or freedom from CDW (Figure 4). The ARR following ASCT was comparable between the cohorts, BEAM 0.015 ±0.044 and Cy 0.033 ±0.11, p=0.97. The frequency of patients with confirmed disability improvement were 55% for BEAM and 49% for Cy-patients, p=0.56. Conversion to secondary progressive MS occurred in 18% of BEAM-treated patients after an average of 4.9 years, and 4.3% in Cy-patients after 3.5 years, p=0.37. Additional DMT was required in 9.1% of BEAM- and 12% of Cy-patients, p=0.63.

Severe AEs were more common in BEAM-treated patients, on average 3.1 (±1.8) for BEAM vs 1.4 (±1.2) for Cy, p<0.001. Febrile neutropenia occurred in 88% of BEAM-patients vs 68% in Cy, p=0.023. Additional severe AEs that were statistically more common in BEAM-patients were serum sickness, hypokalaemia, hypoalbuminaemia, diarrhoea and anorexia. Bacterial infections verified by culture or with undisputable clinical presentation, were more common in BEAM-treated patients, 64% vs 28%, p<0.001. All BEAM-patients needed IV broad-spectrum antibiotics, vs 75% of Cy-patients, p=0.0013. The duration of hospitalisation was on average 3.0 days longer for BEAM-patients compared to Cy-patients, counted from day of stem cell infusion, on top of the two additional days for the BEAM protocol.

Discussion

In this retrospective study, we could not find any statistically significant difference in effectiveness between conditioning with BEAM or Cy, but BEAM was associated with more severe AEs, more bacterial infections including the use of IV broad-spectrum antibiotics, and longer hospitalisation. There was a trend towards BEAM being more effective in NEDA, mainly driven by MRI events. It is possible that a study of a larger cohort could demonstrate a statistically significant advantage of BEAM in preventing MRI events, but it should be acknowledged that such MRI events were most often asymptomatic to the patient.

When a new therapeutic method is introduced for a disease, the first patients will not be the equal to the patients receiving the treatment when it has become clinical routine. BEAM was the preferred choice of conditioning until

