

Improving outcome of haematopoietic stem cell transplantation

Citation for published version (APA):

van Gorkom, G. (2022). *Improving outcome of haematopoietic stem cell transplantation: a possible role for haploidentical donors and ascorbic acid*. [Doctoral Thesis, Maastricht University]. ProefschriftMaken. <https://doi.org/10.26481/dis.20220616gg>

Document status and date:

Published: 01/01/2022

DOI:

[10.26481/dis.20220616gg](https://doi.org/10.26481/dis.20220616gg)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

11

Impact paragraph

Impact paragraph

In this thesis, we explored the role of a haploidentical stem cell donor and of ascorbic acid (AA) (=vitamin C) to improve the outcome of haematopoietic stem cell transplantation (HSCT). In this chapter, the relevance of the results described in this thesis and their scientific and social impact will be discussed.

Real-world data

In Europe, according to the European Society of Blood and Marrow Transplantation (EBMT), a total of 45,364 HSCT were performed in 2020 (autologous (=own) 26,568 and allogeneic (=donor) 18,796). The number one diagnosis for which an autologous HSCT is administered is multiple myeloma (47%), followed by non-Hodgkin's lymphoma (23%). In only 6% of the autologous HSCT the reason for the transplantation is a solid malignancy. The most common diagnosis in allogeneic HSCT was acute myeloid leukaemia (AML) (36%), followed by myelodysplastic syndrome (12%). These HSCT are performed by in total 690 centres.

In the Maastricht University Medical Center, in 2020 and 2021 we performed 105 and 106 autologous HSCT, respectively. Furthermore, we administered 43 allogeneic HSCT in 2020; 13 with HLA identical donor (MRD), 15 with haploidentical donor and 15 with matched unrelated donor (MUD). In 2021, we performed 41 allogeneic HSCT in total; 7 MRD, 21 haploidentical donor and 13 MUD. There has been a substantial increase in the number of haploidentical allogeneic HSCT we performed since the introduction of T cell replete haploidentical HSCT in 2016. We were also a strong advocate for the use of haploidentical donors in the rest of the Netherlands and the other centres followed our example¹. With our research concerning the use of haploidentical donors, we proved systematically that it is a valid alternative donor option in various haematological diseases (acute myeloid leukaemia, chronic lymphatic leukaemia, multiple myeloma). Furthermore, haploidentical HSCT forms the perfect platform for other, newer forms of immunotherapy for which the potential anti-tumour effect is supported by biological mechanisms.

Outcome and costs analysis

HSCT is an intensive treatment for the patients and their family, and it also has a considerable impact on society as this treatment is very costly. This

holds especially true for allogeneic HSCT, which is only used with curative intent in fit patients. When performing these high-risk and expensive treatments it is important to critically review the quality of your treatment by evaluating your own results. This is part of what we did in this thesis. We discovered some shortcomings in our own protocol and by this analysis we could adapt our regimens to improve outcomes for our patients. This increased the cost-effectiveness of the HSCT in our centre. Moreover, we showed that in the real world it is not always possible to generate similar outcomes as published results when adopting a new regimen. Thereby, treatment should be adapted to local protocols. Furthermore, we analysed costs of the different treatment steps for different donor types. In this way we could explore if there were certain choices in treatment regimens to make, which would not influence outcome but could perhaps decrease costs.

Improvement of immune reconstitution with ascorbic acid

Several strategies are used to assist the immune recovery and to prevent infectious complications and relapses after HSCT, for instance by the use of granulocyte-colony stimulating factors (G-CSF) and donor lymphocyte infusions. Most of these treatments are expensive, and furthermore, medication and hospitalisation for these complications are costly. Moreover, infectious complications have a substantial impact on the patients, and can even be fatal.

Interestingly patients that receive a HSCT often have deficient levels of AA in their blood, and immune cells need AA to divide and develop. We argued that it could be beneficial to use AA for boosting the immune system after HSCT. This is a very simple and cheap option that could make a difference in outcome for transplanted patients, who are very susceptible for infections as their immune system is not working well shortly after transplantation. These infections are sometimes even fatal in this patient group. Furthermore, in allogeneic HSCT, the immune system is needed to fight against cancer cells. Boosting the immune system could lead to better disease control and less relapses. Supplementation of AA could improve cost-effectivity in HSCT.

Scientific impact

Before we performed our study on the use of haploidentical HSCT in chronic lymphatic leukaemia patients, it was not known if this type of donor was

suitable for this patient group. We discovered that it is a valid option, and this knowledge helps other haematologists making decisions for their patients.

We are optimistic that the use of AA can be beneficial in HSCT, but do not have the results of our randomised clinical trial (RCT) in autologous HSCT yet. There is a lack of well-designed and reliable RCT's on the effects of AA in cancer, so the knowledge gathered in this study will always be useful to build on for other clinicians in this field. In 1976 an article appeared co-authored by Nobel Prize winner Linus Pauling. It described a clinical benefit of intravenous AA in terminally ill cancer patients². This study was strongly criticized because of methodological flaws and the results could not be repeated in other studies in which oral supplementation was used^{3,4}. Even after this major setback, many studies regarding the effect of AA in cancer patients have been poorly designed. Most of the time there was a lack of supporting preclinical evidence for the specific role of AA in a certain setting. There was also a lot of heterogeneity in treated patients. The persistence of these qualitatively disappointing clinical studies surrounding AA in cancer undermines the real value of this nutrient and weakens efforts to fund additional well-designed RCTs. AA status and the effect of supplementation in these studies was most of the time followed in plasma, which correlates poorly with tissue AA⁵. In this thesis, we describe a method we developed to determine the AA concentration in lymphocytes that does correlate with tissue AA and that can be used in clinical studies. Currently, we are using this method to investigate the effect of tissue levels of AA in patients admitted in our hospital with a COVID-19 infection. In our RCT on the effect of AA supplementation, we examine a specific patient group treated with autologous HSCT for either lymphoma or myeloma, and the effects of AA on the immune system is already proven in preclinical research and can be explained by biological mechanisms.

All the results described in this thesis have been published in international peer review journals with open access. In this way, other researchers and haematologists can benefit from our findings without any limitations.

References

1. van Gorkom GNY, van Gelder M, Wieten L et al. 'Revival' van de haplo-identieke stamceltransplantatie. *Ned Tijdschrift voor Hematologie* 2017;14:359-66.
2. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA*. 1976; 73(10):3685-9.
3. Creagan ET, Moertel CG, O'Fallon JR, Schutt AJ, O'Connell MJ, Rubin J, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Medicine*. 1979;301(13):687-90.
4. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. *N Engl J Med*. 1985;312(3):137-41.
5. Omaye ST, Schaus EE, Kutnink MA, Hawkes WC. Measurement of vitamin C in blood components by high-performance liquid chromatography. Implication in assessing vitamin C status. *Ann N Y Acad Sci*. 1987;498:389-401.