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

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Discussion
1. **Pharmacokinetics of Busulfan and Cyclosporine in Children Undergoing HSCT**

Busulfan dose individualization is now the international standard of care in pediatric HSCT.\(^1\) Although IV administration greatly reduces inter-individual variability in busulfan pharmacokinetic disposition compared to oral administration, approximately 40% of children will still require dose adjustment to achieve an AUC within the very broad target range (900 to 1500 \(\mu\text{M}\cdot\text{min}\)), regardless of the guideline for initial IV busulfan dose selection used.\(^2\)\(^-\)\(^5\)

Cyclosporine dose individualization is also the accepted international standard of care in pediatric HSCT; yet, there is no consensus regarding the target cyclosporine concentration (\(C_0\)) and targets vary widely between centers.\(^6\)\(^-\)\(^9\) Furthermore, there is no consensus regarding the time period during the HSCT process when achievement of the target cyclosporine concentration is critical to prevention of acute graft vs. host disease (aGVHD). Although we have observed an inverse relationship between the development of severe aGVHD and the \(C_0\) prior to neutrophil engraftment,\(^7\) aGVHD prevention will likely be improved through the more skillful application of another pharmacokinetic target for cyclosporine dose individualization.

1.1 **Future Directions**

Further explorations into the pharmacokinetic disposition of busulfan and cyclosporine in children undergoing HSCT will expand our understanding of the determinants of pharmacokinetic variability of both drugs. The influence of patient-related factors such as underlying conditions and genetics as well as factors external to the patient such as drug interactions and administration technique will require evaluation in this regard. Moreover, many agents other than busulfan and cyclosporine used during HSCT are subject to wide, often age-related pharmacokinetic and/or pharmacogenetic variability. Description of the pharmacokinetic disposition of these agents will inform decisions to individualize dosing for HSCT patients.

Investigators have postulated that the patient’s underlying condition may dictate, at least in part, the pharmacokinetic disposition of busulfan after oral administration but it is not clear that this relationship exists with IV busulfan.\(^10\) Since patients with pre-existing liver damage, iron overload, history of pancreatitis, busulfan-thiotepa conditioning, myelodysplastic disease or malignant disease are thought to be at higher risk of hepatic venous occlusive disease (HVOD),\(^11\)\(^-\)\(^16\) the exploration of the pharmacokinetic disposition of busulfan in large populations of children with these conditions would help to determine if this relationship exists. To date, there are no data that describe a relationship between cyclosporine pharmacokinetic parameters and underlying disease other than overt hepatic impairment. The determination of
such a relationship, if it does exist, would lead to subsequent evaluations of specific pharmacokineti

c targets to optimize cyclosporine dose intensity in these populations.

Since glutathione conjugation is a major step in busulfan metabolism, it stands to reason that polymorphis

m in the enzymes involved in this pathway would influence its pharmacokinetic disposition. However, the degree to which the pharmacokinetic disposition of busulfan is determined by pharmacogenetics is controversial.\textsuperscript{18-20} The GSTA1*A2 haplotype was associated with higher busulfan clearance\textsuperscript{20,21} and GSTA1*B has been associated with decreased busulfan clearance.\textsuperscript{18} Confirmation of this association in a larger patient cohort is required.

Cyclosporine is metabolized primarily via CYP3A4 and CYP3A5. Although it is unlikely that pharmacogenetics play a large role in its pharmacokinetic profile after IV administration, genetic variability may influence HSCT outcomes through mechanisms other than pharmacokinetics (see 2.2).

Concurrent drug administration may influence the achievement of busulfan and cyclosporine target pharmacokinetic parameters. While drug-drug interactions may be fairly straightforward to manage when a trough concentration is targeted for dose individualization, an interaction involving drugs where AUC is the target may be more complicated. For example, administration of an interacting drug may significantly alter the trough concentration without resulting in significant changes in AUC. Nevertheless, prospective examinations of the potential interaction of busulfan with drugs such as acetaminophen, phenytoin, metronidazole, voriconazole and posaconazole are not likely to be undertaken due to the potential for negative impact on individual patient outcomes. Studies of the effect of drugs with the potential to alter cyclosporine pharmacokinetic disposition such as voriconazole have been undertaken and guidance for pre-emptive dose has been proposed.\textsuperscript{22} Should the pharmacokinetic target of cyclosporine shift from the $C_0$ to another parameter such as AUC, these studies and recommendations would need to be re-evaluated.