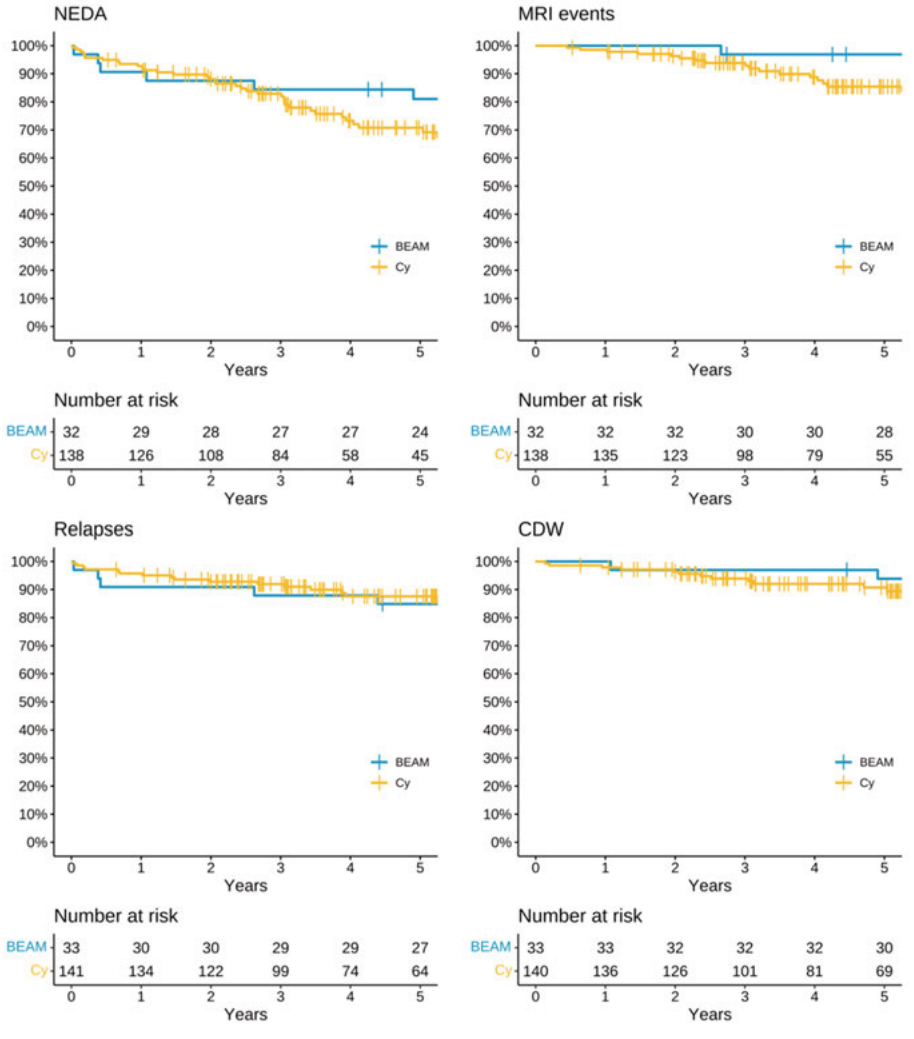

Figure 4. Kaplan-Meier estimation of the probability of maintaining no evidence of disease activity (NEDA), including the secondary endpoints freedom from MRI events, freedom from clinical relapses, and freedom from confirmed disability worsening (CDW) after ASCT up to 5 years of follow-up.

With permission from Bone Marrow Transplantation, Silfverberg et al (2024).[376]

2012 whereas Cy has been the predominant regimen since 2013. As BEAM was primarily used in the beginning of the study period, one can assume that the patients would have had a more aggressive clinical presentation, which is also reflected in the patient characteristics of the cohorts. BEAM patients had more gadolinium-enhancing lesions on MRI, and a higher ARR at baseline compared to Cy patients. However, it is not clear how this would have affected the outcome, as MS-patients with active inflammation benefit the most from ASCT.

Limitations

The limitations of this study are primarily due to the retrospective design, which is problematic when comparing two different treatment regimens. As there was no randomisation, the cohorts were imbalanced in terms of time of treatment and disease activity as has been mentioned above. Changes and developments in clinical routine could have impacted the outcome, both in terms of safety, but also because changes in patient selection could have influenced which patients were selected for ASCT. In this context, it should be added that the pattern of more toxicity and longer hospitalisation was still apparent in 2011 to 2015 when the regimens were used simultaneously.

The limited number of patients in the BEAM cohort restricted the study, especially when the ASCT has been proven to be such an effective treatment resulting in less analysable statistical events. The low number of disease-related events restricted the statistical power and prevented any meaningful regression analysis of factors influencing the outcome.

Paper IV

Results

We identified 64 patients that were treated with ASCT2 from November 2011 to the end of October 2018, of which nine did not meet the inclusion criteria and a further 12 fulfilled at least one exclusion criteria. Thus, 43 patients remained in the final cohort. We needed to identify a further 80 patients to find 43 patients treated with HDM that were eligible for analysis in the final control cohort, the main reasons for exclusion were tandem transplantation at first treatment line or missing data. The HDM-cohort treated before the BBM-period consisted of 21 patients and the later cohort of 22 (Figure 5). Data collection was performed in Jan to Feb 2025.

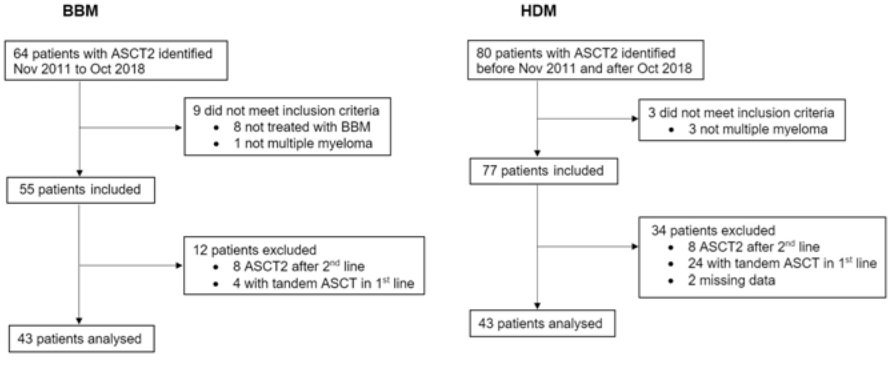

Figure 5. Patient inclusion and exclusion in study IV.

The cohorts were balanced overall, even though there were more female and fractionally older patients in the HDM-cohort. The HDM-treated patients had slightly more comorbidities as measured by the Charlson comorbidity index. The time between ASCT1 and ASCT2 were comparable between both cohorts.

