Stem Cell Transplantation: Home Care, Graft-versus-Host Disease and Costs

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Stockholm 2006
To the ones who have encouraged and believed in me!
This is Patrik who was treated at home.

On his way home the day after ASCT
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SUMMARY

Allogeneic stem-cell transplantation (ASCT) is used to treat malignant and non-malignant diseases of the immunohematopoietic system. Results in terms of survival rate and less complications are continually improving due to better knowledge, supportive care, immunosuppression, new drugs against infections and HLA-typing techniques. In transplant centres worldwide patients undergoing ASCT are treated in protective environments such as laminar airflow rooms, plastic bubbles, or reversed isolation. However, the isolation may lead to undesired psychosocial side-effects for the patient. The main aim of this thesis was therefore to investigate whether it was safe and feasible to treat patients undergoing ASCT during the pancytopenic phase at home instead of at the hospital. Moreover, as the ASCT and post-transplant therapies are considered to be expensive, costs of ASCT and the treatment of severe GVHD grades III-IV were evaluated. Paper I introduces a new approach showing it to be safe to treat patients undergoing ASCT at home as much as possible during the pancytopenic phase. In paper II, home-care was offered and evaluated in a larger group of patients. The study showed that the home-care regimen resulted in significantly reduced needs of total parenteral nutrition (TPN) (p=0.01) and analgesics (p=0.05); fewer patients with acute GVHD grades II-IV were identified (p<0.01); the time to discharge was shortened (p=0.01); there was less transplant-related mortality (TRM) (p<0.01); and there was a significantly better survival (p<0.03), compared with hospital-care. Because less acute GVHD could predispose less chronic GVHD and increase the risk for relapse, we conducted a long-term follow-up study of the patients regarding this (paper III). However, no significant differences regarding chronic GVHD and relapse rate could be found in the home-care group, compared to the hospital-care group. In paper IV, a more developed system for cost analysis was used, were the initial and the five consecutive post ASCT yearly costs were identified. It was showed that re-transplantation (p=0.004), prophylactic use of granulocyte colony-stimulating factors post ASCT (p=0.008), acute leukemia (p=0.008) and major complications, such as GVHD, bacteremia, hemorrhagic cystitis, and veno-occlusive disease of the liver, were associated with increased costs. In contrast, reduced intensity conditioning (p=0.01) and home-care (p<0.05) reduced the costs. In paper V, survival rate and costs regarding treatment of infections and severe acute GVHD (grades III-IV) between 1975 and 2004 were analysed. Since year 1999, the survival rate in patients with GVHD grades III-IV has improved significantly (9% vs. 21%, p=0.02); however, this improvement was found to be related to high costs.

To conclude, home-care may be offered during the pancytopenic phase to patients undergoing ASCT. Home-care may reduce the risk for acute GVHD, improve survival, and reduce the costs for ASCT. Major complications are costly. This thesis forms the basis for future strategies to further improve the patient care and to limit major transplant-related complications and costs.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their Roman numbers:

I  Is it safe to treat allogenic stem-cell transplant recipients at home during the pancytopenic phase? A pilot trial.
   Svahn B-M, Bjurman B, Myrbäck K-E, Aschan J and Ringdén O.
   Bone Marrow Transplantation. 2000;26:1057-1060.

II Home-care during the pancytopenic phase after allogeneic hematopoietic stem-cell transplantation is advantageous compared with hospital-care.
   Blood. 2002;100:4317-4324.

III Long-term follow-up of patients treated at home during the pancytopenic phase after allogenic hematopoietic stem-cell transplantation.
   Svahn B-M, Ringdén O, Remberger M.
   Bone Marrow Transplantation. 2005;36:511-516.

IV Costs of allogeneic hematopoietic stem-cell transplantation.
   Svahn B-M, Alvin O, Ringdén O, Gardulf A, Remberger M.
   Transplantation. Resubmitted.

V Treatment, costs and survival in patients with grades III-IV acute graft-versus-host disease after allogenic SCT during three decades.
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<td>ACD</td>
<td>Acid-citrate-dextrose</td>
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<td>ALG</td>
<td>Anti lymphocyte globulin</td>
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<td>ALL</td>
<td>Acute lymphoid leukemia</td>
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<td>AML</td>
<td>Acute myeloid leukemia</td>
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<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
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<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<td>ASCT</td>
<td>Allogeneic stem-cell transplantation</td>
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<tr>
<td>ATG</td>
<td>Antithymocyte globulin</td>
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<tr>
<td>BM</td>
<td>Bone marrow</td>
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<td>BMT</td>
<td>Bone marrow transplantation</td>
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<td>Bu</td>
<td>Busulphan</td>
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<td>CML</td>
<td>Chronic myeloid leukemia</td>
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<td>CMV</td>
<td>Cytomegalovirus</td>
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<td>CNS</td>
<td>Central nerve system</td>
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<td>CR</td>
<td>Complete remission</td>
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<td>CP</td>
<td>Chronic phase</td>
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<td>CTL</td>
<td>Cytotoxic T-lymphocytes</td>
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<td>CVK</td>
<td>Central venous catheter</td>
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<tr>
<td>Cy</td>
<td>Cyclophosphamide</td>
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<tr>
<td>DFS</td>
<td>Disease-free survival</td>
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<tr>
<td>DLI</td>
<td>Donor lymphocyte infusion</td>
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<tr>
<td>EBMT</td>
<td>European Group for Blood and Marrow Transplantation</td>
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<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
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<tr>
<td>G-CSF</td>
<td>Granulocyte colony-stimulating factor</td>
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<tr>
<td>GM-CSF</td>
<td>Granulocyte monocyte colony-stimulating factor</td>
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<tr>
<td>GVHD</td>
<td>Graft-versus-host-disease</td>
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<td>GVL</td>
<td>Graft-versus-leukemia</td>
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<tr>
<td>Gy</td>
<td>Gray</td>
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<tr>
<td>HC</td>
<td>Hemorrhagic cystitis</td>
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<tr>
<td>HEPA</td>
<td>HEPA filter airflow</td>
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<td>HLA</td>
<td>Human leukocyte antigen</td>
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<td>HSCT</td>
<td>Hematopoietic stem-cell transplantation</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
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<tr>
<td>IBMTR</td>
<td>International Bone Marrow Transplant Registry</td>
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<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>i.v.</td>
<td>Intravenous</td>
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<tr>
<td>KUH</td>
<td>Karolinska University Hospital, Huddinge</td>
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<tr>
<td>LAF</td>
<td>Laminar airflow room</td>
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<tr>
<td>MDS</td>
<td>Myelodysplastic syndrome</td>
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<tr>
<td>MLC</td>
<td>Mixed leukocyte culture (response)</td>
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<tr>
<td>MMF</td>
<td>Mucophenolate mofetil</td>
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<tr>
<td>Mtx</td>
<td>Methotrexate</td>
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<tr>
<td>MUD</td>
<td>Matched unrelated donor</td>
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<td>NMDP</td>
<td>National Marrow Donor Program</td>
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<td>PBSC</td>
<td>Peripheral blood stem-cell</td>
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<td>PCA</td>
<td>Patient controlled administration</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PTLD</td>
<td>Post-transplant lymphoproliferative disorder</td>
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<tr>
<td>PUVA</td>
<td>Psoralen ultraviolet ligth A</td>
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<tr>
<td>RIC</td>
<td>Reduced intensity conditioning</td>
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<tr>
<td>SAA</td>
<td>Severe aplastic anemia</td>
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<tr>
<td>SCID</td>
<td>Severe combined immunodeficiency</td>
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<tr>
<td>SCT</td>
<td>Stem-cell transplantation</td>
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<tr>
<td>TBI</td>
<td>Total body irradiation</td>
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<tr>
<td>TcD</td>
<td>T-cell depletion</td>
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<tr>
<td>TPN</td>
<td>Total parenteral nutrition</td>
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<tr>
<td>TRM</td>
<td>Transplant related mortality</td>
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<tr>
<td>VOD</td>
<td>Veno-occlusive disease</td>
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<tr>
<td>VZV</td>
<td>Varicella zoster</td>
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<td>QoL</td>
<td>Quality of life</td>
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INTRODUCTION

Hematopoietic stem-cell transplantation
Since the first bone marrow transplantation in 1957 (Thomas et al., 1957, Mathe et al., 1959), allogeneic stem-cell transplantation (ASCT) has developed into a routine treatment for leukemia, metabolic diseases, severe combined immunodeficiencies (SCID) and solid tumour diseases. The possibility to use this life-saving therapy is based on major medical breakthroughs, - e.g., the discovery of the human leukocyte antigen system (HLA), the treatments and prophylaxis of graft-versus-host disease (GVHD) and veno-occlusive disease of the liver (VOD), the development of new immunosuppressive drugs and new drugs to treat infections. Also the supportive care has improved by giving total parenteral nutrition (TPN), platelets and blood transfusions.

To prevent infections during the aplastic phase after the ASCT, many strategies are used. Isolation techniques, such as laminar airflow (LAF) room, conventional protective isolation with single room, hand washing, gloves, mask, and gown or HEPA filtered air (HEPA) with or without LAF are used (Buckner et al., 1978, Passweg et al., 1998). Passweg et al. compared conventional protective isolation with single patient room and any combination of hand washing, gloves, mask and gown, HEPA filters, and/or LAF rooms (1998). The study showed a significantly lower transplant related mortality (TRM) and a significantly higher 1-year survival for patients treated in HEPA and/or LAF rooms.

Home-care of patients undergoing ASCT
Important measures have been taken to facilitate the treatment- and life situation for patients with hematological malignancies, - e.g., self-administered, outpatient parenteral antibiotic therapy have been evaluated and found to be a safe therapy alternative during an episode of fever/infections, instead of re-admitting the patient to the hospital. The patients were also found to be satisfied with their increased independence (Johansson et al., 2001). Also self-administration of pamidronate at home has been found to increase the patients’ independence, although they also described a feeling of anxiety (Johansson et al., 2005).

For patients undergoing ASCT, the established isolation during the aplastic phase after the transplantation may lead to undesired psychosocial side effects for the patient and he/she may experience a loss of control and put him/her in a state of dependency (Mack, 1992).

When this thesis was initiated, only one study had specifically explored the possibility of letting patients undergoing ASCT spend some of their time at home instead of in the hospital. This new care approach was introduced in 1992 by Russel et al. (Russell et al., 1992). Patients living close to the hospital were allowed to go home for a few hours during daytime or sometimes over night. It was found that the patients seemed to appreciate their increased freedom and were less anxious about being discharged. Before the new regimen was introduced, the policy was to give all ASCT patients one-to-one nursing care. The mortality data for patients allowed to spend time at home compared favourably with those from hospitals with strict isolation procedures, which led to the conclusion that ASCT may be safely completed in some institutions
without either protective isolation or the need to confine patients continuously in the hospital (Russell et al., 1992).

In 1997 Meisenberg et al. showed that an outpatient, post-transplant management was safe and significantly reduced the hospital stay also for autologous stem-cell transplantation (SCT) patients (Meisenberg et al., 1997).

**Acute and chronic GVHD**

GVHD appears in an acute or chronic phase. Acute GVHD appears most often in the first two to three months after the ASCT. The main target organs are skin, liver, and gut. However, in the chronic phase, other tissues might be involved, - e.g. mucous membranes, conjunctivae, exocrine glands, bronchial tree, and urinary bladder epithelium (Sullivan et al., 1981). Acute GVHD is graded on a scale from 0 to IV. Grade 0 indicates no GVHD, while grade IV indicates a severe, lethal acute GVHD (Glucksberg et al., 1974, Armitage, 1994). To minimise the risk of GVHD, patients are almost always given immunosuppressive prophylaxis with a few exceptions (Table 3). (Lazarus et al., 1984, Sullivan et al., 1989).

**ASCT, GVHD and costs**

ASCT is considered to be an expensive treatment (Mishra et al., 2001, Lee et al., 1998, Lee et al., 2000, de Lissovoy et al., 2005). Mishra et al. showed one-year mean costs for ASCT to be US$ 106,825 (range US$ 24,375-362,429) (Mishra et al., 2001). In this study, no costs for treatment in other hospitals during this year were included. Lee et al. included six-month costs for ASCT patients in a study and showed that the median cost was US$ 196,200 (Lee et al., 1998). In 2000, Lee et al. showed complications to be expensive in both autologous and allogeneic SCT. The study collected costs from hospital admission until discharge up to the first 100 days (Lee et al., 2000).

