Treosulfan pharmacokinetics and dynamics in pediatric allogeneic stem cell transplantation

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APPENDICES

ENGLISH SUMMARY

Treosulfan is an alkylating agent and is increasingly used as part of the conditioning regimen in pediatric allogeneic hematopoietic stem cell transplantation (HSCT) for malignant and nonmalignant diseases. In the last decade, treosulfan has gained popularity, because of its myeloablative and immunosuppressive properties, together with a relatively mild toxicity profile. This is advantageous, because complications related to toxicity of the conditioning regimen are still a major cause of transplant-related morbidity and mortality. From its structural analogue busulfan, we have learned that personalized dosing with the help of therapeutic drug monitoring (TDM), can reduce the risk of acute toxicity and graft failure in pediatric patients undergoing HSCT. But - in contrast to busulfan - only a few studies were performed to investigate the pharmacokinetics of treosulfan in pediatric patients. Furthermore, there are no studies that investigate the relationship with treosulfan exposure and clinical outcome. Also, treosulfan is relatively new in the field of HSCT and knowledge of acute and late side effects using treosulfan in the setting of HSCT with the currently recommended dose range (30-42 g/m^2) is limited. This thesis aims to answer questions regarding pharmacokinetics and pharmacodynamics of treosulfan in pediatric HSCT.

In **Chapter 2**, we have developed a population pharmacokinetic model of treosulfan in pediatric patients and predictive factors for pharmacokinetics such as patient- and transplant characteristics were explored. Treosulfan clearance was significantly influenced by bodyweight and age, but other factors such as underlying disease or estimated glomerular function as a measure of renal function did not. Also, we developed a limited sampling model with 3 sampling moments, which minimizes the burden of sampling.

In **Chapter 3**, the relationship between treosulfan exposure and acute toxicity is described in a multicentre pediatric cohort of 77 patients. We observed high interindividual variability in day 1 treosulfan exposure, which accurately reflects total exposure. The risk of ≥ grade 2 mucositis and skin toxicity was higher in patients with high treosulfan exposure, compared to patients with low exposure. This study

provides the first evidence that there is a possible exposure-toxicity relationship. In **Chapter 4**, we focused on investigating the relationship between treosulfan exposure and long-term clinical outcome in a pediatric cohort of 110 patients, transplanted for a nonmalignant disease. No associations were found with 2-year event-free survival and other outcomes, such as overall survival, engraftment, donor chimerism and graft-versus-host disease (GvHD). Just like in **Chapter 3**, we found a relationship with moderate to severe skin toxicity, but the relationship with moderate/severe mucositis was not as profound. Together, these results indicate a moderate exposure-toxicity relationship, but a relationship with event-free and overall survival could not be found. The clinical value of TDM could be in the prevention of skin toxicity, although implementation of preventive care guidelines could possibly reduce the incidence of cutaneous complications as well. The current evidence do not justify the use of TDM in routine patient care, but can be useful in specific cases and subgroups, such as infants, and warrants further investigation.

While treosulfan is a relatively old drug, originally registered for the palliative treatment of ovarian carcinoma in the mid-90s, only recently it was also registered as part of conditioning treatment prior to allogeneic HSCT in adult and pediatric patients. Treosulfan is given in 3 consecutive doses with a total dose up to 42 g/m^2, a different dosing scheme than in ovarian carcinoma. In the pediatric HSCT program of the Willem Alexander Children's Hospital, some patients experienced myalgia and arthralgia after conditioning with treosulfan, side effects which are not mentioned in the original Summary of Product Characteristics (SmPC). In **Chapter 5** we investigated the incidence, duration, location and severity of myalgia after treosulfan-based conditioning using a natural language processing (NLP) and text mining tool to search through Electronic Health Records and compared this with a cohort of busulfan-treated patients. In a cohort of 114 patients conditioned with treosulfan, myalgia occurred in 30% of patients. Of this group, 44% needed strong opiates and adjuvant medicines such as pregabalin, gabapentin or ketamine. Patients transplanted for sickle cell disease or beta-thalassemia had a higher incidence of myalgia than patients transplanted for other underlying diseases. It is not known why this particular

disease group is at higher risk for this side effect. This can be addressed in future research. This study has provided important new knowledge about treosulfan and its adverse events and also shows the great potential of NLP and text mining tools in health care applications.

With more pediatric patients that survive into adulthood after HSCT, the late effects of the transplant procedure become more important. Endocrine complications, such as gonadal dysfunction, could have a great impact on the quality of life. It is not known if drug exposure influences the prevalence of gonadal dysfunction. In **Chapter 6**, we evaluated the exposure of busulfan and treosulfan in relation to gonadal dysfunction in pediatric patients transplanted for a nonmalignant disease in a retrospective study. In the busulfan cohort, gonadal dysfunction occurred in 63% of patients and low (reduced intensity) busulfan exposure was not associated with a concomitant reduced risk of gonadal dysfunction. In the treosulfan group, gonadal dysfunction occurred less frequently (28%) and we found no association with exposure.

In **Chapter 7**, we have provided an overview of the available evidence for the relationship between pharmacokinetic parameters and clinical outcome or toxicities of the most commonly used conditioning and serotherapy agents in pediatric HSCT and discuss whether TDM of each agent is useful.

In **Chapter 8**, all study results are discussed with perspectives for future research. Although this thesis has provided important new insights in the pharmacokinetics and dynamics of treosulfan, future research is needed to further investigate the possible added value of treosulfan TDM in specific disease categories or patient groups. Also, integrating PK data of other conditioning and serotherapy agents can possibly further optimize results regarding clinical outcome and immune reconstitution. Furthermore, research regarding the late complications of treosulfan, such as endocrine, dental, neurocognitive, hair, ocular and pulmonary problems should be conducted as this aspect becomes increasingly important with more (very young) patients receiving HSCT with a treosulfan-based conditioning regimen.