The rate of busulfan IV administration has recently been raised as a potential determinant of busulfan AUC. (personal communication, Dr. J. Russell, May 26, 2012) This is particularly relevant in settings where the rates of administration of the busulfan dose used to individualize therapy and the adjusted busulfan dose differ significantly. Such is the case where a small busulfan test dose is administered prior to HSCT conditioning to determine the larger busulfan dose to be given to individual patients during conditioning. Similarly, this situation may arise where a large busulfan upward or downward dose adjustment is required following AUC determination. Confirmation that the adjusted busulfan dose has achieved the target busulfan AUC may be required in these circumstances.
1.2 IMPLICATIONS FOR RESEARCH

The implications of the above-mentioned questions regarding the pharmacokinetic disposition of busulfan and cyclosporine in children undergoing HSCT are:

- The relationship between patient underlying conditions and the pharmacokinetics of busulfan and cyclosporine requires evaluation.
- The specific genetic polymorphisms which contribute significantly to the inter-individual variability in busulfan pharmacokinetic disposition should be determined.
- Every effort should be made to compare the pharmacokinetic disposition of busulfan in the absence and presence of drugs with the potential to alter its pharmacokinetics.
- The impact of rate of administration on busulfan AUC requires evaluation.
- Multivariable analysis should be applied to determine which patient and non-patient factors identified as significant predictors of busulfan AUC on univariate analysis should be used to select the initial busulfan dose administered clinically.
- The pharmacokinetic disposition of other drugs administered during HSCT need to be described so that those which display significant inter-individual variability can be identified for further investigation with respect to the relationship between pharmacokinetic parameters and HSCT outcomes.
- Since the number of children receiving HSCT is small, centres should routinely pool their data to evaluate, retrospectively or prospectively, the questions raised here.

2. APPLICATION OF PHARMACOKINETICS IN CHILDREN UNDERGOING HSCT

The availability of a robust limited sampling strategy to estimate busulfan AUC after the first IV every six hourly dose facilitates both clinical care as well as investigations to further elucidate the importance of busulfan dose individualization. Similarly, the relationship, if any, between cyclosporine AUC and HSCT outcomes is as yet unknown. The validated limited sampling strategies described in this thesis afford an opportunity to evaluate this relationship.

2.1 FUTURE DIRECTIONS

In the future, research into the application of busulfan and cyclosporine pharmacokinetics in children undergoing HSCT will include an evaluation of the relationship between HSCT outcomes and pharmacokinetic targets other than busulfan AUC and cyclosporine \( C_0 \). As well, busulfan AUC targets specific to patient’s diagnosis merit evaluation.

Our finding that the maximum busulfan concentration was significantly lower in children who developed HVOD than those who did not is intriguing. Other investigators have hypothesized that patients with high hepatic busulfan clearance may be at higher risk of HVOD due to more extensive hepatic glutathione depletion. Achieving the target busulfan AUC alone may not be
sufficient to mitigate a patient’s risk of HVOD. Similar to what has been suggested for aminoglycoside pharmacokinetic monitoring by Begg et al, the achievement of a target maximum busulfan plasma concentration as well as an AUC target may be required to optimize busulfan therapy.

Based on adult studies which demonstrated safety, IV busulfan is now often given on a once daily basis rather than every six hours since this reduces nursing and pharmacy workload. Since use of the limited sampling strategies developed for use after every 6 hourly administration would be inappropriate, limited sampling strategies to estimate busulfan AUC after once daily administration must be developed and validated. We are currently developing a limited sampling strategy for use after once daily IV busulfan administration.

The accepted busulfan AUC target (every 24 hour dosing: 3600 to 6000 μM·min) is quite broad. It has recently been suggested that adults undergoing HSCT for treatment of acute myelogenous leukemia (AML) and receiving once daily IV busulfan have a higher overall survival rate (75% vs. 55% at 50 days post-HSCT; p=0.049) when the busulfan AUC achieved is < 4000 μM·min (personal communication, Dr. J. Russell, May 26, 2012). We are conducting a retrospective analysis of HSCT outcomes and busulfan AUC achieved based on patient diagnosis to determine whether a prospective study of this question would be appropriate.

As stated above, pharmacogenetics may also influence the busulfan AUC achieved by individual patients. Data in this area are amassing quickly though many findings are discrepant. In the future patients at risk of high busulfan AUC based on genetic factors may be identified prior to HSCT so that either busulfan can be avoided all together or the busulfan dose/target AUC can be adjusted accordingly. Although polymorphisms of metabolic enzymes are not likely to be a significant determinant of cyclosporine pharmacokinetics, HSCT outcomes may be influenced by polymorphisms that determine risk of cyclosporine-induced hypertension or nephrotoxicity. Again, knowledge of these polymorphisms may inform the clinician’s and family’s decision regarding the choice of aGVHD prophylaxis.

