Treosulfan pharmacokinetics and dynamics in pediatric allogeneic stem cell transplantation

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CHAPTER 08

DISCUSSION AND FUTURE PERSPECTIVES

INTRODUCTION

Over the past decade, treosulfan has gained popularity as a conditioning agent prior to pediatric allogeneic hematopoietic stem cell transplantation (HSCT) for both malignant and nonmalignant diseases because of its apparent favourable efficacy and toxicity profile. Unlike its structural analogue busulfan, little was known about its pharmacokinetic (PK) behaviour and its relationship with outcome parameters such as acute toxicity and event free or overall survival. Furthermore, knowledge of late side effects using treosulfan in the setting of HSCT, is limited. The aim of this thesis was three-fold:

1. to investigate the pharmacokinetic behaviour of treosulfan and develop a population pharmacokinetic model,
2. to investigate the relationship between treosulfan exposure, early toxicity and clinical outcome and
3. to acquire knowledge about the acute and late side effects of treosulfan.

PHARMACOKINETICS OF TREOSULFAN

Previous studies have reported great interpatient variability in treosulfan exposure in children [1-4]. However, these studies included only small numbers of patients and therefore factors influencing treosulfan pharmacokinetics could not be assessed properly. Pharmacometrics, which uses mathematical models based on physiology, pharmacology and disease for quantitative analysis of interaction between drugs and patients was used to build a population pharmacokinetic (PopPK) model of treosulfan in pediatric patients in **Chapter 2**. Potential factors influencing pharmacokinetics (covariates) were explored and a limited sampling model was developed. We found that the pharmacokinetic behavior of treosulfan in pediatric patients was best described by a two-compartmental model with first order elimination. Bodyweight with allometric scaling and a maturation function of treosulfan clearance based on postmenstrual age (PMA) were significantly associated with treosulfan clearance. Other covariates,

such as estimated glomerular function (eGFR), sex, underlying disease, conditioning regimen did not improve the model. Current dosing recommendations of treosulfan are based on body surface area (BSA) [5]. It is known that BSA-based dosing can lead to overestimation, especially in younger children. Allometric dosing, with a maturation component accounting for age, is a better way to predict drug doses [6]. Dosing of treosulfan based on bodyweight and age can be used to achieve more comparable exposures throughout the whole age range. This is also shown in a study with pediatric patients that simulated different dosing schemes, including BSA-based according to the Summary of Product Characteristics, an age-based scheme, dosing based on a PopPK model with age and weight as covariate, and a PopPK model with age, weight and creatinine [7]. Dosing according to the PopPK model with weight and age achieved better predictable treosulfan exposures across all ages, while BSA-based and age-based dosing led to higher exposures in very young children (<2 years old). The addition of creatinine did not improve target attainment. With that being said, there still is unexplained variability of ~30% in treosulfan clearance that could not be attributed to one of the explored covariates. Uncovering covariates can further optimize treosulfan (initial) dosing. Possible interesting covariates mentioned by others are blood pH and body temperature, because of the pH- and temperature-dependent conversion of treosulfan to its metabolites [8].

TREOSULFAN PHARMACOKINETICS AND THE RELATIONSHIP WITH EARLY TOXICITY AND CLINICAL OUTCOME

Building on the experience with personalized dosing of busulfan using therapeutic drug monitoring (TDM), we hypothesized that pharmacokinetic parameters of treosulfan, in particular area under the concentration-time curve (AUC), could also have a relationship with toxicity and efficacy. In **Chapter 3**, we studied the relationship between treosulfan AUC and early toxicity in a cohort of 77 pediatric patients, transplanted for nonmalignant or malignant diseases. In **Chapter 4**, we studied treosulfan exposure in relationship to long term clinical outcome (2-year event free survival, EFS), in a cohort

of 110 pediatric patients with nonmalignant diseases. The results of these studies are summarized and discussed in **Chapter 7.** Briefly, high interindividual variability was observed for day 1 treosulfan AUC. High day 1 treosulfan AUC (>1750 mg*h/L) was associated with an increased the risk of ≥ grade 2 skin toxicity. Although a relationship was found with ≥ grade 2 mucositis in the study described in **Chapter 3**, this could not be confirmed in **Chapter 4**. Only a relationship with all grade mucositis was found, probably because of the lack of patients with malignant diseases, of whom 50% experienced grade ≥2 mucositis. More importantly, no associations were found between treosulfan AUC and 2-year EFS and other outcome parameters, such as 2-year overall survival (OS), engraftment, chimerism (at 1 year) and graft-versus-host disease (GvHD). Two other studies investigated the relationship between treosulfan exposure and outcome in pediatric stem cell transplantation [7, 9]. While one study reported an association of high treosulfan exposure with transplant-related mortality [7], the other reported only a trend towards such an association, but not with EFS [9]. These differences could possibly be explained by interindividual variability in exposure between the studies, which was much higher in the two aforementioned studies [7, 9]. Taken all these results into account, a moderate exposure-toxicity relationship is seen, but this is not evident and consistent for (event free) survival. While TDM could be used to prevent skin toxicity, the use of other measures, such as preventive skin care, could also reduce the incidence of ≥ grade 2 skin complications [10, 11]. We think that the current evidence does not justify the use of TDM in routine patient care, but can be useful in specific cases and subgroups - such as infants, certain disease types or patients with comorbidities - and warrants further investigation.