Costs and consequences were evaluated in a cost-effectiveness (per gained life-year, by ASCT) study. In this study, patients with no available donor were compared with patients who received an ASCT. Patients with acute myeloid leukaemia (AML) in complete remission (CR) (2nd CR) had a better outcome, while acute lymphoid leukemia (ALL) (1st CR) patients had similar outcome and similar costs with ASCT, compared to those who received conventional therapy (Barr et al., 1996). Some studies have been performed comparing different regimens; in a comparison between costs of treatment using chemotherapy vs. ASCT or autologous SCT, the total cost for both ASCT and autologous SCT were found to be significantly more expensive compared to chemotherapy (p≤0.01 and p≤0.0001, respectively) (Dufoir et al., 1992). In a study comparing costs regarding T-cell depletion vs. un-manipulated grafts for the prevention of GVHD in ASCT, no difference between the groups was found (de Lissovoy et al., 2005).

None of the previous studies followed up costs as long as up to five years after the ASCT and none investigated costs and survival in relation to treatments for infections and severe acute GVHD grades III-IV. Acute GVHD (grades III-IV) is torturous for the patients as well as expensive. To investigate if treatments such as anti-T-cell antibodies, liposomal amphotericin-B, i.v. IgG and/or other therapies improved the survival rate and if the time with severe GVHD were prolonged, we performed an evaluation of this including costs.
HISTORY

In 1891, Brown-Sequard and d’Arsonaval, due to an anecdotal report, performed allogeneic bone marrow transplantation (BMT) by giving a patient who suffered from anemia due to leukemia bone marrow orally. This was of course not successful but a guideline for the future. In 1922, Fabricious & Moeller, investigators from Denmark, showed that if the legs of guinea pig had been shielded during total body irradiation (TBI), the usual depression of platelet counts and post irradiation hemorrhagic diathesis was prevented (Fabricious-Moeller, 1922).

It took several years until Jacobson et al. took the next step when they showed that mice exposed to lethal doses of irradiation were saved from death by shielding the spleen, a hematopoietic organ (Jacobson et al., 1949). They also noticed that the protecting effect could be accomplished by an intraperitoneal injection of spleen cells. This was discovered in the late 1940s and was of great interest, since nuclear bombs were used at the end of World War II. Nuclear irradiation makes bone marrow non-functional, a condition that ends in death.

Lorenz et al. showed that mice exposed to lethal doses of irradiation could be protected from death by injecting syngeneic bone marrow (Lorenz et al., 1951). They also showed that marrow could be used to protect the patient from lethal irradiation (Lorenz et al., 1952, Lorenz and Congdon, 1954). Later, Main et al. showed that skin from an allogeneic marrow donor was accepted by the marrow recipient (Main and Prehn, 1955). Ford showed that colonization of the recipient by donor cells minimized the lethal effect of TBI (Ford et al., 1956). He used the term “radiation chimera” for animals showing a foreign hematopoietic system after TBI followed by allogeneic stem-cell transplantation (ASCT).

These advances lead to much research, but Donnall Thomas and his team produced the first significant research. They performed the first successful ASCT in human (Thomas et al., 1957). A patient suffering from endstage leukemia had been irradiated with lethal doses and reconstituted with bone marrow from a sibling. This patient was not cured, but it was possible to see that the donor stem-cells developed into hematopoietic cells. For this important milestone, Donnall Thomas was awarded with the Nobel Prize 1990.

The late 1950s and early 1960s were filled with frustration and disappointment. Most transplants were performed in endstage leukemia patients who often died before evaluation. If they received grafts, they died from GVHD or infections (Bortin and Saltzstein, 1969). Many recipients got their grafts from donor tissues that were not typed.

The knowledge of the HLA-system developed during the 1970s and is one reason for successfully performed stem-cell transplantations today (Dausset, 1958, Van Rood et al., 1958). This discovery made it possible to match donor and recipient. Two patients suffering from severe combined immunodeficiency and Wiskott-Aldrich syndrome, respectively, were transplanted with cells from matched sibling donors in 1968 and they are still alive (Gatti et al., 1968, Bach et al., 1968).

Improved immunosuppression was another important step to improve ASCT results. Initially, methotrexate (Mtx) was used as a single agent to prevent GVHD (Storb et al., 1986, Ringden et al., 1993). During the 1980s, cyclosporin alone or
combined with corticosteroids or Mtx was used (Storb et al., 1986, Ringden et al., 1986, Ringden et al., 1993). Cyclosporin combined with Mtx significantly decreased GVHD and improved survival compared to monotherapy. This combination has been used since then.

In 1974, the United Kingdom established the first registry for unrelated donors: The Anthony Nolan Registry. The mother of Anthony Nolan, a patient who was unable to be matched with a suitable donor, started this donor registry. The first ASCT using an unrelated donor to treat a patient suffering from a hematological disorder was performed by Hansen et al. (Hansen et al., 1980). Today there are about nine million healthy donors in registries all over the world. The largest organisation is the National Marrow Donor Program (NMDP) in USA, with about six million donors. In Sweden, the Tobias Registry has 40,000 donors. Until the end of 2005, about 2,400 transplantations have been performed in Sweden. Of these, about 1200 transplantations have been performed at KUH/Huddinge and more than 400 were with unrelated donors.

Definition
Allogeneic stem-cell transplantation involves non-genotypic stem-cells from a healthy donor if the recipient is not an identical twin. If the recipient is a genotypic identical twin, the transplantation is a syngeneic transplantation. The same technique as with ASCT is used with autologous stem-cell transplantation (SCT), but the treatment uses the patient’s own stem-cells.

The HLA system
All children inherit human leukocyte antigen from their parents, one haplotype from the mother and one from the father. The HLA system is divided in two parts – class I and II. Class I contains HLA-A, -B, and -C. Class II includes DR, DP, and DQ. In 1958, Dausset described the first HLA; Dausset called the antigen MAC (HLA-A2) (Dausset, 1958). In 1968, HLA-A and -B were established. HLA-C was identified 1971 and HLA-D in 1980 (Dupont et al., 1980). Dupont also established that antigens in the HLA-A and HLA-B locus linked to the locus HLA-DR and defined the mixed leukocyte response (MLC). To be a compatible donor, HLA-A, -B, and -DR have to be identical. The outcome after ASCT is very much up to the HLA-typing technique. It is important to find a donor who is identical for as many HLA antigens as possible.

In the early days, major blood group incompatibility was not accepted. Graw et al. was the first to transplant successfully blood group A to a recipient with blood group O (Graw et al., 1974). This was done after plasmapheresis where Witebsky’s A substance lowered the anti-A antibody titre in the recipient. ABO-mismatched transplantation do as well as ABO-matched graft (Buckner et al., 1978). Today erythrocytes in the stem-cell graft are removed if the donor has a major ABO mismatch.

Donors and sources
To perform an ASCT, a healthy HLA-compatible or partly matched donor has to be available. There are several donor alternatives: a sibling donor, other related donors, or an unrelated donor. Different sources can be chosen from these donors: bone marrow (BM), peripheral blood stem-cells (PBSC), umbilical cord blood, or fetal liver cells. An HLA-identical sibling donor is preferable; the possibility of HLA-identity when having
a sibling is 25%. A genotypic twin can provide cells that are identical to the recipient but unfittingly associated with increased risk of relapse. The chance to have an identical twin donor is around 1%. If there are no siblings, an unrelated HLA–compatible donor can be almost as good as a sibling donor (Ringden et al., 1995). If there is no suitable HLA-identical donor, an HLA mismatched or cord blood donors may be alternatives.

In Paris in 1998, Gluckman performed the first cord blood transplantation (Gluckman et al., 1989). The cord blood graft was from an HLA-identical sibling. One decade later, unrelated cord blood was used for hematopoietic stem-cell transplantation (HSCT) (Kurtzberg et al., 1994, Wagner et al., 2002). Unrelated cord blood graft may be used in children because cell dose is important and should be above 2 x 10^7 nucleated cells/kg. If there are enough stem-cells in the graft, it can also be used for adult patients. Advantages with cord blood are that the naïvety of the graft produces less risk of viral infection and lowers risk of GVHD. A disadvantage is that less stem-cells/kg recipient weight leads to longer time to engraftment, a high risk of graft failure, and an increased risk of infections (Broxmeyer et al., 1989). Furthermore, if in the future stem-cells or lymphocytes are needed to treat the patient, it is impossible to harvest more cells from the same donor. Short-term survival in recipients of cord blood transplantations is similar to that of recipients of bone marrow from related or unrelated donors (Gluckman et al., 1997).

If there is no HLA-compatible related or unrelated donor available and the patient has a high-risk disease, a haploidentical family member may be used (Hughes-Jones et al., 1991, Aversa et al., 1994). This is recommended especially in pediatric recipients (Handgretinger et al., 2001). Another source is fetal liver cells, which can be injected in the uterus to treat the fetus with for example SCID (Touraine et al., 1991). Immunocompetent fetuses will reject the transplant (Westgren et al., 1996).

In addition, finding a compatible donor requires screening of the donor and recipient for herpes viruses, such as cytomegalovirus (CMV). If the recipient is CMV seronegative, a seronegative donor is preferred (Paulin et al., 1986). If the recipient is CMV seropositive and gets a T-cell depleted related graft or a graft from an unrelated donor, the donor should preferentially be CMV seropositive (Ljungman et al., 2003). A female donor to a male recipient has a worse outcome than any other gender combinations (Gale et al., 1987). Younger donors give more cells, and a high celldose is preferable for the recipient (Paulin, 1992, Sierra et al., 1997, Ringden et al., 2003).

A patient who gets an identical HLA-matched graft has a significantly increased survival, compared with patients who get one or two antigen mismatched grafts (Horowitz et al., 1989). Even so, sometimes the only alternative is to use a haploidentical family donor or an unrelated donor. Hobbs et al. were probably the first to perform ASCT using haploidentical family donors in 1981 (Hobbs, 1981) and the first to use unrelated donor graft was Hughes-Jones et al. (Hughes-Jones et al., 1991). All donors have to go through a medical check up before a donation can be established.

**Harvesting**

Except for fetal liver cells and umbilical cord blood harvesting, there are two ways to harvest hematopoietic stem-cells. In the past, the most common way was to harvest stem-cells from the posterior iliac crest. This is done by introducing a needle into the iliac cave and aspirating one to three ml of BM with blood. The aspiration is repeated
until an acceptable cell count has been reached. For patients suffering from malignant
diseases, more than 2.0x10^8 nucleated cells/kg body weight is acceptable and for
patients suffering from non-malignant diseases, more than 3.0x10^8 nucleated cells/kg
body weight is desirable (Storb et al., 1977).

The aspirated BM is filtered into a bag containing heparin and/or acid-citrate-
dextrose solution (ACD). This procedure is performed at the operating room under
sterile conditions and with the donor in general or spinal anesthesia. After this
procedure, most donors are back to work within 14 days. Some donors suffer from
anemia even after getting back the earlier collected autologous blood, and most of them
have pains in the hip.

Today PBSC more often are used after stimulating the donor with granulocyte
colony-stimulating factor (G-CSF) for four to five days. This stimulation can cause
side-effects, such as headache, muscle pain, and bone pain, which can be treated with
paracetamol per os (Champlin, 1996, Dreger et al., 1994). The first peripheral blood
stem-cell transplantation was autologous and performed in the late 1970s (Goldman et
al., 1978). Eleven years later, Kessinger et al. showed that PBSC were useful also in an
allogeneic setting (Kessinger et al., 1989). It takes three to five hours to harvest PBSCs.
The procedure does not cause anemia and will not keep the donor from work the
following day. With PBSC collection, more stem-cells are collected, which is preferable
for the patient.

The use of PBSC or BM was discussed in the beginning because of the 10-fold
higher number of T-cells in PBSC, a number that was thought to increase the risk for
GVHD (Kessinger et al., 1989). PBSC resulted in faster hematopoietic reconstitution of
neutrophils and platelets, the risk of acute GVHD, survival rate and TRM were similar
compared to BM grafts (Schmitz et al., 1995, Bensinger et al., 1995, Ringden et al.,
2000, Remberger et al., 2001). However, PBSC was associated with more chronic
GVHD (Remberger et al., 2005, Storek et al., 1997).

BM is more frequently used for children and younger adult recipients, because
they have a better survival rate using BM compared to PBSC donors (Eapen et al.,
2004). This may be because children often have younger donors and younger donors
produce a higher stem-cell dose when aspirated from the BM, compared with older
donors. The BM also contains mesenchymal stem-cells in contrast to PBSC (Eapen et
al., 2004). The stem-cells are given i.v. to the recipient.

Indications for ASCT
The patient should be given the best possible treatment and therefore ASCT has to be
compared with alternative treatments in all cases. ASCT is a curable treatment for
malignant and non-malignant diseases. Before ASCT, patients are treated with lethal
doses of chemotherapy and thereafter the patient is rescued by fresh stem-cells from a
healthy donor.