The induction treatment has changed more than once during this study period. Before 2006, the induction treatment in first line was restricted to vincristine, adriamycin and dexamethasone. Between 2006 and 2008, the predominant therapy of choice was cyclophosphamide and dexamethasone. From 2009 and onwards patients were generally treated with bortezomib, cyclophosphamide and dexamethasone, where cyclophosphamide was replaced by thalidomide in some cases, and from 2018, this replacement was instead made with lenalidomide. For second line therapy, bortezomib was introduced in 2008, and lenalidomide in 2013. The first use of daratumumab and carfilzomib in second line treatment was done in 2020, thus only affecting the HDM-cohort. Consolidation therapy was only used in HDM-patients. Maintenance therapy with lenalidomide was given to eight BBM-patients for an average of 10 months, whereas 15 patients in the HDM-cohort received maintenance with either thalidomide, lenalidomide or bortezomib for an average of 16 months.

The average time until neutrophil granulocytes were 0.5 $x10^9$/L or more were similar 13.4 (±1.70) vs 13.0 (±2.86) days for BBM- and HDM-patients respectively, p=0.43, though G-CSF were used in six (12%) patients treated with BBM and 23 (53%) patients with HDM, p=<0.0001. The average time until engraftment was 13.7 (±2.11) for the BBM, and 14.1 (±3.63) for the HDM cohort, p=0.54. The average time of hospitalisation after stem cell infusion, including such outpatient care, were 16.7 days (±4.38) for BBM- and 15.3 days (±2.57) for HDM-patients, p=0.074.

The KM-estimated median TNT for BBM-treated patients was 28.9 months (CI 24.2-34.9) after ASCT1 and 21.4 months (CI 15.6-29.7) after ASCT2, a difference of 7.5 months or a relative reduction of 26%. The corresponding median TNT for HDM-treated patients was 32.1 months (CI 25.0-42.2) after ASCT1 and 19.4 months (CI 16.4-40.0) after ASCT2, a difference of 12.7 months or a relative reduction of 39%, p=0.198 (Figure 6). The KM-estimated median PFS for BBM-treated patients was 21.6 months (CI 18.8-29.0) after ASCT1 and 18.4 months (CI 14.0-23.7) after ASCT2, a difference of 3.2 months or a relative reduction of 15%. The corresponding median PFS for HDM-treated patients was 25.0 months (CI 20.7-37.4) after ASCT1 and 15.4 months (CI 11.2-26.6) after ASCT2, a difference of 9.6 months or a relative reduction of 39%, p=0.0122

The other secondary effectiveness outcomes could not show any difference between conditioning with BBM or HDM, but all showed a trend towards BBM having a higher effectiveness. Following the ASCT2 the KM-estimated

