Optimization of pediatric haematopoietic stem cell transplant outcomes through the application of pharmacokinetics and supportive care

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Summary
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This thesis describes research done with the aim of optimizing outcomes in children undergoing haematopoietic stem cell transplant (HSCT) through the application of pharmacokinetics and supportive care. The use of pharmacokinetics to individualize exposure to busulfan and cyclosporine; the assessment of the symptom burden of children receiving chemotherapy including HSCT conditioning and the application of evidence to improve chemotherapy-induced nausea and vomiting (CINV) control during conditioning are emphasized.

In Part 1, our work to describe busulfan pharmacokinetics in children and the association between dose intensity (AUC) and HSCT outcomes (hepatic venous occlusive disease (HVOD), engraftment failure and overall survival) is presented. We observed age-related differences in first-dose pharmacokinetic parameters in a cohort of 47 patients. Specifically, total body clearance when corrected for body surface area was significantly lower in children < 1 year of age (76 ± 33.1 vs. 99 ±57.3 mL/min/m²) and in children < 4 years of age (84 ± 52.8 vs. 103 ± 50.4 mL/min/m²). Busulfan AUC achieved after the first dose was not associated with HVOD or other transplant outcomes. However, busulfan doses in all children included in this study were individualized to achieve an AUC of 900 to 1500 µM·min after the third busulfan dose which may have obscured any association between overall dose intensity and HSCT outcomes. Nevertheless, acknowledging the relationship between busulfan dose intensity and HSCT outcomes documented in adults and the wide variation in busulfan total body clearance observed in children by us and others, busulfan pharmacokinetic monitoring and dose adjustment to achieve the conventional AUC target is recommended in children.

Part 1 also presents our efforts to substantiate the relationship between cyclosporine trough concentrations (C₀) and aGVHD in children undergoing HSCT since target C₀ values vary widely between centres. We observed an inverse relationship between severe aGVHD and the median cyclosporine C₀ achieved during the week before engraftment (OR, 0.99; CI, 0.97 to 1.00; p=0.0454). Our later work determined that the relationship between cyclosporine C₀ and AUC after the first dose is only moderate though significant (Spearman’s ρ 0.628; p = 0.002). In acknowledgement of the strong relationship between cyclosporine AUC and outcomes in solid organ transplant and the demonstrated need to achieve the target C₀ before engraftment, we developed an initial IV cyclosporine dose for use in children undergoing HSCT that is likely to achieve the AUC targeted in renal transplant patients (4200 µg/L·hr). We conclude that the achievement of a cyclosporine C₀ target from 100 to 200 µg/L is important to control aGVHD. The impact of cyclosporine AUC targets remains to be determined.
**Part 2** describes our work to transfer the findings of the studies presented in part 1 to the bedside. Traditionally, characterization of AUC requires a minimum of 8 samples. This number of samples is onerous. The blood volume required may represent a significant proportion of an infant’s total blood volume especially if a large discard volume is required for each sample. Furthermore, the number of samples represents a significant workload for nurses or phlebotomists to obtain and for laboratory technicians to assay. A limited sampling strategy which reliably estimates AUC using two to four samples would permit AUC determination even in young infants and would reduce nursing and laboratory workload. Two and three point limited sampling strategies for busulfan AUC determination after the first IV dose were developed and validated. A four point limited sampling strategy for determination of cyclosporine AUC after the first IV dose and a three point limited sampling strategy for determination of cyclosporine AUC after subsequent IV doses were also developed and validated. All limited sampling strategies had acceptable bias and precision. These limited sampling strategies enable future evaluations of busulfan and cyclosporine AUC for clinical and research purposes.

In **Part 3**, our work that aims to optimize the supportive care of children receiving chemotherapy, including HSCT conditioning, is presented. Our first attempt to understand the experience of children receiving cancer treatment was through the eyes of their parents. Adapting a survey used for adult cancer patients, we asked 200 parents of children aged 4 to 18 years who were receiving active cancer treatment to rank the prevalence, severity and degree of bother of 69 or 71 symptoms, depending on the age of their child. This work helped us understand the symptom burden of these children and to appreciate the difference between symptom prevalence, severity and bother and the importance of evaluating both physical and psychosocial symptoms.

Given the subjective nature of many of the symptoms experienced by children with cancer, it is important to obtain their self-assessment of the severity and bother of these symptoms. As a first step to adopting, adapting or developing a pediatric self-report symptom assessment tool, we evaluated the published pediatric symptom assessment scales. Of the eight pediatric self-report symptom assessment scales identified, none had been used to screen for symptoms. There is therefore a need to develop such a scale or to adapt one of the existing scales.

Since parents ranked chemotherapy-induced nausea among the top five most severe and bothersome symptoms in their children, we believe it to be important to improve CINV control. We used established guideline adaptation methodology to synthesize the available literature and develop guidelines for the classification of chemotherapy emetogenicity in children and to prevent acute CINV in children. One of the research gaps identified in this...
process was the lack of pediatric formulations for many antiemetic agents, including aprepitant. The investigation of novel agents in younger children is often hampered by the lack of an appropriate pediatric formulation. To facilitate future investigation of the efficacy and safety of aprepitant in young children, an extemporaneous oral liquid aprepitant formulation with acceptable stability was developed.\textsuperscript{16}

In summary, this thesis focuses on optimization of drug-related outcomes in children undergoing HSCT. The pharmacokinetic disposition of busulfan and cyclosporine in this population has been described and limited sampling strategies which can be used to apply pharmacokinetics for the benefit of individual patients have been developed. Guidelines for the prevention of CINV have been produced using rigorous methodologies with the aim of improving the supportive care of children receiving chemotherapy, including HSCT conditioning.