ACUTE AND LATE SIDE EFFECTS OF TREOSULFAN

In general, it is noticed that treosulfan is well tolerated in pediatric patients. Common (but moderate) side effects are gastrointestinal, mucosal and skin related. Transient elevation of liver enzymes are also commonly reported [5]. Because treosulfan is relatively new in the field of HSCT it is possible that some less known acute side effects have not been observed or registered yet, possibly because of lack of awareness.

In the pediatric HSCT program of the Willem Alexander Children's Hospital, clinical observations of myalgia and arthralgia after conditioning were reported increasingly by both nurses and physicians in patients treated with treosulfan-based conditioning. 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. 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 risk of experiencing myalgia than patients transplanted for other underlying diseases. The cause of this higher incidence is unknown. Pre-transplant disease history, altered pain perception and genetic predisposition are factors that could be of influence and warrants further investigation. This study has provided important new knowledge about treosulfan and its adverse events and this information has led to a more standardized (early) pain management approach when patients experience myalgia after conditioning in the pediatric HSCT program of the Willem Alexanders Children's Hospital. This study also shows the huge potential of NLP and text mining tools in healthcare applications. With the increasing amount of physician- and nurse-reported information being stored in Electronic Health Records, validated text mining tools can help to extract medical information more efficient in order to assess treatment effectiveness and safety in clinical practice [12].

As a result of the growing popularity of treosulfan as a conditioning agent prior to HSCT for nonmalignant diseases, the need for information on the late effects of treosulfan is growing. More pediatric patients survive into adulthood and complications of the transplant procedure, especially endocrine complications such as gonadal dysfunction, could have a great impact on the quality of life. Only a few studies have reported on the endocrine complications of busulfan and treosulfan-based conditioning [13-16]. These studies indicate a more favourable toxicity profile for treosulfan. However, it is unknown if drug exposure influences the prevalence of endocrine complications. 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 busulfan exposure (i.e. reduced intensity conditioning) was not associated with a reduced risk of gonadal dysfunction. In the treosulfan group, gonadal dysfunction occurred less frequently (28%) and we found no association with exposure. Future research should preferably include larger patient numbers with sufficient follow-up time, so that other covariates, such as age at HSCT and underlying condition, can also be taken into account.

FUTURE PERSPECTIVES

Finding a conditioning regimen that is efficacious, but has minimal side effects is very challenging. Significant improvements have been made to optimize conditioning regimens by using less toxic agents, less toxic combinations and dose optimization. Treosulfan has been introduced as a less toxic alternative for busulfan, now a little over 10-15 years ago. Still, knowledge about the pharmacokinetics and dynamics of treosulfan in the pediatric HSCT setting is limited, as are results on long term clinical outcome. This thesis has provided important new insights in the pharmacokinetics and dynamics of treosulfan, but are we there yet? There are still some questions that remain unanswered and can be addressed in future research.

Treosulfan exposure in specific disease types and patient groups

Our research mainly focused on nonmalignant pediatric patients. Treosulfan is also used as a conditioning agent for malignant diseases and the relationship between treosulfan exposure and clinical outcome parameters, such as relapse, have not been investigated in the pediatric setting. It is not known if the currently available data can also be applied to malignant diseases, such as acute lymphoblastic leukemia (ALL). Recently, the first results of the For Omitting Radiation Under Majority age (FORUM) study have been published; a prospective, randomized, controlled trial in which busulfan- and treosulfan-based conditioning regimens are directly compared

to a traditional total body irradiation (TBI)-based regimen in pediatric patients with ALL [17]. The randomization study was prematurely stopped when the relapse incidence in both chemotherapy arms was found to be significantly higher compared to the TBI-based arm. No difference in relapse rate was found between the busulfan- and treosulfan-based arms. However, a difference between the two chemo-based arms in the FORUM study is that a significant proportion of patients in the busulfan arm had PK analysis performed, with subsequent TDM. For treosulfan, TDM-adjusted dosing was not performed. We have conducted an add-on study in the FORUM trial focused on the PK of treosulfan and its relationship with clinical outcome. The data of this add-on study are currently being collected and the final analysis has to be awaited, but so far preliminary data do not point to a clear correlation between exposure and relapse [18]. Furthermore, identifying specific patient groups that could benefit from TDM of treosulfan should ideally be performed. Such a study requires large number of patients and can be difficult to establish. Collaboration of centers all over the world is needed to answer these questions. Currently, a study to perform a patient-level meta-analysis on treosulfan PK and outcome is being set up with centers participating worldwide, which will investigate the relationship between treosulfan drug exposure and disease type and the extent of donor chimerism post-conditioning as well [19].