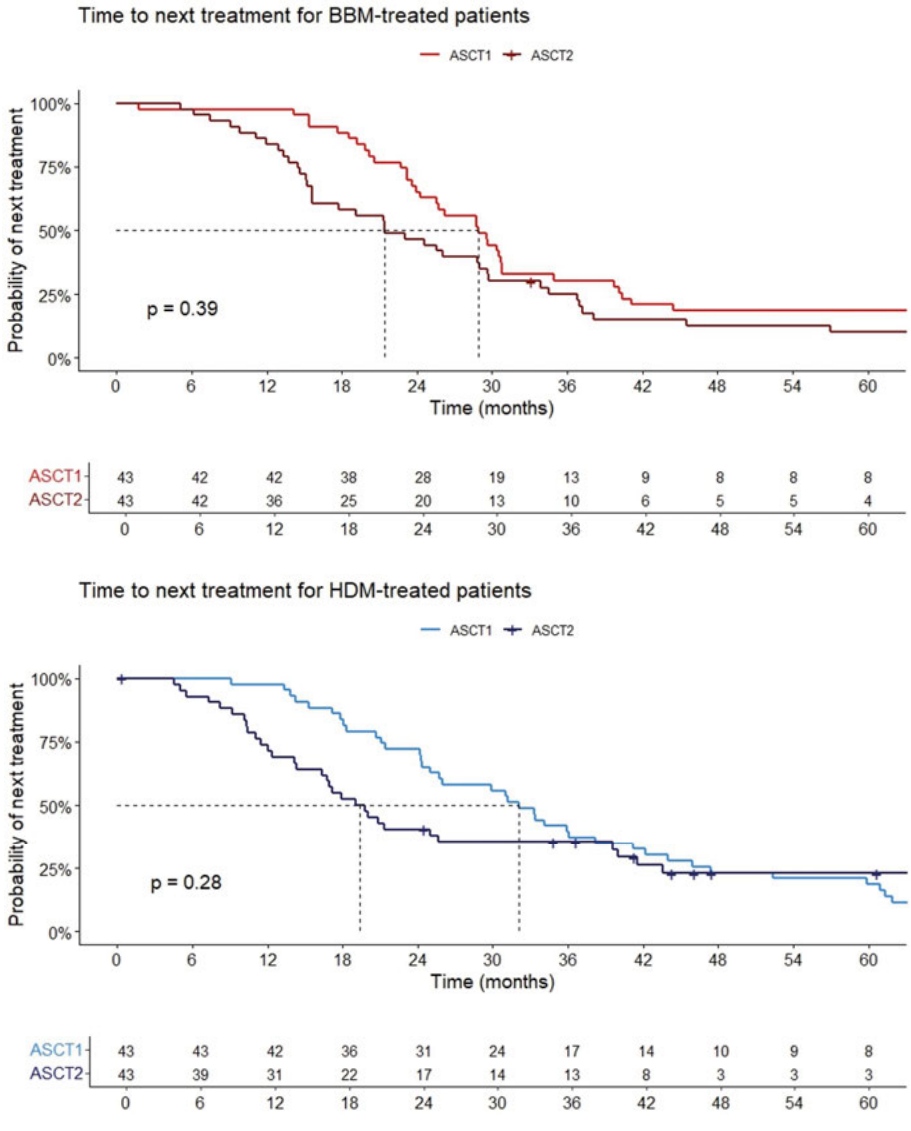

Figure 6. Time to next treatment comparing ASCT2 with ASCT1 (which always was HDM) for patients treated with BBM or HDM in ASCT2.

Abbreviations: ASCT1 - Autologous haematopoietic stem cell transplantation in first treatment line (excluding tandem transplantation), ASCT2 -Autologous haematopoietic stem cell transplantation in second treatment line, BBM – Bortezomib, bendamustine and melphalan, HDM – high-dose melphalan

median TNT was 21.4 months vs 19.0 months (p=0.84), the KM-estimated median PFS was 18.4 vs 15.4 months (p=0.92), and the KM-estimated OS was 72.2 vs 51.5 months (p=0.14). After two years the OS was 88% in the BBM- and 79% in the HDM-cohort. The TNT after ASCT2 was on average 0.75 of

the TNT after ASCT1 for each individual patient treated with BBM, and 0.66 if treated with HDM, p=0.41.

There was no short-term TRM in the BBM-cohort, but one patient died of ASCT-related chronic diarrhoea more than 2.5 years after ASCT. In the HDM-cohort the TRM rate was 2.3%.

There was no statistically significant difference in the frequency of total numbers of AEs between the cohorts. The most common severe AE were febrile neutropenia in both cohorts and showed a trend of being more common in BBM-patients, 26 BBM-patients vs 17 HDM-patients, p=0.052. In the BBM-cohort, oral mucositis and hypokalaemia were more common, and in the HDM-cohort nausea was more common. There were 13 patients in the BBM-cohort that received parenteral nutrition at any point during the first 100 days following ASCT, compared to 19 patients in the HDM-cohort, p=0.18.

Discussion

The main finding of this retrospective cohort study is that BBM-conditioning was not statistically superior to HDM in patients with relapsed MM following first-line ASCT. However, BBM showed a non-significant advantage in TNT, PFS and most notably in OS and had a significant advantage in limiting the decrease in PFS from ASCT2 compared to ASCT1. The addition of bortezomib and bendamustine to melphalan did not result in any unexpected safety issues.

Although, a slight trend of superiority was seen in the effectiveness parameters of the study, they were quite similar for TNT and PFS, as opposed to OS that showed a clearer tendency towards BBM being more effective. The KM curves of TNT and PFS crosses each other, most likely explained by the relatively less effective induction treatment in the early HDM-, compared to the latter HDM-cohort, that received more effective induction treatment and often with addition of consolidation or maintenance therapy. This could not be seen in the KM curves of OS, where there is a more notable trend for superiority of BBM. Even though difficult to assess, a theoretical explanation for this could be the ability of bendamustine to sensitize myeloma-cells to the cytotoxic effects of melphalan and possibly suppress certain myeloma clones to a greater extent than melphalan only.

To account for inter-patient variability, we used the difference in TNT and PFS between the first and second autologous stem cell transplantation as a within-subject endpoint, allowing each patient to serve as their own control. Notably, our analysis revealed a trend toward improved effectiveness in patients who received BBM-conditioning in TNT and a significant advantage in ability to decrease the drop between ASCT1 and ASCT2, suggesting a potential clinical benefit that merits further investigation.