Issues that are decisive are the patient’s age, status of the disease, and an available
donor. The following diagnoses are accepted indications of ASCT: AML in first
remission or later if the patient is a child (Gale and Butturini, 1989, Gale, 1979). Acute
lymphoblastic leukemia (ALL) in second remission or later; and ALL in first remission
if the patient is considered to be a high-risk patient. Criteria for high-risk includes:
BCR/ABL gene rearrangement, the L3 FAB morphologic type (Burkiitt’s-like), high
blast counts (WBC > 30x10^9/L) at diagnosis, cytogenetic chromosomal abnormalities as t (4;11) and t (1; 19), or −7, +8, age <2 or >15 years, central nerve system (CNS) involvement, mediastinal mass, >6 weeks to obtain remission, or relapse during therapy (Barrett et al., 1989, Wetzler et al., 1999).

Results have improved with time and five-year disease free survival (DFS) are today 59% for patients suffering from AML and transplanted in complete remission (CR) 1. This is results from the International Bone Marrow Transplant Registry (IBMTR) and the corresponding results from the European Group for Blood and Marrow Transplantation (EBMT) are 57%. For children the results are better, 80% - 90%, if transplanted early.

Other indications for ASCT are chronic myeloid leukemia (CML) in chronic phase (CP) (Goldman, 1993) if the CML does not respond to Imatinib (Glivec®) (Pitini et al., 2003). Myeloma grade III has been identified as an indication for ASCT. Intensive myeloablative chemotherapy treatment followed by an autologous transplantation, or an autologous transplantation followed by an allogeneic, is presently evaluated in multicentre studies. Myelodysplastic syndrome (MDS) is a reason for ASCT if the patient does not respond to ordinary treatment, if there are high numbers of blasts in the marrow, or if the patient requires transfusions due to cytopenia. High-risk lymphomas are often treated with autologous transplantations, but in some cases it may be an indication for allogeneic transplantation.

**Non-malignant indications for ASCT**

For severe aplastic anemia (SAA) in patients below 40 years of age, early transplantation is preferable if an HLA-identical sibling donor is available. If patients do not respond to first line therapy, antithymocyte globulin (ATG) and cyclosporin or other immunosuppression, they may be treated with an HLA-matched unrelated donor (Svenberg et al., 2004). Too many blood transfusions sensitise the patient and increase the risk of graft failure (Storb et al., 1977).

Patients with immunodeficiencies such as severe SCID do not have a healthy immune defence and are unable to reject the graft. Therefore, conditioning may not be needed in severe cases where transplantation is done upfront using maternal T-cell depleted stem-cells. However, conditioning is recommended for immunodeficiencies using non-maternal grafts.

Patients with metabolic diseases (diseases with different enzymes produced by hematopoietic cells) can be helped with stem-cells from a healthy donor (Hobbs, 1981, Krivit et al., 1995, Peters et al., 1996, Good, 1975, Good, 1987, Good and Verjee, 2001, Ringden et al., 1988, Hoogerbrugge et al., 1995). These diseases include mucopolysaccharoidoses like Hurler’s disease and Maroteaux-Lamy. Patients with Hurler’s disease require transplantation before two years of age before too many symptoms, especially from the central nerve system are visible, to give meaningful results (Krivit et al., 1995).
Table 1. Diagnosis curable with allogenic stem-cell transplantation

<table>
<thead>
<tr>
<th>Malignant diseases</th>
<th>Non- Malignant diseases</th>
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<tr>
<td>Acute lymphatic leukemia (ALL)</td>
<td>Immunodeficiencies:</td>
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<td>Severe combined</td>
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<td></td>
<td>immunodeficiency (SCID)</td>
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<td>Acute myeloid leukemia (AML)</td>
<td>Wiscott-Aldrich</td>
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<td>Chronic myeloid leukemia (CML)</td>
<td>Chédiak-Higashi</td>
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<td>Chronic lymphocytic leukemia (CLL)</td>
<td>Chronic mucocutaneous</td>
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<td>candidiasis</td>
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<td>Lymphoma</td>
<td>Kostmann’s agranulocytosis</td>
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<td>Multiple myeloma</td>
<td>Mucopolysacchariodosis</td>
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<td></td>
<td>Hurler disease</td>
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<tr>
<td>Myelodysplastic syndrome (MDS)</td>
<td>Maroteaux-Lamy</td>
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<td>Lipidosis</td>
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<td>Metachromatic leukodystrophy</td>
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<td>Adrenoleukodystrophy</td>
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Experimental indications for ASCT

Solid tumours like kidney, colon, gynecologic, pancreatic, and prostate cancer may be helped by ASCT. Childs presented results regarding patients suffering from metastatic kidney cancer (Childs et al., 2000) and Barkholt published results from KUH on patients suffering from colon cancer and patients with kidney cancer (Barkholt et al., 2003, Barkholt et al., 2005). The results show that around one third to one half of the patients respond. Autoimmune disease like psoriasis, multiple sclerosis and inflammatory gut diseases, like Crohn’s disease and ulcerous colitis can be cured (Hinterberger et al., 2002). This was shown when patients suffering from a disease indicated for ASCT also had an autoimmune disease.

STEM-CELL TRANSPLANTATION

Pre ASCT

Before the recipient can be approved for transplantation, he or she has to get through several medical examinations.

*Heart*: To determine the dose of cyclophosphamide (Cy) (maximum dose is 60 mg/kg bodyweight for two days), the condition of the heart must be determined for instance by determination of cardiac ejection fraction (Storb and Thomas, 1972).

*Lung*: The lung has to be clear with no infiltrate. Infiltrate immediately before start of conditioning can be lethal for the patient and must be treated before start of conditioning, if possible.

*Dentist*: A dentist should check mouth and teeth to avoid infections during the neutrophenic phase. If status is not acceptable, this has to be taken care of before start of conditioning.

*Blood*: Blood samples are needed to evaluate current status. Herpes simplex virus (HSV) is checked to see if prophylaxis with acyclovir is indicated. If herpes virus titre...
are more than 10,000 IgG titers (>10 000 ELISA), prophylaxis is preferable (Lundgren et al., 1985).

**Bone marrow:** In some malignant diagnosis, such as ALL, AML, and CML, the BM has to be checked to secure that the patient still is in remission before start of conditioning. With advanced disease the outcome is poor (Ringden et al., 1987).

**Liquor:** In patients with CNS leukemia or a high risk for CNS-leukemia, a liquor analyses must be done to discover if there are any malignant cells in the CNS. Such patients need additional intrathecal injection post transplantation. When the patient has passed the medical examination and there is a suitable donor available, the pre-transplant chemoradiotherapy can start.

**Conditioning**

Until some years ago, it was thought that conditioning was necessary to create space for the new cells and also reduce possible residual malignant cells in the bone marrow. The most common conditioning was Cyclophosphamide (Cy) 60 mg/kg body weight for two consecutive days, followed by a single dose of TBI of 10 gray (Gy). In Seattle, this conditioning was used with a cobalt 60 radiation source (Thomas et al., 1977). The Minnesota group introduced a linear accelerator as an alternative radiation source (Kim et al., 1977), a method that has been used for many years by many centres including KUH/Huddinge. Today we know that the most important reason for conditioning is to suppress the patient’s immune system to reduce the risk of rejection and also to get rid of remaining malignant cells. It is more likely that the malignant cells disappear due to the anti-leukemia or anti-tumour effect associated with ASCT. The most common conditioning for ALL still is Cy and TBI. However, irradiation is given as fractionated doses 300 cGy/day for four consecutives days to reduce side-effects like pneumonitis, inhibited growth, mental development, secondary tumours, cataract and endocrinological disturbances (Peters et al., 1979, Song et al., 1981). Acute complications including fever, vomiting, and parotitis are also reduced with fractionated irradiation. In the late 1960s, busulphan (Bu) combined with Cy became an alternative conditioning (Santos and Haghshenass, 1968). Bu instead of TBI can be used in most patients (Deeg et al., 1984, Sanders, 1991, Witherspoon et al., 1989, Ringden et al., 1994). The most common dose is 4 mg/kg body weight on four consecutive days (Santos et al., 1983, Tutschka et al., 1987) or according to Bu concentration in blood (Hassan et al., 1996, Hassan, 1999). Carefully monitoring of Bu concentration in blood may reduce toxic side-effects like VOD of the liver and hemorrhagic cystitis. Bu is usually administrated orally. If i.v. administration is required, Bu may be more toxic to the patient. However, contradictory data exist. To minimise the toxic effect, liposomal Bu i.v. can be an alternative in the future (Hassan et al., 2002). For small children, a study is ongoing at KUH/Huddinge to see if liposomal i.v. administered Bu is superior to orally administered Bu.

For many years, myeloablative conditioning with high doses of chemoradiotherapy has been the treatment of choice. However, even with no controlled studies between myeloablative and non-myeloablative conditioning, non-myeloablative conditioning is now used more and more. Non-myeloablative conditioning (also called reduced intensity conditioning (RIC) is preferable if older patients are to be accepted for ASCT, or if the patient has any organ dysfunction or is in bad condition (Slavin et al.,
1998, McSweeney et al., 2001). Ongoing studies will discover which patients can benefit from RIC. When using RIC, lower doses of radio-chemotherapy are given, mainly to suppress the patients’ immune system. The idea is that the graft will kill the remaining malignant cells through the graft-versus-leukemia (GVL) even if less acute GVHD appears, which may be due to less cytokine release. RIC is a tempting alternative with fewer side-effects and is less costly (IV).

When choosing conditioning, the recipient’s disease, disease stage, age, donor, and condition have to be taken in consideration. In high-risk malignancies, myeloablative conditioning is preferable. Patients with ALL or AML type M4 or M5 who have or have had CNS involvement are treated with methotrexate (Mtx) intrathecally twice before transplantation and six times after ASCT.

To recipients of unrelated donor transplants at the KUH/Huddinge, ATG is part of the conditioning as rejection and GVHD prophylaxis. Patients (most often children) with inborn errors of metabolism receive full myeloablative conditioning to reduce the risk of rejection.

Cell infusion
The turning point for most patients is cell infusion. All patients have a central venous line; this is usually placed in the vena jugularis externa before stem-cell infusion, blood pressure, temperature, and central venous pressure are measured. Furosemide may be necessary to increase urinary output if the central venous pressure or the blood pressure increases during stem-cell infusion. The donated stem-cells circulate through the bloodstream making their way to the BM, where they can start to reproduce hematopoietic stem-cells in the recipient. Infusing the stem-cells into the BM cavity has been tried, but the results are similar to i.v. introduction (Hagglund et al., 1998). In most cases, the infusion of cells is a simple procedure, but some patients negatively react to ACD solution. In addition, in some patients with a high titre of isohemagglutinines, there are too many ABO-incompatible red cells in the graft. Similar to blood compatibility, BM is ABO-compatible but if there is a minor ABO-mismatch with few expressed ABO-antigens it can be infused without red cell depleted. If there is a major expression of ABO antigens in the donor’s red cells and this is not expressed in the recipient’s cells, this is a major ABO-mismatch. The presence of isohemagglutinines in the recipient plasma specific for these antigens will result in severe hemolysis. Therefore, all major ABO-mismatched donor marrow stem-cells are red-cell depleted (Buckner et al., 1978). The transfusion laboratory always checks the stem-cell product (graft) before infusion to check the blood groups in the donor and recipient and the antibody titre. When PBSC are transplanted, there are not enough erythrocytes to provoke a reaction, but the patient can still react against the ACD solution. If patients negatively react to graft treatment (breathing difficulties, fever, illness, or unconsciousness), corticosteroids can help. The infused volume is 500-1500 ml with BM grafts compared to 250-500 ml with PBSCs. If the recipient is a small child (<15 kg), it may be necessary to reduce the volume to 15 ml/kg (otherwise the volume is not a problem). It may be desirable to get as high CD34+ cell dose as possible. A BM CD34+ dose above 3x10^6/kg is associated with better survival and reduced TRM, a PBSC CD34+ dose above 6x10^6/kg is correlated to a reduced relapse risk and better survival (Ringden et al., 2003). Engraftment can be defined when neutrophils reach 0.5
x $10^9$/L for two consecutive days. Most patients reach $1.0 \times 10^9$ neutrophils/L by day +24 (Storb et al., 1986).

**Protective care**

To prevent infections during the aplastic phase after ASCT, many strategies are used. Recently, improved prophylaxis, diagnostics, and treatment of bacterial, viral, and fungal infections have become available. The neutropenic period often persists for about 2-4 weeks. Isolation techniques such as LAF room, conventional protective isolation with single room, hand washing, gloves, mask, and gown or HEPA filtered air with or without LAF are used (Buckner et al., 1978, Passweg et al., 1998). For children under two years of age, plastic “bubbles” sometimes are used. As with a laminar airflow room, all food and equipment have to be sterilized before it passes through a lock and into the “bubble”. This is not just inconvenient for the patient, it demands more staff and is expensive. In 1998, Passweg JR et al. published a comparative study on outcome after treatment in different environments (Passweg et al., 1998). That study noted a decrease risk of TRM if the patient was treated in HEPA and/or LAF isolation compared to reversed isolation. The benefit was stronger if the donor was an HLA-identical sibling donor.

