

# Improving outcome of haematopoietic stem cell transplantation

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Summary/Samenvatting



## Summary of results

The aim of this thesis was to improve the outcome of patients after haematopoietic stem cell transplantation (HSCT), by the evaluation of alternative donors and optimisation of immune cell reconstitution after HSCT. One of the problems is donor availability, but our hope was that this could partly be solved by using haploidentical family donors that are widely available. Another major problem is the slow immune reconstitution after HSCT, which leads to infectious complications and relapses. Since we observed in previous studies that ascorbic acid (AA) is essential for the development of T cells and NK cells *in vitro*, and many of our patients had low serum AA concentrations, we aimed to explore the role of AA in boosting the immune system after stem cell transplantation.

### Part 1 Haploidentical stem cell transplantation as alternative donor strategy

In **chapter 2, 3, 4** and **5** we assessed the role of the haploidentical family donor for allogeneic HSCT.

**Chapter 2** describes the outcome allogeneic HSCT in chronic lymphatic leukaemia (CLL) when using a haploidentical donor. High-risk and relapsed CLL patients nowadays are mostly treated with novel agents, and outcomes have improved significantly over the last few years. However, when “fit” patients are refractory to one or more of these novel agents, allogeneic HSCT is a valuable option that can even be curative in these patients, who would otherwise have a dismal prognosis. We analysed the outcome of 117 patients, that received a haploidentical HSCT for CLL and whose data were available in the EBMT registry. Thirty-eight percent of these patients experienced long term (5 year) overall survival (OS), which makes a haploidentical donor a valid alternative in CLL patients if no HLA-identical donor is available. The outcome was not influenced by the use of post-transplantation cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis. The most important risk factor for a poor prognosis was refractory disease at the time of the HSCT. In conclusion, this retrospective multicentre registry study shows that CLL patients, that have high-risk CLL and otherwise good risk transplantation characteristics, can be transplanted with a haploidentical donor, but preferably at the time of remission. However, at this time, because of the huge advances in CLL treatment and thereby highly increased overall

survival with the use of novel agents, allogeneic HSCT is hardly performed, and is only seen as last resort in fit and young patients that are refractory for novel agents.

In **chapter 3**, we evaluate the introduction of the haploidentical HSCT with PTCy as GVHD prophylaxis in our centre. Outcomes using this alternative donor type were similar to matched related donor (MRD) and matched unrelated donor (MUD) HSCT in our hands. However, non-relapse mortality (NRM) was high due to infectious complications. For this reason, we adapted our policy at the ward to prevent viral respiratory infections and added cotrimoxazole as prophylaxis against pneumocystis jirovecii pneumonia (PJP).

As we did not see any difference in clinical outcome between a MUD and haploidentical family donor, we investigated if costs and resource utilization could be an influence in donor choice in **chapter 4**. Costs pre-transplant for search and acquisition of the graft were significantly higher in MUD HSCT, but the costs in the transplant phase were highest in haploidentical HSCT due to longer hospitalisation, and subsequently use of more blood products, medication, and laboratory tests. This was due to slower immune reconstitution after PTCy. In total, there were no significant differences in costs between MUD and haploidentical HSCT.

**Chapter 5** describes the outcome of a multicentre phase 2 clinical trial, in which we transplanted poor risk multiple myeloma (MM) patients using a killer cell immunoglobulin-like receptor (KIR)-ligand mismatched haploidentical donor. The aim was to investigate if natural killer (NK) alloreactivity could improve the anti-tumour response, as it was seen in vitro. Primary endpoint was progression-free survival (PFS) after 1.5 years, and stopping rules were installed in case interim results made a benefit unlikely. After the inclusion of 12 patients, the study was terminated prematurely, since all evaluable patients (9) relapsed within a median time of 90 days. However, we observed that haploidentical HSCT was safe in these patients, as there was a high engraftment rate, low NRM (18% at 1 year), and no unexpected adverse events.

## Part 2 Ascorbic acid to boost the immune system after stem cell transplantation

In **chapter 6** and **7**, we developed a method for intracellular AA determination and reviewed the known effects of AA in cancer treatment to start further research to investigate the effect of AA on the immune system after stem cell transplantation.

In previous research, we discovered that serum AA levels were low in haematological malignancies. However, serum AA is not well correlated with the total body storage, while leukocyte AA levels do. Before starting a clinical trial to investigate the effect of AA supplementation on the immune system, we decided to develop a method to measure intracellular AA in various types of leucocytes. The validation of this method is described in **chapter 6**. The measurement of AA in peripheral blood mononuclear cells (PBMC's) and plasma was performed with hydrophilic Interaction Liquid Chromatography (HILIC) and UV detection and proved to be reliable and reproducible. As expected, there was no correlation between plasma and PBMC AA levels in healthy volunteers.

In **chapter 7**, we performed a systematic review regarding the effect of AA in the treatment of patients with cancer. A total of only 19 trials were included, as extensive research on this subject is lacking. Furthermore, there was a large heterogeneity in patient and disease characteristics, in interventions and in outcome measures. In only 4 of these studies, randomisation was used to determine treatment. Because of all these limitations, it was difficult to draw any definitive conclusions. Overall, we could not prove any clinically relevant effects of AA supplementation in cancer patients on OS, clinical status, quality of life and performance status. However, treatment with AA is likely to be safe since there were almost no serious adverse events and only mild side effects, even with very high doses of AA intravenously.

**Chapter 8** contains the research protocol of a clinical intervention study in which we test the hypothesis that AA might improve immune reconstitution in autologous HSCT. The study is a double-blind randomized placebo-controlled trial in which patients that undergo an autologous HSCT for MM or lymphoma in the Maastricht University Medical Center (MUMC) are treated with either high dose AA or placebo for 6 weeks. Primary endpoint is the day of

repopulation (return of neutrophil level to at least  $0.5 \times 10^9/l$ ) after autologous stem cell transplantation.