Regarding the safety analysis, there were differences in the frequency of specific AEs, but this should be interpreted cautiously as there were many

such safety outcomes. The overall interpretation is that adding bortezomib and bendamustine to high-dose melphalan, seemed to be well tolerated and comparable with HDM. The frequency of febrile neutropenia was highest in the early HDM-cohort and diminished over time, thus much more uncommon in the latter HDM-cohort. This could be the explanation for the trend of BBM-treated patients experiencing more febrile neutropenia.

We conducted simple and multivariable regression analysis to assess the most important confounders of TNT after ASCT2. The most important variables for the outcome were the time between ASCT1 and ASCT2, the Charlson comorbidity index and the depth of best response prior to ASCT2. In the multivariable regression analysis, conditioning with BBM rather than HDM with prolongation of TNT with 5.0 months, p=0.1632.

Limitations

There are several limitations of this study due to its rather small cohort-sizes and retrospective design. The main limitation of the study was the disparity in time of the two cohorts. The treatment of MM has changed substantially during the last 20 years, influencing the added result of the ASCT in the first two treatment lines of myeloma-treatment. The study period spanned from 2006 to 2023 for ASCT2. This has implication for the comparability of the cohorts as the management and treatment of MM has changed during the study period. Secondly there are relatively more patients in the second HDM-cohort who has not yet progressed, been treated or died at the time of data collection, which could lead to an underestimation of the effectiveness parameters in the HDM-cohort. On the other hand, relatively more patients with high-risk cytogenetics have been excluded from the later HDM cohort when tandem transplantation was introduced in 2013. Additionally, daratumumab was only used in late HDM patients, and as the drug has been proven to be very effective for treating MM this disparity constitutes an advantage for the HDM cohort.

As this study is retrospective and observational, another limitation is that local and individual traditions could have affected when, how and how often patients were assessed, when treatment was initiated, and which other treatments were used.

Conclusions

I. In paper I, we conclude that COVID-19 constitutes a higher risk of mortality and hospitalisation for patients with haematological malignancy treated with ASCT compared to the general population. The risk of contracting SARS-CoV-2 seems comparable. The risk of mortality, the need for hospitalisation, oxygen or intensive care seemed lower in this study compared to previous studies of mainly hospitalised patients. The results suggest that ASCT should not be withheld due to the COVID-19 pandemic, if it is clinically motivated, patients are well informed and prophylactic measures are taken.

II. In paper II, we report that treatment with ASCT was followed by maintenance of NEDA over 5 years in 73% of RRMS-patients, without compromising safety. There was no treatment-related mortality and adverse events were manageable. These findings support what is currently the only randomised controlled trial of ASCT for RRMS,[218] suggesting that the results are generalisable to routine health care. We believe that ASCT could benefit a greater number of MS patients and should be included as a standard of care for highly active MS.

III. In paper III there was no significant difference in effectiveness between BEAM and Cy conditioning when used for RRMS. The BEAM protocol was associated with more severe AEs, more febrile neutropenia and longer hospitalisation. As the cohorts were not entirely comparable, it is difficult to draw any solid conclusions regarding how the effectiveness of the regimens. Nevertheless, our findings, along with previous reports, support the use of Cy over BEAM for conditioning in ASCT for RRMS, due to its preferable safety profile.

IV. In paper IV, combining bortezomib, bendamustine and melphalan as conditioning therapy at ASCT for previously transplanted relapsed multiple myeloma was well tolerated but not superior to high-dose melphalan, although a trend towards better effectiveness was seen most notably in overall survival. The relative reduction in progression-free survival between ASCT2 and ASCT1 was significantly lower in the BBM-cohort, motivating further investigation in larger studies.

Future perspectives

Research in medical sciences, as all others, is conducted in the borderlands of current knowledge and the unknown. The importance and relevance of a method such as ASCT is constantly changing and adapting to new discoveries and technologies. Much of the medical community is gazing beyond the era of treating malignancies with chemotherapy, towards treatments with more specified targets, to achieve better responses, and even cure, while limiting the toxicities of the treatment. In this perspective, ASCT represents the old-fashioned and obsolete. However, it stands as the best available treatment until the next best treatment has arrived. The fact that ASCT still stands tall in the treatment of both MM and lymphoma after 40 years is a confirmation of its effectiveness. The future role of ASCT is unknown; when will it be used, how will it be performed and for which patients.