Patients going through ASCT are easily infected due to their immunocompromised situation. They have to be protected from as many bacteria, viruses, and fungi as possible. This can be done in HEPA or LAF, conventional isolation, or by treating the patient at home as much as possible. At home there may be less multi-resistant bacteria and patient’s immune system may already be adapted to the bacteria.

Patients treated at KUH, Huddinge are treated in conventional single rooms with filtered air and a giro lock. Before entering the room, staff should wash their hands and wear gowns. In the room, patients are allowed to have one relative stay with them. The equipment in the room includes a TV, video, bicycle, and a table where they can place a computer or something else. All patients have a private bathroom with a shower, an amenity that encourages the patient to leave the bed and exercise. The first publication according home-care showed promising results, which resulted in a possibility for the patients treated at the hospital to exercise outdoors. They were allowed to take a walk after 6 pm when there are fewer people in the corridors. All clothes and sheets the patient uses must be cleaned three times a week. The patients and their relatives staying in the room must shower every day. Potted indoor plants are not allowed in the ward. When neutrophils are between $<0.5 \times 10^9$/L on the way down, and $\geq 0.2 \times 10^9$/L for two consecutive days on the way to recover, there are a few dietary restrictions. For example, fresh salad and unpeeled fruit is not acceptable.

**Supportive care**

In many ways supportive care has improved during the last few years. Total parenteral nutrition, platelets and blood transfusions are important parts of the supportive care. Many side effects and complications are clinically diagnosed, making it important to have experienced nurses and physicians to evaluate the patients. Common complications are toxic side effects such as immunosuppression and aplasia due to the conditioning and the treatment given before ASCT. The side effects include mucositis,
infections, HC and liver damage, such as VOD of the liver. Most infections originate from the recipient. To reduce some side effects, prophylaxis is used to prevent pneumocystis carinii, gut bacteria, and fungal infection.

Mucositis often causes serious pain post-ASCT (Chapman et al., 1985). According to the International Association for the Study of Pain, pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. The patient is emotionally and physically involved in the pain, which may make it difficult to classify. The best way to measure pain is to ask the patient. If it is difficult to get sufficient pain relief, an early consultation with a pain specialist is an option. Many patients with cancer are used to painkillers. If they are addicted to narcotics, it is important to stop or reduce the medication before start of conditioning.

CNS related side effects from analgesics are nausea, vomiting, drowsiness, sedation, nightmares, anxiety, euphoria, dysphonic, depression, paranoia, hallucinations and respiratory depression. Other side effects are dry mouth and obstipation, sweating, and urinary retention (Enck, 2000). It is important for survival to minimize sedatives and analgesics to make it possible for a patient to be active and contribute to health. Mucositis pain is common after ASCT; 76% to 90% of the patients receiving myeloablative conditioning suffer from mucositis (Chapko et al., 1989). Patients receiving non-myeloablative conditioning experience less severe mucositis. Mild mucositis appears as erythema and/or mild oral inflammation. This can progress to severe mucositis with ulcers, mucous damage, and patches that are painful to touch. Bleedings often complicate the cleaning of the mouth, which is difficult but necessary. Local and/or intravenous anesthetics can be helpful in serious cases. Viscous lidocaine can be used as topical anesthetics and narcotics as intravenously anesthetics. It is important to encourage and help the patient to eat as much as possible. Intravenous nutrition is not as good as oral intake, but is often necessary. When mucositis damages the oral cavity to such an extent that it is impossible to eat, a feeding tube and/or TPN is the only alternative (Berger, 2001).

Bone pains are not as common as mucositis pain but have to be taken seriously. Some diagnoses, such as multiple myeloma or treatment with corticosteroids for GVHD are associated with bone pains and need to be treated with analgesics. Several studies show that the use of patient controlled administration (PCA) pump is preferable to staff controlled administrated analgesics (Hill et al., 1990, Zucker et al., 1998, Holmer Pettersson, 2004). Patients use less drugs and describes better pain control when they use PCA. This way to administrate analgesics has been used with good results even for children from the age of 4 years (Dunbar et al., 1995).

Studies comparing several kinds of analgesics found morphine to be the drug of first choice (Coda et al., 1997). Neither the drug nor the way to administrate it gives complete pain relief in these severe cases. It is necessary to tell the patients that the drug used will help them tolerate pain, but pain will not disappear completely. With this knowledge it is easier to get satisfactory control of the pain.

Nausea and vomiting are most common when conditioning is ongoing, but sometimes pain remains for up to a month after ASCT. There are several antiemetica that can be tried. It is important to only use a few drugs in the clinic. If the effect is insufficient, the dose may be increased.
Complications in ASCT

Hemorrhagic Cystitis (HC)

HC is a relatively rare, inconvenient and costly side effect of ASCT. Among other factors, this is caused by acrolein. Acrolein is a urinary by-product of oxazophosphorine metabolism that causes direct damage to the mucosa in the bladder. Cy is an oxazophosphorine drug and frequently used for conditioning. Other causes are viruses such as CMV-virus (Russell et al., 1994), adenovirus (Miyamura et al., 1989) and BK-virus (Bedi et al., 1995, Childs et al., 1998) alone or together with GVHD (Seber et al., 1999). If conditioned with Bu and Cy, patients have an increased risk to develop HC compared with patients conditioned with Cy and TBI (Ringden et al., 1994). Sencer showed that patients who received pelvic irradiation or Bu had an increased risk for HC (Sencer et al., 1993). To prevent HC, 2-mercaptoethane sodium sulfonate (mesna) is used during and after Cy infusion together with hyper hydration and alkalisation of the urine. This treatment may reduce the toxic effect from acrolein. A combination of hyper hydration and bladder irrigation with sorbitol has some benefits according to Meisenberg (Meisenberg et al., 1994). Most HC resolves by itself, but in severe cases many methods have been tried. Local treatment of the mucosa with Sukralfat, Alum, Formalin, Phenol, or silver nitrate has been tried. Formalin requires general anesthetic assistance and Phenol and requires the bladder to be surgically opened. These methods also produce side effects like renal papillary necrosis and reflux. When the patient is bleeding, it is important to keep the bladder free from clots by ensuring high fluid intake using an i.v. or directly to the bladder via a suprapubic catheter. Sometimes it is necessary to locate the bleeding and empty the bladder by cystoscopy. These patients are vulnerable to infections that have to be treated accordingly. In these cases, supportive care includes blood products and analgesics.

Hassan et al. has shown that adjusted doses of Bu after blood concentration are associated with decreased risk of HC (Hassan et al., 1996, Hassan, 1999). Although rare, mortality by HC is seen in severe cases with additional complications such as infections and uremia. However, it is very difficult to distinguish death in HC from co-morbidities (Baronciani et al., 1995).

VOD

VOD is a vascular complication, sometimes with reversed circulation in the liver. One hypothesis is that VOD results from injury of the endothelium in the hepatic sinusoids and terminal hepatic venules. This results in narrowing or obliteration of the terminal hepatic venules and sublobular veins. Congestion and ischemia from reduced sinusoidal blood flow result in hepatocyte necrosis. It most often appears within 30 days after transplantation, but later onset has been reported (Lee et al., 1997, Toh et al., 1999). The symptoms are jaundice, fluid retention, weight gain, right-upper-quadrant pain, liver enlargement, and a rise in bilirubin and transaminases (Jones et al., 1987, McDonald et al., 1984). In a prospective study from the EBMT including 631 allogenic transplanted patients, the incidence of VOD was 8.9% (Carreras et al., 1998). The incidence of VOD has been reported to differ between 10% and 60%, and it varies between centres due to conditioning and patient characteristics.
The diagnostic is mainly clinical and may vary due to the diagnosing physician. A transjugal or transfemoral liver-biopsy is one way to get a histologic evidenced diagnosis. The risk of severe hemorrhages makes it difficult to do a percutaneous liver biopsy. Ultrasound, elevated liver enzymes, and bilirubin are other parameters that can help uncover the diagnosis.

Risk factors are conditioning with busulphan and cy, progestogen treatment, age more than 20 years, Karnofsky performance less than 90%, pre-transplant fungal infection, and previous abdominal irradiation, (Hagglund et al., 1998, Carreras et al., 1998, Ringden et al., 1994), and administration of Myelotarg (gemtuxumab oxogamicin) an anti-CD33 monoclonal antibody (Tack et al., 2001, McDonald, 2002).

The prognosis of VOD is due to severity. Some patients with severe VOD may be treatable while some are incurable (McDonald et al., 1993, Carreras et al., 1998). Severe VOD is often associated with a mortality of 30-50% and involve multi-organ failure, which makes it difficult to treat. Many studies have been performed to evaluate the use of different drugs as prophylaxis to minimise the risk of VOD. Heparin was tried by Attal (Attal et al., 1992). Ursodeoxycholic acid was evaluated in a randomised trial (Ruutu et al., 2002). The ursodeoxycholic acid group had less liver toxicity and better survival as compared to the non-treated controls.

To get as good results as possible, it is important to treat VOD early after diagnose (Bearman et al., 1997). Anticoagulantia such as heparin and actilyse have been tried for treatment of VOD (Laporte et al., 1992). However, actilyse was associated with a high risk of hemorrhages (Ringden et al., 1992). Liver transplantation was tried in a few experimental cases (Bunin et al., 1996, Dowlati et al., 1995, Nimer et al., 1990, Norris et al., 1997, Ringden et al., 1992). Acetylcystein was successfully used in a few patients and is now evaluated as prophylaxis in a prospective randomised study (Ringden et al., 2000). Good renal perfusion without reducing the intravascular volume is essential. It is important to discontinue or reduce drug toxicity to the liver and kidney. Today defibrotide seems to be the drug of choice. Several studies have shown fair results with defibrotide (Bianchi et al., 1993, Richardson et al., 1998, Abecasis et al., 1999, Chopra et al., 2000, Jenner et al., 2000).

Graft failure and graft rejection
It is important to detect graft failure or rejection as early as possible. With non-functioning graft, there is a high risk of infections and mortality. In the 1970s and 1980s, the mortality was 80% to 90% due to primary graft failure. Today these numbers have decreased by 40% to 50%. Graft failure is described as primary or secondary. No evidence of recovering of granulocyte counts after transplantation indicates primary graft failure. When the graft shows inadequate function, it is called secondary graft failure. Primary graft failure can be suspected when the pancytopenic period is prolonged after transplantation and secondary graft failure when the pancytopenia reappears after initial engraftment. The time between transplantation and a secondary graft failure was reported as late as eight years after ASCT (Dufour et al., 1999). To verify the diagnoses, a bone marrow aspiration or biopsy has to be done. Low cellularity or an empty marrow clearly indicates graft failure. Both primary and secondary graft failure may be due to graft rejection or poor graft function. Graft rejection is due to immune reaction against minor or major histocompatibility differences between the
recipient and donor. All donor cells are lost. Reasons for rejection are the same as for graft failure: immunisation by previous blood transfusions, low cell dose in the graft, or a T-cell depleted graft. To treat graft failure or graft rejection, it is important to withdraw all marrow suppressive drugs, give growth factors like granulocyte monocyte colony-stimulating factor (GM-CSF) and a second transplantation, a stem-cell boost or buffy coat with or without conditioning (Remberger et al., 1998). The most effective strategy against graft failure is to optimise the transplantation associated procedures that can decrease the risk for graft failure. This includes increased conditioning.

Graft versus host disease (GVHD)

In 1957, van Bekkum called GVHD a “secondary disease”. He noticed that allogeneic stem-cell infusion was followed by diarrhea, severe weight loss, and skin lesions. GVHD appears in an acute or chronic phase. Acute GVHD appears most often in the first two to three months after ASCT. Most patients do not get GVHD before engraftment even if it is possible. Sometimes it appears later, and after donor lymphocyte infusion (DLI) it appears in an acute form often late after transplantation. Target organs are skin, liver and gut. The lymphoid system and lymphocytes initiated the disease (Santos and Cole, 1958, Gowans et al., 1962, Medaware, 1963). In the 1960s, Billingham listed the criteria for GVHD (Billingham, 1966).

1. The graft had to contain immunologically competent T-cells.
2. The host had to express transplantation antigen that are lacking in the graft to be known as an unknown tissue to the graft.
3. The host had to be incompetent of monitoring an effective immunological reaction against the graft.