Treosulfan in combination with other agents

Pharmacological research in the field of HSCT is usually focused on one agent at a time to optimize the studied drug. However, in the case of conditioning agents, these are almost never given alone, but are combined with both other chemotherapeutic agents and/or serotherapy and concomitant drugs. Together with other transplantation related covariates, varying combinations of these agents can have different effects on clinical outcome. Since PK data of more agents have become available, such as fludarabine, and the serotherapy agents anti-thymocyte globulin (ATG), anti-T lymphocyte globulin (ATLG) and alemtuzumab, an integrated approach may eventually be required to achieve optimal results regarding clinical outcome and immune reconstitution [20-26].

Clinical outcome of HSCT with treosulfan-based versus busulfan-based conditioning

With treosulfan being used more often as the backbone in the conditioning regimen, similarities and differences in outcome between treosulfan-based and busulfan-based conditioning are becoming more clear. In general, it seems that there are no major differences in overall survival (OS) between treosulfan-based and busulfan-based myeloablative conditioning. This is shown in both malignant as nonmalignant pediatric cohorts [17, 27-30]. In the FORUM study with pediatric ALL patients, both the busulfan and treosulfan arm show an 2-year overall survival of 77% [17]. In a study with thalassemia major patients, the 2-year OS rates were 92.7% and 94.7% for busulfan and treosulfan, respectively [28]. In a very recent study in patients with Wiskott-Aldrich syndrome (WAS), the OS rates at last follow up were 89.3% and 89.4% for busulfan and treosulfan, respectively [27]. Looking at other outcome parameters, such as event-free survival (EFS), relapse, treatment-related mortality (TRM), GvHD, donor chimerism and the need for secondary procedures, differences can be seen. Although no differences in EFS, relapse, TRM and GvHD were reported in the FORUM study and similar results were observed in studies performed in chronic granulomatous disease (CGD), severe combined immunodeficiency (SCID) and leukocyte adhesion deficiency (LAD) type I and II [17, 29-31], the study in WAS patients reported a higher incidence of graft failure, mixed donor chimerism and more frequently received secondary procedures (e.g. 2nd HSCT, stem cell boost or donor lymphocyte infusion) in patients receiving treosulfan-based conditioning [27]. The necessity of a 2nd HSCT was also higher for treosulfan conditioned patients with thalassemia major compared to busulfan conditioned patients [28]. It is difficult to interpret these data, because it is possible that there is some kind of bias introduced in these retrospective studies. The underlying disease and the need to use a fully myeloablative regimen can play a role. Also, administration of serotherapy and stem cell source can influence the degree of engraftment as well. In **Chapter 4** we found a higher incidence of mixed donor chimerism in patients conditioned with treosulfan and fludarabine compared to treosulfan, fludarabine and thiotepa. The addition of thiotepa might attribute to

a higher donor chimerism rate. Difficult as it is, it would be of great value to try to investigate which factors influence the level of donor chimerism in future research. Still, treosulfan-based conditioning is an excellent alternative for busulfan-based conditioning with good clinical outcome in a large variety of diseases, especially with more data becoming available regarding the favourable late effects of treosulfan.

Late effects of treosulfan

As mentioned before, research on late effects of treosulfan has become more and more important. Research should not only focus on endocrine complications, but should also include other late effects such as dental, neurocognitive, hair, ocular and pulmonary problems. This would be preferably studied in a single disease group, as a heterogeneous cohort is more difficult to analyze. However, such studies are difficult to perform and input from multiple centers is needed to gain a sufficient number of well documented patients. Different initiatives are currently being set up, for instance in RAG1-SCID within the RECOMB consortium [32].

CONCLUSION

Treosulfan has shown to be an effective and safe conditioning agent in pediatric HSCT for malignant and nonmalignant diseases. This thesis has shown that there is considerable interpatient variability in treosulfan exposure. While there is a (moderate) exposure-toxicity relationship, no relationship with clinical outcome is found which makes treosulfan (compared to busulfan) an easy to use conditioning agent without requirement of TDM in the majority of patients. The information from the increased use of treosulfan has added to the knowledge of acute and late side effects, although more research on the late effects with longer follow up is still needed and eagerly awaited.

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