This thesis touches on several aspects of how a treatment evolves to adapt to a new therapeutic landscape. What to do with the treatment in the situation of a pandemic? Can we treat other diseases with the same method, for which it was not designed, in a safe and effective way? Can we improve the method by incorporating new agents? These questions are relevant and important to address if a certain therapeutic method should be able to stay up-to-date and stay in use.

Study I was conducted during the peak of the COVID-19 pandemic in 2020 and tempers the alarming studies that were published in the first year of the pandemic. It underscores the importance of using robust methodologies that include all patients within the population rather than only those who are hospitalised, to accurately assess the impact of a novel infectious agent on a specific patient group.

Although the timing of the next pandemic is unknown, we can be sure that it will happen repeatedly. Our study highlights the need for the scientific society to react more moderately and avoid overreliance on rapidly produced studies where patient selection is not clearly defined or representative.

While the role of ASCT in management of MM is increasingly being questioned, growing evidence supports its effectiveness in the field of autoimmune diseases in general and RRMS in particular. This research program includes the most ambitious study of AEs for ASCT for MS to date, an area which is

the major reason for the hesitation to use this method in MS. Furthermore, this study program evaluates which conditioning regimen is preferred at ASCT in MS, aiming to minimize treatment related risks without compromising therapeutic effectiveness.

The use of ASCT for autoimmune disease has been limited since the method was first introduced, though the effectiveness of the treatment is excellent. It may be due to the idea of giving chemotherapy to patients without a malignancy. With this study, we confirm the effectiveness of ASCT, as two thirds of the patients have had no new sign of the disease 10 years after the treatment. Additionally, we can show no treatment-related mortality and manageable adverse events from 16 years of experience. With this study, we can show the feasibility of ASCT in routine healthcare, making it a motivation to use the method for highly active RRMS.

Although the use of Cy increased in use in the last years, it is still controversial which conditioning regimen is favourable in ASCT for multiple sclerosis. The results of paper III follow the rationale that the BEAM protocol is myeloablative and of slightly higher intensity than Cy. There is a tendency of BEAM showing more effectiveness, but that comes with the cost of significantly more toxicity. As the toxicity is also what is holding the method back, especially for non-malignant diseases, there is a clear rationale for choosing the least toxic method to achieve good results.

For ASCT to be more used in the treatment of MS, clearer evidence of which patient should be selected is needed. It is a challenge, in a time where many new exciting, and much less toxic, therapeutic options have emerged. It takes a long time to evaluate whether they can challenge ASCT in terms of effectiveness. It is difficult to say which way the method will go in terms of treating MS, but as long as there is hesitation, the use of ASCT for autoimmune disease will be held back. If nothing else, ASCT could hold a place for patients with immune systems that has run amok and there is nothing else to do but to pull the emergency brake. It would be in the interest of many young patients who have seen their neurological abilities rapidly deteriorate, to avoid any such episode in the future. If more patients would be presented with the option of ASCT, it is likely that the use would increase.

Multiple myeloma can be regarded as a success story of ASCT treatment, but it might very well be the next indication where ASCT is outcompeted. For example, the recently reported Triangle trial challenges the benefit of ASCT if adding ibrutinib maintenance for mantle cell lymphoma.[377] The development of novel therapeutic agents is far more extensive for MM than for mantle cell lymphoma. It is not unlikely that continuous treatment with a broadly effective novel agent, used until progression will show superiority over ASCT in the near future. Such development is desirable, but it can also be a case of weighing pros and cons. Many novel cancer agents are carrying a high economic burden for health care systems. It might not always be feasible to treat

until progression when the cost per year significantly exceeds the cost of performing an ASCT.

In MM, ASCT performed after induction therapy can keep the patient in remission for more than ten years, a few examples of this can be seen in paper IV. However, it is not all the patients who can enjoy such effect of the treatment. Patients with p53-abberrations, a tumour suppressor protein, often referred to as the guardian of the genome, has significantly poorer prognosis. If p53 is not functioning correctly, it diminishes the body's ability to fight cancer including MM. Additionally, p53-abberations, or deletion of the whole short arm of the chromosome carrying the p53-gene, as part of a del(17p) results in decreased susceptibility to chemotherapy.[378,379] Furthermore, patients with high-risk cytogenetics including del(17p), or the long arm of chromosome 13 (del(13q)) as well as translocations such as t(4;14) have been shown to have less benefit of ASCT.[380,381] These patients, along with old or unfit patients not eligible for ASCT, would benefit greatly of superior and less toxic alternatives to ASCT, but then again that would be the case for all patients.