Donor T-cells are triggering GVHD. Risk factors for GVHD are known as mismatched donor, unrelated donor, infections or immunity to several herpes virus, high age of the recipient and female donor to a male recipient (if the female donor is pregnant or receives blood transfusions, the risk is even higher) (Gale et al., 1987, Bostrom et al., 1990). Another important factor for development of GVHD is the environment of the host. For example, gnotobiotic mice that are treated in a germ-free environment failed to develop severe GVHD and mice that are heavily treated with antibiotics have lower incidence of GVHD (van Bekkum and Knaan, 1977). In clinical studies, patients suffering from aplastic anemia have been treated in LAF, and patients treated with antibiotic prophylaxis showed less GVHD grades II-IV (Vossen et al., 1998, Storb et al., 1983). If the patient contracts non-myeloablative conditioning with less reduction of immune competent cells, the frequency of GVHD seems lower compared to myeloablative conditioning (Slavin et al., 1998, McSweeney et al., 2001). However, there is an increased risk of graft failure.

To minimise the risk of GVHD, patients are given immuno-suppressive prophylaxis.

Skin: GVHD may start with a mild rash involving palms and the bottom of the feet. It could be associated with fever and spread to the whole body and in severe cases result
in bullous lesions. The diagnosis is most often made clinically, but a skin biopsy can sometimes help. Corticosteroids are the first choice of treatment.

**Liver:** The liver or the gut is the next organ involved. More seldom, liver or gut GVHD shows up before any signs of skin GVHD. Acute GVHD of the liver shows leaking enzymes from the liver with hyperbilirubinemia and sometimes also elevation of alkaline phosphates and transaminases (Deeg, 1993). There are many differential diagnoses to be considered when it comes to liver GVHD. Toxic reactions from previous given cytostatic treatment, conditioning and cyclosporin toxicity have to be considered as well as VOD of the liver and infections as viral hepatitis or fungal infection.

**Gut GVHD:** Symptoms of gut GVHD are nausea, vomiting, diarrhea, and abdominal pains with cramping. Hemorrhagic diarrhea is a sign of more advanced GVHD. Gut GVHD has to be separated from other possible diagnosis such as viral gastroenteritis due to CMV, EBV, rotavirus, adenovirus, bacterial infections like clostridium difficile, or toxic side effects from TBI or chemotherapy. To confirm GVHD diagnosis and exclude differential diagnosis, a biopsy from the gut sometimes is necessary. Often both GVHD and infections are involved.

**Grading of acute GVHD**
Acute GVHD is graded on a scale from 0 to IV. Grade 0 indicates no GVHD, while grade IV indicates a severe lethal acute GVHD (Glucksberg et al., 1974, Ringden and Nilsson, 1985).

**Prophylaxis and treatment of GVHD**
GVHD grades III-IV is associated with increased disabilities, mortality, and high costs. With no immune prophylaxis, 50% of the recipients of HLA identical sibling grafts will die from GVHD according to animal studies (Storb et al., 1973). In the clinical setting, prophylaxis against GVHD is almost always given after ASCT with a few exceptions (Lazarus et al., 1984, Sullivan et al., 1989). Mtx or cyclosporin used as single agents are not as effective as combined treatment. The most common prophylaxis is therefore Mtx and Cyclosporin combined (Storb et al., 1986, Ringden et al., 1993). If fast engraftment is desired, for example because of ongoing infection, corticosteroids can be used instead of methotrexate. For patients receiving cord blood, which have delayed engraftment, the preferable prophylaxis is a combination of cyclosporin and corticosteroids. This combination is less toxic than cyclosporin combined with Mtx and hopefully it will shorten the time to engraftment.

To avoid GVHD, for example when using mismatched donors, in vitro TcD of the graft is used (Bacigalupo et al., 2001, Lee et al., 2002). However, TcD increases the risk for recurrent disease, rejection, and/or graft failure (Marmont et al., 1991). At KUH, partial in vivo T-cell depletion using antithymocyte globulin (ATG) are used if the donor is unrelated in non-malignant disorders, or to decrease rejections. The results are encouraging (Ringden et al., 1998, Remberger et al., 1999). If the patient is allergic to rabbit or if ATG doesn’t have the desired effect, anti-lymphocyte globulin (ALG) or campath (anti-CD52) can be used instead of ATG. Prophylaxis also includes tacrolimus,
mucophenolate mofetil (MMF), or rapamune. There are several ongoing studies to find better prophylaxis against GVHD. Perhaps mesenchymal stem-cells can be an alternative as prophylaxis and to treat severe gut GVHD (Le Blanc et al., 2004).

Despite prophylaxis, a proportion of the patients will develop GVHD. The first choice of treatment for all kind of GVHD is corticosteroids. If not given as prophylaxis, cyclosporin or tacrolimus are added. MMF, ATG, anti-lymphocyte globulin (ALG), OKT-3 (monoclonal antibodies), anti-IL2 (anti-interleukin2, Zenapax®), anti-TNF-α, Infliximab (Remicade®) may be used as second time therapy either alone or in combinations.

Thalidomide and psoralene together with ultraviolet light (PUVA) are other alternatives to treat GVHD. In severe cases of liver GVHD or VOD, a liver transplantation may be necessary (Bunin et al., 1996, Dowlati et al., 1995, Nimer et al., 1990, Norris et al., 1997, Ringden et al., 1992).

Severe acute GVHD is extremely difficult and expensive to treat. The mortality for patients with grades III-IV acute GVHD is between 50-100%. This grading may sometimes be made due to outcome rather than at one time point (Martin et al., 1998, Martin et al., 1998).

**Chronic GVHD**

Chronic GVHD is the leading reason for late non-relapse mortality (Socie et al., 1999) and is associated with a decreased quality of life (QoL) (Syrjala et al., 1993, Duell et al., 1997, Sutherland et al., 1997).

In the 1970s when long-time survivors after ASCT first were seen, chronic GVHD also appeared (Siimes et al., 1977, Hood et al., 1977). The first comprehensive descriptions were published in 1979-81 (Graze and Gale, 1979, Shulman et al., 1980, Sullivan et al., 1981). Chronic GVHD reminds one of autoimmune systematic collagen vascular diseases and includes clinical manifestations of dermatitis, keratoconjunctivitis, generalized sicca syndrome, an oral mucocitis, esophageal and vaginal strictures, liver disease, and pulmonary insufficiency (Sullivan et al., 1981). The disease can be classified as limited or extensive (Shulman et al., 1978, Shulman et al., 1980). In limited diseases, skin and/or liver are involved. If any other tissues or organs are involved, it is classified as extensive chronic GVHD. Chronic GVHD can also develop in a sub-clinical setting where there are histological signs, but no clinical signs. Chronic GVHD arising out of acute GVHD is called progressive; if acute GVHD has resolved before chronic GVHD appears, it is called quiescent or interrupted; it is called de novo if there is no previous acute GVHD. Chronic GVHD most often appears >100 days after transplantation. Chronic GVHD has been detected as early as 31 days after transplantation and may appear several years after transplantation. In long time survivors, 30% to 50% will develop chronic GVHD (Ringden et al., 1985, Sullivan et al., 1981, Storb et al., 1983). In 2002, Lee et al. reported that 30% to 50% of the recipients with HLA-identical sibling donors and 50% to 70% of recipients with unrelated donors develop chronic GVHD with a median time to onset of 4-6 month after transplantation (Lee et al., 2002).

Risk factors for chronic GVHD are acute GVHD, higher patient age, and additional treatment such as buffy-coat after transplantation (Storb et al., 1983, Bostrom et al., 1990, Ringden et al., 1985, Remberger et al., 2002, Carlens et al., 1998). Herpes
virus may have an impact on chronic GVHD as discussed in some studies. Lönnqvist observed that CMV frequently preceded the onset of chronic GVHD (Lönnqvist et al., 1990). Nevertheless, Atkinson et al. presented infections and sunburn to be immunostimulating events for chronic GVHD (Atkinson, 1990). Hyper- or hypopigmentation, lichenoid papules, or local erythema after allogeneic stem-cell transplantation can indicate chronic GVHD. It could be located anywhere in the skin and progress rather rapidly especially if immunosuppressive treatment has been disposed.

Symptoms of chronic GVHD in the liver are elevated enzymes and alkaline phosphatases. Jaundice indicates obstructed bile duct damage that can progress to cirrhosis with esophageal varices. As for acute GVHD, it is important to distinguish chronic GVHD from toxic reactions, viral hepatitis, and hemolysis. A liver biopsy may sometimes be necessary to establish the diagnosis. Histopathology of chronic GVHD is characterized by basal cell degeneration and necrosis (Shulman et al., 1978, Shulman et al., 1980).

Involvement of other tissues such as the mouth with lichen planus-like striae and plaques, ulcerations, atrophy, erythema, and dryness may be present (Schubert et al., 1984, Heimdahl et al., 1985). Dry eyes, bronchiolitis obliterans, may also be present (Roca et al., 1982, Wyatt et al., 1982). The sicca syndrome also involves vaginal strictures and stenosis (Corson et al., 1982). Most treatment in these cases is symptomatic. Mild chronic GVHD is associated with improved survival at least in patients with early leukemia due to the GVL-effect (Horowitz et al., 1990).

**Graft versus leukemia (GVL)**

In 1968, Mathé summarised 21 allogenic transplanted patients and found six patients with graft failure, eight of fifteen who engrafted died of severe GVHD but had no evidence of leukemia, two died with less severe GVHD and no leukemia, one with acute and chronic GVHD survived for 20 months and died of infection. The last four patients had minimal GVHD and died from recurrent disease (Mathe, 1968, Mathe et al., 1974). This summary indicated an anti-tumour effect and described that patients with GVHD are susceptible to infections.

Bortin et al. established the term GVL (Bortin et al., 1973, Bortin et al., 1973, Bortin, 1974), and showed that the immune-mediated anti-tumour reactivity is important to outcome. A study in mice showed an anti-leukemia effect after ASCT although most mice died from GVHD (Barnes and Loutit, 1957). However, with increased immunosuppression, the incidence of GVHD was decreased. The group from Seattle showed that GVHD decreased the risk of relapse after ASCT and that chronic GVHD had a better anti-leukemia effect compared to acute GVHD (Weiden et al., 1981). Several studies have confirmed this (Horowitz et al., 1990, Sullivan et al., 1989, Ringden et al., 1996, Remberger et al., 2002).

After delayed donor T-cell infusion, it is possible to obtain a lymphohematopoietic GVH reaction without any systemic GVHD. Barens compared leukemia mice after ASCT conditioned with TBI with mice receiving stem-cells from syngenic donors. He noticed that the first group survived longer but died from GVHD (Barnes et al., 1956). After this study, Barnes proposed that allogeneic stem-cell transplantation had an anti-tumour effect (Mathe et al., 1965).
Tolerance
Tolerance means that the immune system tolerates foreign tissue. Tolerance leads to less immunemediated side effects after ASCT. Tolerance to foreign tissue was first described in 1957 (Billingham and Brent, 1957). Main and Prehn described tolerance in 1955 when they showed that mice could tolerate a skin transplant after TBI. The pathophysiology regarding tolerance became apparent in early 1968 (Mathe, 1968). If patients become tolerant, it means the patients will tolerate the transplanted stem-cells, which is foreign tissue to the patient. The patient doesn’t have to be full chimera (100% donor) to tolerate the new tissue. Clinical tolerance can be defined as graft-acceptance with no immunosuppression (Hentschke et al., 2002).

Infections
Patients referred for ASCT have different histories of previous treatment. For example, a patient with an inborn error of metabolism and an intact immune system have a different course of chemotherapy pre and post transplantation experience compared with a patient treated for acute leukemia with several periods of neutropenia. Allogeneic transplanted patients are conditioned with lethal doses of chemotherapy and they are severely immunosuppressed after ASCT (Paulin et al., 1987, Witherspoon et al., 1981). This treatment is enough to obtain infections even in a protective environment. Risk factors for infections are acute and chronic GVHD, splenectomy, prolonged time to engraftment, prolonged immunosuppressive therapy, and infections itself. An important predisposing factor for bacterial infections are prolonged neutropenia (Mossad et al., 1996, Nosanchuk et al., 1996). Not surprisingly, therefore, infections are common and often life-threatening (Thomas et al., 1975, Thomas et al., 1975, Ringden et al., 1985, Meyers and Thomas, 1988, Paulin et al., 1987, Atkinson et al., 1979, Atkinson et al., 1982).

At least half of the transplanted patients experience an infection short after transplantation. Fever of unknown origin is expected to be bacterial in 85%. As short time as possible to engraftment and infection prophylaxis can reduce the incidence of infections after ASCT. Granulocyte infusions may be used as a prophylaxis or as a therapeutic treatment (Buckner et al., 1978). Due to immune incompetence, patients are advised to avoid contact with infected persons during the first three to six month after ASCT. The immune recovery increases successively after engraftment but takes around a year for patients without chronic GVHD and longer with chronic GVHD even if serum immunoglobulin levels (IgG and IgM) recovers in around three months after transplantation (Noel et al., 1978, Paulin et al., 1985).

