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

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General Introduction, Thesis Aim and Outline
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INTRODUCTION

The optimization of any activity requires a full understanding of the available tools, the ability to use them deftly and a quick appreciation of the need for new tools as well as the skills required to develop and validate them. Optimization of haematopoietic stem cell transplant (HSCT) drug-related outcomes in children is no different. Pharmacokinetic monitoring and evidence-based guidelines are two tools available to optimize the care of children as they move through HSCT.

For example, busulfan is an appropriate conditioning agent for children with acute myelogenous leukemia, neuroblastoma and other conditions. To achieve the balance between efficacy (achievement of neutrophil engraftment) and safety (avoidance of hepatic sinusoidal obstruction syndrome), busulfan dosing must be individualized to achieve a certain dose intensity defined as either the area under the concentration versus time curve (AUC) or steady-state concentration (Css).\(^1,2\) The busulfan AUC or Css target in current use in pediatric HSCT has been extrapolated from evidence in adult HSCT patients with chronic myelogenous leukemia. Similarly, the dose intensity of cyclosporine, an agent given to prevent acute graft-versus-host disease (aGVHD), must be individualized to achieve optimal HSCT outcomes.\(^3,4\) However, which pharmacokinetic parameter (trough whole blood concentration \(C_0\) or AUC) has the strongest link to HSCT outcomes is controversial.\(^5\) Evidence-based guidelines, a second tool, synthesize evidence into recommendations for consideration by clinicians. Such guidelines are especially challenging in pediatric oncology due to the low quality of evidence often available.

New tools are required to apply pharmacokinetic principles to busulfan dose individualization as a routine clinical practice. Specifically, a validated limited sampling strategy is required to minimize blood loss in children. Limited sampling strategies are also required to begin to explore the strength of the association between cyclosporine AUC and HSCT outcomes such as aGVHD. New evidence-based guidelines are required to provide optimal, evidence-based supportive care to children undergoing HSCT. Guidelines for acute chemotherapy-induced nausea and vomiting (CINV) prophylaxis, for example, aim to mitigate one of the most distressful treatment-related adverse effects reported by adult and pediatric cancer patients. Guidelines such as this also highlight the existing research gaps within the field.

This thesis highlights efforts focused on increasing clinicians’ ability to use busulfan and cyclosporine skillfully through descriptions of their pharmacokinetic disposition, the application of pharmacokinetic principles to optimize patient outcomes and on maximizing the ability of clinicians to provide supportive care that is focused on the patient’s priorities and is evidence-based.
THESIS AIM

This thesis aims to:

- describe the pharmacokinetic disposition of busulfan and cyclosporine and its clinical significance in children undergoing HSCT;
- develop tools to facilitate the bedside application of pharmacokinetics in the setting of pediatric HSCT and
- optimize the supportive care of children receiving chemotherapy including HSCT conditioning, especially the control of CINV

THESIS OUTLINE

Part 1 of this thesis describes busulfan and cyclosporine pharmacokinetics in children undergoing HSCT and its clinical significance.

Part 2 of this thesis describes the development of tools which facilitate the incorporation of busulfan and cyclosporine pharmacokinetics into the routine care of children undergoing HSCT.

Part 3 describes efforts to optimize the supportive care of children receiving chemotherapy including HSCT conditioning. Symptom assessment and CINV control optimization are emphasized.