It surely would be a beautiful thing, if medicine could move away from treating patients with such toxic compounds that have been described in this thesis, which affect all cells that happen to be dividing at the time of exposure to the treatment. Until that day, studies like these will continue to search for ways of reaching remission and cure, in a safer way, and to lesser cost for the patients.

Populärvetenskaplig sammanfattning

Benmärgen är ett halvflytande organ som finns inuti håligheterna i stora ben hos alla däggdjur, och det är den som bildar blodets celler. Blodcellerna delas upp i röda blodkroppar (som transporterar syre från lungorna till kroppens celler), vita blodkroppar (som är vårt aktiva immunförsvar) och blodplättar (som stillar blödning). Läran om benmärgens sjukdomar kallas för hematologi.

Autolog blodstamcellstransplantation (ASCT) är en metod som utvecklades för att behandla cancersjukdomar som har sitt ursprung i benmärgen. Autolog betyder att man tar stamcellerna från patienten själv och inte från en donator. Metoden består av flera steg och börjar med att man stimulera blodstamcellerna att lämna benmärgen och ta sig ut i blodcirkulationen. Detta åstadkoms genom att behandla patienten med en kombination av tillväxtfaktorer och cellgifter. När detta har skett skördar man stamcellerna med en apparat som renar ut stamcellerna ur blodet. Därefter fryses stamcellerna ned i flytande kväve, och hålls frysta till dess att patienten ska få tillbaka sina stamceller igen. Under tiden får patienten återhämta sig, innan det är dags att behandla patienten med höga doser cellgifter som syftar till att ta bort så många sjuka celler som det går.

Cellgifter verkar mot celler som delar på sig, oavsett om cellerna är friska eller sjuka. Ett av cancercellers karaktärsdrag är att de delar sig ovanligt ofta, och därför påverkas de mycket mer än kroppens friska celler av cellgifter. Det organ i kroppen där cellerna delar sig oftast är benmärgen, som alltså utgör den begränsande faktorn när man behandlar med höga doser cellgifter. Att ta ut blodstamcellerna innan ASCT syftar till att skydda dem mot cellgifterna, och gör att det är möjligt att behandla benmärgscancern tuffare än vad som annars skulle ha varit möjligt.

När cellgifterna har utsöndrats tinar man upp stamcellerna och återför dem till patienten via blodet. Stamcellerna letar sig tillbaka till sitt normala hem i märgrummen i alla stora ben i kroppen och börjar därefter att dela på sig, vilket ger upphov till nya blodceller. Vanligtvis tar det 10–14 dagar för de nya blodcellerna att komma ut i blodcirkulationen, och under denna tid är patienten mycket känslig för infektioner, kan vara lättblödande och behöva transfusion av röda blodkroppar och blodplättar. Andra vanliga biverkningar kommer från kroppens slemhinnor som exempelvis illamående, sår och diarréer.

Den första studien i den här avhandlingen utfördes under COVID-19 pandemins första år och utvärderade hur patienter som behandlades med ASCT under det året påverkades om de blev smittade med SARS-CoV-2 (viruset som orsakar COVID-19). Under lång tid var de enda vetenskapliga rapporter som fanns tillgängliga relativt alarmistiska och rapporterade mycket höga dödstal bland hematologiska cancerpatienter, vilket ledde till att många transplantations-center tvekade till att fortsätta ge behandlingen. I studien samkördes data från Socialstyrelsens register för smittsamma sjukdomar, där alla som testats positivt för SARS-CoV-2 registreras, med alla patienter som hade behandlats med ASCT i Sverige. Av 442 patienter som behandlades blev 20 (4,5%) smittade med SARS-CoV-2-viruset. Två tredjedelar av dessa behövde inte sjukhusvård, men båda de patienter som behövde intensivvård dog sedermera till följd av COVID-19. Studien kunde visa att trots att detta var mitt under COVID-19-pandemin, var problemet begränsat och risken att bli smittad efter ASCT var jämförbar med resten av befolkningen.

I den andra studien beskriver vi hur det går för patienter med skovvist förlöpande multipel skleros (MS) som behandlas med ASCT. MS är en autoimmun sjukdom vilket innebär att kroppens immunförsvar har börjat attackera sig själv. Vid MS sker dessa attacker mot det centrala nervsystemet (hjärnan och ryggmärgen), varför patienter med denna diagnos får olika typer av neurologiska funktionsnedsättningar. MS är den vanligaste orsaken till kronisk neurologisk funktionsnedsättning bland unga vuxna i världen. Behandlingen av MS syftar till att minska immunförsvarets attack mot nervsystemet.