Patients who receive PBSC do not have as many infections as BM recipients (Storek et al., 2001). This may be due to the higher dose of CD34 cells and lymphocytes in the graft and the shortened neutropenic phase. Late infections are rare in patients with HLA-identical sibling donors. Patients with unrelated donors or with chronic GVHD independent of donor are predisposed to infections (Ochs et al., 1995). Infections are divided into three groups: bacterial, fungal, and viral infections.
**Bacterial infections**

Most bacterial infections come from the patient himself/herself and can cause septicemia. The most common are alpha streptococci from the oral flora. Another common cause of septicemia is coagulase negative streptococci (Sparrelid et al., 1998). This may be associated with the central venous catheter (CVK) all patients have (Mattsson et al., 1991, Donnelly, 1995, Petersen et al., 1986). Decontamination of the gut and use of broad-spectrum antibiotics have decreased septicemia due to gram-negative agents (Winston et al., 1979). Ulceration of the gastric mucosa leaves an open door for gram-negative bacteria to enter the blood circulation and cause septicemia. The most dangerous bacteria are pseudomonas and multi-resistant staphylococcus aureus. Most bacterial infections are resolved with antibiotics. If this treatment is unsuccessful, the CVK has to be removed because it is a common reason for infections (Ruppel et al., 1994).

Septic shock is a frightening lethal complication during the neutropenic phase after ASCT. Streptococcus mitos is the most frequently isolated streptococci causing septic shock (Steiner et al., 1993). Septic shock is also associated with capillary leak syndrome (Funke et al., 1994). The regimen to diagnose and to treat infections differs between centres. At KUH/Huddinge, the procedure starts with a physical examination that includes a blood, throat, CVK, and urine cultures. If respiratory symptoms are present, a chest x-ray is performed. Thereafter, broad-spectrum antibiotics are given.

**Fungal infections**

Immunosuppressed patients treated with immunosuppressive drugs or having an immunosuppressive disease are predisposed for fungal infection. Fungal infections are opportunistic infections often with lethal outcome after ASCT. Candida albicans, candida parapsilosis, and candida glabrata are the most common pathogens causing fungal infection during the neutropenic phase after ASCT. Aspergillus fumigatus is not as common in Sweden, due to the cold climate; however, it is associated with life-threatening infections. The overall incidence is between 2% and 40% and contributes to death in 10% to 30% (Wingard et al., 1987, Tollemar et al., 1989). The incidence of invasive fungal infection is approximately 10% (Clift, 1984, Tollemar et al., 1989). The mortality rate for invasive candidiasis post ASCT are 70% and for aspergillus 90% (Meyers et al., 1983).

Marr et al. from Seattle found two peaks for aspergillus to appear, one at 16 and another 96 days after ASCT (Marr et al., 2002, Marr et al., 2002). The incidence of death from fungal infections has been reduced to 5% with early and better antifungal treatment (Andstrom et al., 1996).

Risk factors for invasive fungal infection are splenectomy, CMV or HSV seropositive recipient, low infused cell dose, acute GVHD grade II to IV, ATG treatment, higher recipient age, fungal colonisation, longer neutropenia, total body irradiation, AML, HLA-mismatched transplantation, and IgA anti-candida antibody (Tollemar and Ringden, 1991). As prophylaxis against candida colonisation, fluconazol can be used in a dose of 400 mg orally for adults and 12 mg/kg/day for children. Fluconazol protects for candida in both early and late dissemination (Slavin et al., 1995). Itraconazole is a better alternative for protection against aspergillus (Morgenstern et al., 1999).
Isolation in LAF or inhalation of amphotericin B spray can also be used as prophylaxis against aspergillus (Meunier et al., 1991, Trigg et al., 1997, Ward, 1997). Aspergillus is air and waterborne. Some units suggest giving sponge baths rather than showers. In some centres, a previous aspergillus infection itself is a contraindication for ASCT. However, with new methods to detect fungal infections early and with new treatments such as liposomal amphotericin B, voriconazol, itraconazol and caspofungin for prophylaxis and treatment, patients have an improved survival rate.

**Viral infections**

Herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and CMV are the most common herpes viruses that can cause infections post ASCT. All of them are life-threatening, but new more sensitive techniques to detect viral infection and knowledge about risk factors for infections help establish adequate prophylaxis and treatment to reduce mortality (Ljungman et al., 1993, Gor et al., 1998). Acyclovir and leukocyte-filtered blood products are frequently used prophylaxis. Virus infections can be expected any time after ASCT and its most common appearance after ASCT is shown in Figure 1.

![Fig. 1. Time frame for different herpes virus infections, relapse, and acute and chronic GVHD in relation to time post-BMT. VZV, varicella zoster; CMV, cytomegalovirus; HSV, herpes simplex virus; CGVHD, chronic GVHD; aGVHD, acute GVHD; relapse, recurrence of hematologic malignancy after ASCT. Published with permission from Cambridge University Press (Ljungman P, Einsele H. Viral infections. In: Atkinson K, Champlin R, Ritz J, Fibbe WE, Ljungman P, Brenner MK, eds. Clinical Bone Marrow and Blood Stem Cell Transplantation. 3rd Edition. Cambridge University Press).](image)

GVHD predisposes infections and vice versa. The frequency of reactivation of HSV can be reduced using acyclovir as prophylaxis (Meyers et al., 1980). Lundgren et al. suggested that all patients with HSV IgG titers more than 10000 ELISA should be given prophylaxis with acyclovir (Lundgren et al., 1985).

EBV infections are associated with post-transplant lymphoproliferative disorder (EBV-PTLD). Biopsy-proven EBV-PTLD and EBV-burden in peripheral blood are
strongly correlated (Rooney et al., 1998). This does not mean that all EBV positive blood samples give the diagnosis of PTLD (Gartner et al., 2002). The new polymerase chain reaction (PCR) technique may be too sensitive to be predictive. However, an increase in DNA copies of several logs may suggest a risk for EBV PTLD.

Several studies show that CMV is reactivated in up to 60% of the patients after ASCT depending on CMV seropositivity in donor and recipient and to some extent given CMV-prophylaxis (Meyers et al., 1986, Gratama et al., 1985, Paulin et al., 1986, Jacobsen et al., 1986). Symptoms of CMV-disease are high fever, nausea, vomiting, dysphagia, hepatitis, interstitial pneumonitis, and occasionally chorioretinitis and encephalitis (Cordonnier et al., 1983). There is a strong correlation between GVHD and CMV interstitial pneumonitis reported in various studies (Meyers et al., 1982, Meyers et al., 1986, Paulin et al., 1989, Cordonnier et al., 1983, Cordonnier et al., 1986). CMV causes immunosuppression that may pave the way for other infections (Paulin et al., 1985, Paulin et al., 1987). Previous the mortality of CMV pneumonitis was 90%; this has been decreased to 50%. (Reed et al., 1987, Ljungman et al., 1992).

By PCR diagnosis of CMV and presumptive therapy using gancyclovir or foscarnet the incidence of CMV disease has decreased from around 10% to less than 2% (Ljungman et al., 1996, Reed and Meyers, 1987).

Adenovirus can cause conjunctivitis, hemorrhagic cystitis, gastroenteritis, and upper respiratory infections in immunocompromised patients. Adenovirus infections can be life-threatening and different studies showed a varying frequency of mortality. The virus is most common among children (31%) compared to adults (13.6%) (Flomenberg et al., 1994).

Hepatitis B and C are other infections that can be reactivated or transferred from a positive donor or by blood transfusion (Ljungman et al., 2002). Loss of specific antibodies will frequently appear after ASCT. This increases the risk to contract earlier encountered viruses. Approximately one-year post ASCT is the optimal time to start vaccinations to establish new protection against measles, varicella zoster, parotitis, and hepatitis B (Ljungman et al., 1990). In the meantime, it is most important to diagnose and treat viral infections.

**Cellular therapy**

Cellular therapy with cytotoxic T-lymphocytes (CTL) such as CMV-CTL or EBV-CTL is effective treatment and prevention of CMV (Walter et al., 1995) or EBV disease. EBV-CTL was used to treat EBV-PTLD successfully (Papadopoulos et al., 1994) and can also be used as prophylaxis in high-risk patients for EBV-CTL (Gustafsson et al., 2000).

The use of cellular therapy increases every year. Especially DLI have been shown to provide an immunotherapeutic effect on malignant diseases (Johnson and Truitt, 1995, Johnson et al., 1999). The use of reduced conditioning can be followed by DLI to provide more efficient immunotherapy or graft versus tumour effect (Storb et al., 1997). It has been a successful treatment for relapsed CML after ASCT (Kolb et al., 1995, van Rhee and Kolb, 1995). Mesenchymal stem-cells are experimentally used to treat severe GVHD. Leukemia specific CTL may enable an anti-tumour effect and this treatment has been investigated but is not yet in the clinic.
AIMS OF THE THESIS

The overall aim of this thesis was to investigate whether it was safe and feasible to treat patients undergoing ASCT during the pancytopenic phase at home instead of at the hospital. Moreover, ASCT is known to be an expensive treatment and therefore further aims were also to evaluate the costs for ASCT and of severe GVHD.

Specific aims for papers I-IV were:

- to study if it was safe and feasible to treat patients undergoing ASCT at home during the pancytopenic phase by performing a pilot study (paper I).

- to investigate whether home-care was advantageous compared to hospital-care in a larger group of patients (paper II).

- to investigate whether an increased risk of relapse existed in the home-care group because of less acute GVHD (paper III).

- to determine the total costs for ASCT and to identify the pre- and post-transplant conditions or factors associated with increased or decreased costs (paper IV).

- to determine how the treatment, costs and survival rate for patients with acute GVHD grades III–IV have changed over three decades.
MATERIAL

Patients

*Paper I*

Since March 1998, all patients in the Stockholm area considered eligible for home-care were asked if they wanted to participate in a pilot study meaning that they would be cared for at home as much as possible during the neutropenic phase after ASCT. Twenty-two patients were asked and eleven choose to be treated in their homes post-ASCT (home-care group). Eleven patients wanted to stay and be treated at the hospital (control group). There were four females and seven males in each group. The median age was 44 (range 15-54) years for the home-care group and 45 (range 29-64) years for the hospital-cared patients. Medical data regarding the patients in the two groups is given in Table 2.

Table 2.  Medical data regarding study group and controls

<table>
<thead>
<tr>
<th></th>
<th>Home-care group (n)</th>
<th>Controls (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-malignant disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>High risk patients (beyond 1st remission or 1st chronic phase)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Low risk patients</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

There were some conditions that had to be fulfilled at home before the patients in the home-care group were allowed to return home.

- There had to be a relative or friend able and willing to stay at home with the patient.
- The temperature of the tapped water had to be at least 50°C
- No pets were allowed
- No pot flowers were allowed
- The clouts and sheets used by the patient had to be cleaned three times a week.
- The driving-distance had to be less than two hours from the hospital.

*Papers II and III*

The 11 patients from paper I were also evaluated in study II and III. In addition, 25 patients treated at home were included. Thus, the home-care group now consisted of 36 patients. The home-care group was compared to two control groups: control group 1 consisted of patients choosing the hospital-care alternative. This group consisted by the end of year 2000 of 18 patients. However, as it could have been a bias to choose a control group this way, another control group (2) was created consisting of patients that could not be offered home-care because they came from other parts of the country or from abroad. These patients were transplanted almost during the same time period and were matched for prognostic factors with the home-care patients.

Patient and donor characteristics, diagnosis, conditioning regimens and immuno-suppressive therapy for each group in paper II and III are showed in Table 3.
Table 3.  Patient and donor characteristics, diagnosis, conditioning regimens, and immunosuppressive therapy

<table>
<thead>
<tr>
<th></th>
<th>Home-care</th>
<th>Controls 1</th>
<th>Controls 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Recipient’s gender (M/F)</td>
<td>25/11</td>
<td>11/7</td>
<td>18/18</td>
</tr>
<tr>
<td>Recipient’s age</td>
<td>42 (14-58)§</td>
<td>45 (15-64)</td>
<td>38 (15-60)</td>
</tr>
</tbody>
</table>

**Diagnoses:**
- Acute myeloid leukemia: 11 7 11
- Acute lymphoid leukemia: 9 3 10
- Chronic myeloid leukemia: 7 3 8
- Myelodysplastic syndrome: 4 0 4
- Lymphoma: 3 2 2
- Chronic lymphoid leukemia: 2 1 1
- Myelofibrosis: 0 1 0
- Adrenoleukodystrophy: 0 1 0

**Stage of disease:**
- CR1: 19 9 20
- CR2: 6 3 6
- CR>2: 2 1 2
- PR: 2 2 2
- Relapse: 3 0 2
- Low risk*/advanced: 19/17 11/7 20/16

**Donor type:**
- Identical twin: 1 0 0
- HLA-identical sibling: 10 7 12
- Unrelated donor: 25 11 24
- Donor’s gender (M/F): 25/11 10/8 19/17
- Donor’s age: 38 (19-56) 37 (10-60) 36 (19-61)
- BM/PBSC: 13/23 6/12 16/20
- Nucleated cell dose x 10⁸/kg: 8.7 (1-27.6) 10.0 (0.7-16.8) 6.0 (1.0-13.2)*
- G-CSF after SCT: 36 (100%) 17 (94%) 30 (82%)
- Female donor to male recipient: 5 (10%) 4 (24%) 7 (19%)

**Conditioning:**
- Cy/TBI: 19 9 20
- Bu/Cy: 11 8 10
- Holoxan, Paraplatin + etoposide (re-transplantation): 1 0 1
- Flu/Bu/ATG: 5++ 1 5

**Immunosuppression:**
- CyA + MTX: 33 16 34
- CyA + pred: 0 2 1
- CyA + MMF: 1 0 0
- None (1 twin, 2 re-transplants): 2 0 1

**Follow-up, months:** 15 (3.3-35.9) 21.8 (9.5-32.4) 22.5 (5.9-65.6)

Abbreviations: Cy = cyclophosphamide; TBI = total body irradiation; Bu = Busulfan; ATG = antithymocyte globulin; CyA = cyclosporine; MTX = methotrexate; pred = prednisolone; MMF = mycophenolate mofetil; § median (range) low risk: 1* CR, 1* chronic phase; advanced: beyond these stages; * p=0.054 vs. home-care; ** one got Cy instead of Bu.
**Paper IV**
In paper IV all patients who had undergone ASCT during the years 1998 and 1999 were followed-up regarding costs. There were 121 ASCT performed in 116 patients, five were thus re-transplantations. Twenty-three patients were excluded since we could not determine all their costs.

**Paper V**
All patients with severe, acute GVHD grades III-IV, who had undergone ASCT during the three decades between 1975 and 2004 were identified. A total of 99 patients were included. However, 11 patients had to be excluded due to lack of information. The patients were divided into three groups.

**METHODS**

**Papers I and II**
After conditioning and cell infusion in the hospital, the patients in the home-care group were allowed to go home. A trained nurse from the ASCT ward visited the patients every day to check the status of the patient; draw blood samples, check the blood pressure, weigh the patient, and check daily oral intake of fluid and food. The main concern was the risk of septic shock. If needed, the nurse at home gave the patient i.v. antibiotics, analgesics, Mtx, blood products and/or TPN. Antibiotics were given if the patient had fever >38.5°C with or without a positive blood culture. During the visit at home there were always time for the patient and the relatives to ask questions and to discuss with the nurse.

**Paper III**
The charts for all the patients included in paper I and II were evaluated for acute and chronic GVHD, CMV test results, relapse, TRM and survival. The shortest follow up time was three years.

**Paper IV**
All in- and outpatient costs during five years in the remaining 93 patients were collected. The in-patient costs included all costs related to a patient from the first day of admission to the ASCT-ward until discharge and also all costs of readmission to any hospital in the Stockholm area. All costs from the out-patient clinics were also identified. This could be done by the cost–per-patient system used at the KUH.

**Paper V**
The patients were divided into three groups due to changes in treatments in order to get comparable groups: A 1977-1989, B 1990-1999 and C 2000-2004 with 31, 25 and 32 patients in each group, respectively. ATG or OKT3 were used as GVHD treatment in all three groups; 17 patients in group A, 6 in group B and 1 in group C. CellCept® was given to six patients in group B compared to nine in group C. There were only four
patients in group C who received Remicade® (anti-TNF-α, infliximab) and Zenapax® (anti-IL-2, daclizumab). The most costly treatment of infections is AmBisome®, which was used in groups B and C. The costs for the treatment of acute GVHD grades III–IV and infections were calculated on the basis of 2003 years’ prices.

**Statistics**

Different statistical methods were used for the different studies. For all papers (papers I-V), statistical significance was accepted if \( p < 0.05 \).

**Papers I and II**

Descriptive statistics were used for nominal data. The Fisher’s exact test was applied to compare distributions of patients with septicaemia and the Mann-Whitney \( U \)-test was used to compare days with fever, TPN, antibiotics, transfusions and other data.

**Papers II and III**

The probability of GVHD, transplant-related mortality (TRM), relapse, leukemia-free survival (LFS) and survival rates were compared using the method of Kaplan-Meier with the log-rank test (Mantel-Haenszel) (Peto and Peto, 1972). Cox’s regression model was used for the multivariate analyses (Cox, 1972) only factors with \( p = 0.1 \) in the univariate analyses were included in the multivariate analyses. The following factors were analyzed: home-care and hospital-care, type of donor (sibling/unrelated), source of stem-cells (BM and PBSC), diagnoses, stage of disease (early: 1st remission or chronic phase, or late: more advanced), gender, age, results from CMV serology, fever, bacteremia, acute GVHD (grades 0-I vs. II-IV), time to engraftment, absolute neutrophil count (ANC >0.5 \( \times 10^9/\text{l} \)), nucleated cell dose, donor age, donor gender and female donor to male recipient. Only patients surviving more than 30 days were included in the analyses of acute GVHD. A minimum of 90 days of follow-up was a criterion for relapse and chronic GVHD. In paper III, home-care was the main factor tested, whereas all the other factors were included to control for differences between the groups. The home-care patients were compared to the two control groups taken together to improve the statistical power of the analyses.

**Paper IV**

The Mann-Whitney \( U \)-test was used for two-group comparisons. Multivariate analyses, using forward stepwise multiple linear regressions, were used to analyze the treatments and complications associated with various costs. Only factors with \( p > 0.2 \) in the univariate analyses were introduced into the multivariate forward stepwise analyses.

**Paper V**

Survival was analyzed by the Kaplan-Meier product limit method and using the log-rank (Mantel-Haenzel) test, taking censored data into account. In the uni- and multivariate analyses of factors associated with death, the Cox proportional hazard regression method was used. Factors with a loading of \( p \leq 0.10 \) in the univariate analyses were included in the backwards elimination multivariate analyses. Factors included in
the univariate analyses were: sex and age of recipient and donor, type of donor, disease stage, nucleated cell dose, AB0 compatibility, conditioning, ATG as part of conditioning, grade of acute GVHD, stem-cell source, sex mismatch, retransplantation, year of ASCT, bacteremia, and G-CSF given after ASCT. In the analyses of factors associated with higher costs, we used the Mann-Whitney $U$-test for two-group comparisons and forward stepwise multiple linear regressions for the multivariate analyses.

**Ethical considerations**

Before the home-care study was initiated, considerable concern was put on the basic ethical question whether it at all would be ethically acceptable to treat the ASCT patients at home during the pancytopenic phase, as the safety of the new regimen was not known. An application was sent to the local Ethics Committee at Huddinge University Hospital. Ethical approval was granted (Dnr 449/97). Applications for the last two cost studies were also submitted. However, the Ethics Committee considered both these cost analyses as quality follow-up studies (Dnr 469/03).
RESULTS

Papers I-III
Paper I shows that home-care in ASCT patients is safe. These patients need advanced care and support and it was showed that this was possible to deliver at home. There were several advantages for the patients with home-care as shown in papers I-III. It was also found that the home-care regime led to significantly shorter time to discharge to the outpatient clinic, less acute GVHD grades II-IV, less TRM and better survival (paper II). Other outcome variables, such as days with fever, bacteremia, antibiotics, TPN, time in hospital, engraftment, transfusions, etc. are showed in Table 4. The long-term follow-up in paper III showed no increased risk of relapse in the home-care group. Furthermore, there were no differences in the incidence of chronic GVHD or CMV infections between the home-care groups and the group treated at the hospital. Instead it was a significantly decreased risk of TRM and an increased survival in the home-care group.

Table 4. Outcome variables, such as days with fever, bacteremia, antibiotics, total parenteral nutrition (TPN), time in hospital, engraftment, transfusions, etc.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Home-care</th>
<th>Controls 1</th>
<th>Controls 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=36</td>
<td>n=18</td>
<td>n=36</td>
</tr>
<tr>
<td>Days at home</td>
<td>16 (0-26)</td>
<td>2 (0-11)***</td>
<td>0 (0-3)***</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>4 (0-39)</td>
<td>27 (2-74)***</td>
<td>24 (8-73)***</td>
</tr>
<tr>
<td>Days to discharge*</td>
<td>19 (10-41)</td>
<td>29 (13-76)**</td>
<td>24 (8-73)*</td>
</tr>
<tr>
<td>Days with fever =38.5°C</td>
<td>2 (0-8)</td>
<td>3 (0-24)</td>
<td>2 (0-17)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>9 (25%)</td>
<td>8 (44%)</td>
<td>14 (39%)</td>
</tr>
<tr>
<td>Days on i.v. antibiotics</td>
<td>7 (0-24)</td>
<td>12 (0-55)</td>
<td>7 (0-35)</td>
</tr>
<tr>
<td>Days on i.v. analgesics</td>
<td>1 (0-24)</td>
<td>15 (0-71)</td>
<td>6 (0-31)*</td>
</tr>
<tr>
<td>Days on TPN</td>
<td>4 (0-39)</td>
<td>23 (0-55)***</td>
<td>10 (0-43)***</td>
</tr>
<tr>
<td>Days to WBC &gt;0.2 x 10⁹/l</td>
<td>13 (8-20)</td>
<td>12 (10-22)</td>
<td>12 (8-19)</td>
</tr>
<tr>
<td>Days to ANC &gt;0.5 x 10⁹/l</td>
<td>15 (9-22)</td>
<td>15 (11-22)</td>
<td>15 (8-22)</td>
</tr>
<tr>
<td>Days to platelets &gt;30 x 10⁹/l</td>
<td>17 (0-71)</td>
<td>19 (11-180)</td>
<td>17 (0-210)</td>
</tr>
<tr>
<td>Days with G-CSF</td>
<td>6 (2-17)</td>
<td>6 (0-20)</td>
<td>6 (0-12)</td>
</tr>
<tr>
<td>No. of platelet transfusions (units)</td>
<td>6 (0-19)</td>
<td>10 (0-54)</td>
<td>6 (0-26)</td>
</tr>
<tr>
<td>No. of erythrocyte transfusions (units)</td>
<td>4 (0-12)</td>
<td>7 (0-40)*</td>
<td>4 (0-34)</td>
</tr>
<tr>
<td>CMV reactivation (before discharge)</td>
<td>5 (14%)</td>
<td>7 (39%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>CMV reactivation (over all)</td>
<td>21 (58%)</td>
<td>11 (61%)</td>
<td>19 (53%)</td>
</tr>
</tbody>
</table>

*p=0.05, **p<0.01, ***p<0.001 vs. home-care group
* from day of transplantation

Paper IV
The total, median cost of five post-transplant years was 139,414 (52,095-345,640) €. The costs were highest during the first year with median in-patient and out-patient costs of 100,650 € and 13,066 €, respectively. The total cost during the first year was higher
in patients with acute GVHD grades III-IV (RelativeHazards (RH) 1.35, p=0.003), bacteremia (RH 1.33, p=0.005), VOD of the liver (RH 1.32, p=0.005), prophylaxis with G-CSF (RH 1.31, p=0.01), acute leukemia (RH 1.32, p=0.008) and treatment in hospital instead of at home (RH 1.20, p=0.07). During the early transplant period, a second transplantation (RH 1.35, p=0.004) and HC (RH 1.24, p=0.03) were associated with higher costs. The total five-year cost declined with longer survival rates (r=0.4028, p<0.001) and reduced intensity conditioning (RH 0.79, p=0.024)

**Paper V**

We found a significantly increased 1-year survival in group C (transplanted during 2000-2004) (21%) as compared to 9% for group A (1977-1989) and 8% for group B (1990-1999) (p=0.02). The time before having an acute GVHD was also delayed related to when in time the ASCT was performed (Fig. 2). Death by acute GVHD was associated with re-transplantation (p<0.001), grade IV acute GVHD (p<0.001), HLA-mismatch (p<0.009), and transplantation before year 2000 (p=0.015). ASCT after 1990 (p=0.003) and grade IV acute GVHD (p=0.03) were associated with increased costs. The time the patients were suffering from acute GVHD grades III-IV did not differ between the three groups.

![Fig. 2. Time to acute graft-versus-host disease grade III in patients undergoing ASCT over three different time periods, from 1977 through 2004.](image-url)
DISCUSSION

Papers I-III

These studies showed that home-care during the pancytopenic phase was feasible and safe. The home-care regimen also led to less acute GVHD grades II-IV and better survival. However, unfortunately home-care could only be offered to those living close to the hospital and the specialized ASCT unit. None of the patients in this study changed their decision to stay at home as much as possible during the pancytopenic phase after ASCT.