Sedan 1990-talet har man beskrivit att man kan behandla autoimmuna sjukdomar med ASCT. Man tror att ASCT nollställer immunförsvaret och på så vis kan man släcka ut angreppet på den egna kroppen.

Vi samlade alla 174 patienter med skovvist förlöpande MS som hade genomgått ASCT fram till år 2020 i Sverige och utvärderade behandlingseffekten med hjälp av data från det svenska MS-registret. Patientjournaler användes för att bedöma biverkningar av behandlingen. Många av patienterna hade aktiv MS med mycket inflammation innan ASCT, men trots det hade två tredjedelar (65%) inte något tecken till aktivitet i sjukdomen 10 år efter behandlingen. Vi kunde också visa att en majoritet av patienterna (54%) förbättrades i sin neurologiska funktionsnedsättning efter behandlingen, vilket är ovanligt vid andra behandlingsmetoder. Patienterna hade i genomsnitt 1,7 skov per år innan ASCT och 0,035 efter behandlingen. Ingen patient dog av behandlingen. Vi kunde med denna studie visa att ASCT är en effektiv och säker behandlingsmetod även när den används i klinisk rutinsjukvård utanför vetenskapliga behandlingsstudier.

Den tredje studien använder samma data som samlades in för den andra studien, men här jämför vi de två mest använda cellgiftsbehandlingarna som ges

vid ASCT, s.k. konditioneringsbehandlingar. Dessa två är högdos cyklofosfamid tillsammans med antikroppsbehandlings som riktar sig mot T-celler, och en kombination av fyra olika cellgifter (BEAM) och samma T-cellsbehandling. Det finns inte någon samstämmighet i vilken av dessa behandlingar man ska välja vid ASCT för MS. I studien jämförde vi 33 patienter som behandlades med BEAM och 141 patienter som fick högdos cyklofosfamid. Vi kunde inte påvisa någon statistisk skillnad i hur effektiva behandlingarna var, men däremot gav BEAM mer svåra biverkningar, mer infektioner när immunförsvaret var lågt och krävde längre sjukhusvård. Våra resultat stödjer därför att välja högdos cyklofosfamid framför BEAM vid ASCT för MS.

I den fjärde studien utvärderar ny kombination av konditioneringsbehandling för sjukdomen multipelt myelom (MM) som är en form av benmärgscancer. MM är en kronisk sjukdom som drabbar ungefär 700 personer i Sverige per år,[382] och utgör 10% av hematologisk cancer och 1% av all cancer generellt. ASCT har använts i behandlingen av MM sedan 1980-talet, men bara till i övrigt väsentligen friska patienter upp till drygt 70 år. Den helt dominerande konditioneringsbehandlingen är (och har alltid varit) högdos melfalan, trots att många nya behandlingar för MM har kommit in på marknaden de senaste 20 åren. Bortezomib är en sk proteasomhämmare som förhindrar cancerceller att återanvända sina egna proteiner. Bendamustin är ett cellgift som tillhör samma grupp som melfalan.

I den här studien jämför vi hur behandlingskombinationen bortezomib-bendamustin-melfalan (BBM) står sig mot högdos melfalan (HDM) hos patienter som har fått återfall av MM efter att ha fått ASCT i första behandlingslinjen. Mellan 1 november 2011 och 31 oktober 2018 behandlades sådana patienter med BBM på Akademiska sjukhuset i Uppsala. Som jämförelse har vi identifierat patienter som fick HDM i samma situation före och efter denna period. Vi inkluderade 43 BBM och 43 HDM-patienter och jämförde båda grupperna med varandra. Generellt sett förväntar man sig en kortare behandlingseffekt när man ger ASCT andra gången jämfört med den första. Vi kunde se att den relativa minskningen i tid till sjukdomen hade återkommit var mindre hos BBM-behandlade patienter, vilket talar för att kombinationen är mer effektiv. Dessutom kunde vi ana en skillnad i överlevnad, även om den inte vara statistiskt säkerställd, till fördel för BBM. Biverkningar var i stort sett likvärdiga, förutom att det fanns en trend emot att BBM gav mer feber i den infektionskänsliga perioden som följer efter en ASCT. Sammanfattningsvis såg vi en trend av bättre effektivitet för BBM i alla effektmått inklusive en antydan om bättre överlevnad, vilket motiverar ytterligare och större studier med denna behandlingskombination.

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