When the patients are treated at home, the family can spend more time together. Although there were only two children included in this study, home-care allowed these children to have access to their own toys and computers. They could have their friends and teacher help them with schoolwork at home. All patients treated at home were able to be more active compared with patients confined to hospital-care. E.g. some patients did their laundry, made their beds, and vacuum cleaned their homes during the pancytopenic phase. Some patients even have helped prepare dinner, although this can be difficult due to nausea. The patients were encouraged to take a walk in the open air every day, and together with all other physical exercises this probably helped the patient recover earlier compared to the patients treated at the hospital.

Patients undergoing SCT including ASCT cared for at the hospital report a high symptom distress and a poor health-related QoL both at admission (Larsen et al., 2003) and during the hospital care period before discharge (Larsen et al., 2004). A long-term follow-up of Swedish ASCT patients showed that these patients still reported a poorer health-related QoL as compared to a population group, up to four years post-ASCT (Edman et al., 2001).

As regards the health-related QoL in this thesis, we chose not to compare the patients at home with the controls as we initially focused on if it was possible at all to treat ASCT patients safely at home. At present, a new randomised trial is being planned to investigate whether the home-care leads to an improved self-reported health-related quality of life in these patients.

The study showed that home-care had several advantages compared to hospital-care. The home-care patients could be discharged faster although the times to engraftment of ANC and platelets were the same between the groups. The home-care patients required less TPN, probably because they had a better oral intake of food and fluid as compared to the hospital-care patients. The daily physical activities and close family-care may have been of importance for the better oral intake. It was found that the home-care patients were less likely to develop acute GVHD grades II-IV than the controls. The reasons for this may also have been better nutrition and less pathogenic bacterias at home, although this was not confirmed by any significant difference in bacteremia between the two groups. Infections can predispose for GVHD, for instance, gnotobiotic mice have a lower risk of developing GVHD (van Bekkum and Knaan, 1977, Jones et al., 1971). A clinical study have shown that patients treated in laminar airflow rooms were less likely to develop GVHD than those treated in regular hospital rooms (Storb et al., 1983). These studies showed that the absence or reduced amount of bacterias decrease the risk of acute GVHD. Another possible explanation for the decreased risk for acute GVHD during home-care may be that patients at home perceive
less stress than patients cared for in the hospital (Ferrara et al., 1999). Stress may trigger the release of cytokines like IL-1, IL-6 and interferon-γ, which in turn may trigger acute GVHD. This is so far a hypothesis, but we will study cytokine levels in ASCT patients treated at home and in the hospital.

Regarding safety analyses, the main concerns were the risks of septic shock or adult respiratory distress syndrome (ARDS). These are fatal complications regardless if the patients are treated in the hospital where an immediate intervention with intensive care can be started. However, no patients in any of the three groups died from these conditions.

Another concern was related to the possibly increased risk for infection during home-care, as this group of patients were not isolated. There are studies that showed reduced aspergillos infection rates in patients treated in strict isolation (Sherertz et al., 1987, Kelsey et al., 1990). All patients treated at home were told not to have pot flowers or to take walks near construction sites, because the risk of aspergillosis. However, they were allowed and encouraged to take walks in the fresh air. No patient in the home-care group has acquired a clinical aspergillosis infection. Indeed, such infections have been shown to be rare in our ASCT patients (Tollemar et al., 1989). The reduced prevalence of aspergillosis infections may be due to our cool climate.

Relapse is a major cause of mortality after ASCT in hematological malignancies (Thomas et al., 1975, Thomas et al., 1975, Ringden, 1997). The risk of relapse is increased in patients without chronic GVHD (Weiden, Sullivan et al. 1981). Acute GVHD predicts chronic GVHD. Because there was a decreased incidence of acute GVHD in the home-care group, the incidence of relapse may have been increased. The probability of chronic GVHD was similar between the two groups and so was the probability of relapse. Therefore, despite a lower risk of acute GVHD, home-care did not result in a decreased graft-versus-leukemia effect.

Thirty-six patients agreed to be treated at home, while 18 could not for different reasons - e.g., because they didn’t have any caregiver at home; it was difficult for them to arrange the care of their pets temporarily; the water temperature at home was too low; or they believed it was more safe to be treated at the hospital. The 18 patients treated at the hospital served as a control group. The selection procedure could have introduced a bias in which the controls treated in the hospital were less psychologically fit and therefore had a worse prognosis than those treated at home.

There were 25 males and 11 females included in the home-care study, which reflects the fact that in general, more men than females are transplanted. Between 1975 and 2004 at KUH Huddinge, 68% of the patients undergoing ASCT have been males.

The total cost for the home-care regimen was lower because these patients could be discharged earlier. Home-care is probably also associated with lower costs than hospital-care since home-care patients require less treatment with TPN and antibiotics. In addition, TRM was significantly reduced in the home-care group compared with the hospital care group and more lives were thereby saved. However, home-care in ASCT can only function if experienced nurses and physicians from an ASCT unit are always available. Regular visits at home including clinical and physiological follow-ups by experienced nurses is part of the concept. Hospital beds must be available for the home-care patients when needed in case of an emergency or high fever.
Paper IV
We found home-care to be less costly as compared to hospital-care. Therefore, we wanted to evaluate the overall costs of ASCT including home-care. Higher costs were associated with major complications, which have also been found in one other study (Lee et al., 2000). However, what specific complications that are costly have not been investigated before. Complications like GVHD, VOD and HC are expensive and associated with a poor outcome. Better strategies for prevention and treatment need to be developed. It also shows that it is expensive to use G-CSF after ASCT to get faster engraftment, since it increases the risk of acute GVHD (Remberger et al., 2003, Ringden et al., 2004). A novel finding was that patients suffering from acute leukemia are more costly to transplant than patients with other diagnoses. This may be because these patients are most often heavily treated with chemotherapy before the start of the conditioning and therefore predisposed for complications such as -e.g. liver toxicities, and mucositis. Reduced intensity conditioning is less toxic to the patient and therefore this was cheaper compared to myeloablative conditioning.

Paper V
Treatment costs and survival rates in patients with acute GVHD grades III-IV after ASCT during three decades were evaluated. The outcome for patients with severe acute GVHD is very poor, regardless of whether the patients received high-dose steroids or anti-T-cell antibodies (Remberger et al., 2001). Furthermore, the causes of death are often due to infectious complications such as CMV pneumonia or invasive fungal infections (Ljungman et al., 1998, Wingard et al., 1987). Severe acute GVHD appeared later in the groups transplanted during 1991-1999 and 2000-2004, compared to 1977-1990. The reason for this is unclear, but since 1985, almost all patients had been treated with prophylactic immunosuppression, consisting of cyclosporine combined with a short course of methotrexate(Ringden et al., 1995). This therapy dramatically reduces the probability of developing grade II–IV acute GVHD and improved survival compared to mono-therapy with only methotrexate or cyclosporin (Storb et al., 1986). This more effective prophylaxis may have delayed the onset of acute GVHD. Another possible reason for the delayed appearance of GVHD may be that reduced intensity conditioning has been used in recent years, which is associated with a reduced and delayed probability of acute GVHD compared to myeloablative therapy.

There was no significant difference in time with severe acute GVHD grades III-IV and there were no difference in organ involved in severe GVHD between the three time periods. Therefore the only positive finding was the significantly increased survival in group C between 2000-2004.

The increased incidence of survival in group C cannot be entirely explained by new expensive drugs, since the number of patients treated with the drugs in respective group are too low. However, taken together improved diagnostics, treatment and care may explain the improved survival.
CONCLUSIONS

Home-care during the pancytopenic phase after SCT has several advantages, such as faster discharge, reduced need for TPN, a lower incidence of acute GVHD, lower TRM, and lower costs than patients treated in the hospital.

ASCT can be less costly if severe complications can be avoided. Higher costs are associated with re-transplantation, acute leukemia, G-CSF prophylaxis, hospital care, myeloablative conditioning, and major transplant-related complications.

Costs and survival in patients with GVHD grades III-IV after ASCT have increased in patients treated after 2000. The reason for better survival is unclear but better diagnostics, new drugs and care may have contributed.

FUTURE PERSPECTIVES

A randomised trial was discussed as part of this thesis, but it was decided not to perform such a trial, since there were too few patients available to get sufficient statistical power. The home-care project was financed for three years from the Cancer Society. In the Stockholm area there are only about 12 ASCT patients per year eligible for home-care meaning the initial group would have considered of only 36 patients before randomisation. Moreover, in this first feasibility and safety study we wanted to give as many patients as possible the opportunity to be treated at home.

An international, multi-center, randomised controlled trial is at present planned to further investigate the advantages and possible disadvantages of home-care following ASCT. This trial will also include patient self-reported data - e.g., health-related quality of life and perceived health.

We will also determine pathogens at home and at the hospital and compare the bacterial flora in the gut in the two groups and its role for development of GVHD. The bacterial gut flora and its toxic products may trigger acute GVHD (Ferrara et al., 1999). Stress may pave the way for more GVHD by inducing cytokine release. Therefore, we want to study stress-induced cytokines like IL-1, IL-6 and interferon-γ in patients treated at home vs. at the hospital. One hypothesis is that patients at home may perceive less stress than those in the hospital.

It is my hope that in the future home-care after ASCT will be used also at other units all over the world because of its many advantages for the patients as compared to hospital treatment.
POPULÄRVETENSKAPLIG SAMMANFATTNING

Hemsjukvård, ”transplantat-kontra-vård” reaktion och kostnader vid allogen stamcellstransplantation


Eftersom säkerhetsanalysen var sammanställd, där elva patienter vårdats i sina hem, kunde hemmsjukvård introduceras såsom en förmodad säker behandlingsform. Hemsjukvård erbjuds därefter till en större grupp patienter som utvärderades. Studien visade att hemmsjukvården resulterade i signifikant lägre behov av intravenös näringsstillförsel och smärtstillande medel; färre patienter hade akut GVHD grad II-IV; tid till utskrivning förkortades; transplantationsrelaterad dödlighet var lägre; och det var en signifikant bättre överlevnad i jämförelse med de som vårdats på sjukhus.

Eftersom färre av de hemmsjukvårdade patienterna fick akut GVHD grad II-IV, befarades en eventuellt ökad återfallsrisk pga att akut GVHD ökar risken för kronisk GVHD, som i sin tur minskar risken för återfall. Vid en långtidsuppföljning av patienterna som vårdats hemma och jämförts med två kontrollgrupper i artikel I-II kunde ingen skillnad ses mellan grupperna avseende återfall och kronisk GVHD. Långtidsöverlevnaden var bättre hos patienterna som vårdats hemma.

Eftersom ASCT och efterbehandling anses vara dyr så studerades även kostnader för ASCT under fem år. Det visade sig att retransplantation, förebyggande behandling med tillväxtfaktor (G-CSF), akut leukemi och större komplikationer som allvarlig GVHD, infektioner, hemorragisk cystit och veno-occlusiv sjukdom i levern var associerade med högre kostnader. Hemmsjukvård och reducerad förbehandling inför ASCT innebar lägre kostnader.


Sammanfattningsvis: Hemsjukvård kan erbjudas till patienter som genomgår ASCT. Hemsjukvård kan reducera risken för akut GVHD, förbättra överlevnaden och minska kostnaderna vid ASCT.

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TACK TILL


Olle Ringdén, min bihandledare som stått ut med mig i vått och torrt. Tack Olle, utan dig hade det aldrig blivit en avhandling.

Ann Gardulf, som redan när projektet startade antydde att det skulle kunna bli en avhandling av det. Tack för detta och för din aldrig sinande rättningslust.

Inger Hammarberg, som har en ängels tålamod. Tack för att du gjorde min avhandling till en avhandling. Du är värd din vikt i guld.


Ole Alvin, som liksom Mats aldrig ger upp även om analyser måste kompletteras eller köras om mitt i sommaren. Tack för att Du bidrog med din kunskap och tack också för dina uppmunrande ord.


Marie Wiström and Maria Elbander, tack till er som alltid ser till att vi har personal som kan åka hem till patienterna. Ni är oumbärliga.

Majvor Hoglund-Lindecrantz and Ulla Stenson Bull, tack till Er som inte bara fått hjälpa mig med avhandlingen utan allt annat också som måste bli gjort under samma tid.

Alla patienter och anhöriga som gjort detta möjligt.

Tack Maria för att du hjälpte mig läsa och skriva och motivera pappa.

Tack Peter för att du alltid finns till för mig och hjälper mig med dataproblem.

Tack min Man för att du fortfarande vill vara gift med mig.
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