If cyclosporine AUC is a better predictor of aGVHD than is \( C_0 \), the current practice of cyclosporine dose adjustment to achieve a target \( C_0 \) would not be expected to lead to optimal aGVHD prophylaxis since the correlation between cyclosporine \( C_0 \) and AUC is not strong. Thus, there may be an opportunity to improve aGVHD control by identifying and prospectively validating cyclosporine AUC targets. Indeed, we are using the limited sampling strategies described in this thesis to estimate cyclosporine AUC after the first and subsequent IV doses in an ongoing, prospective, multi-centre study to evaluate the influence of cyclosporine AUC on HSCT outcomes. This study will identify the most appropriate cyclosporine pharmacokinetic
target (e.g. AUC, $C_0$ or maximum concentration) for dose individualization in children. The relationship of this parameter with aGVHD as well as with hypertension, nephrotoxicity, relapse and engraftment will require confirmation in a larger cohort.

Biomarkers of aGVHD risk have been identified in adult HSCT patients\textsuperscript{35} and warrant investigation in children. The ability to adjust the intensity of aGVHD prophylaxis during the course of HSCT in individual patients based on biomarkers is intriguing. Whatever the aGVHD prophylaxis regimen and whatever the pharmacokinetic target ($C_0$ or AUC) of the agents used, the impact of increased or decreased immunosuppression before and during HSCT based on an individualized aGVHD risk assessment deserves study.

Many of the agents used during HSCT are subject to wide, often age-related pharmacokinetic and/or pharmacogenetic variability. Examples of these include thymoglobulin, cyclophosphamide, mycophenolate mofetil, tacrolimus and methotrexate. Investigation into the relationship between the pharmacokinetic disposition of these agents and HSCT outcomes such as aGVHD, chronic graft versus host disease and viral reactivation would likely serve to further optimize HSCT outcomes. We currently have studies underway to evaluate the influence of thymoglobulin pharmacokinetics and cyclophosphamide pharmacokinetics and pharmacogenetics on HSCT outcomes.

2.2 IMPLICATIONS FOR RESEARCH
Ideas for progress in the area of the clinical application of pharmacokinetics in the care of children undergoing HSCT include:

- The strength of the relationship between busulfan pharmacokinetic parameters (e.g. maximum concentration, AUC) and HVOD merits examination as does the interaction between these parameters.
- The need to fine-tune the target busulfan AUC for use in specific diagnoses such as AML must be determined.
- A limited sampling strategy for reliable prediction of busulfan AUC after once daily administration to children must be developed.
- The contribution of pharmacogenetics to busulfan-related clinical outcomes must be determined and evidence-based recommendations should be developed to facilitate the incorporation of this information into clinical decision-making.
- The relative importance of AUC, $C_0$ and other parameters as a pharmacokinetic target in cyclosporine dose individualization will be determined in the near future. The findings of the currently on-going study will likely require confirmation in a larger and more varied sample.
• Adjustment of the extent of aGVHD prophylaxis before and during HSCT through the use of biomarkers to predict aGVHD risk may provide a mechanism to further optimize aGVHD control.

• The relationship between pharmacokinetic parameters of other drugs used in HSCT which display significant inter-individual variability and HSCT outcomes needs to be determined. Appropriate pharmacokinetic targets for those drugs for which there is a significant relationship must then be determined in prospective studies.

• Since the number of children receiving HSCT is small, centres should routinely pool their data to evaluate, retrospectively or prospectively, the questions raised here.

3 SUPPORTIVE CARE OF CHILDREN UNDERGOING HSCT

It is obvious that much of the symptom burden borne by children receiving antineoplastic treatment, including HSCT conditioning, is subjective and can only be fully assessed by children themselves. It is therefore imperative that tools be developed that allow even very young children to communicate the severity of their symptoms and the extent to which the child is bothered by them.

CINV is one of the most severe and most bothersome adverse effects of chemotherapy identified by adult patients and parents of children with cancer. Cancer patients consistently rank chemotherapy-induced nausea and/or vomiting among the most severe and distressing adverse effects of treatment. Children undergoing myeloablative hematopoietic stem cell transplant (HSCT) receive highly emetogenic chemotherapy and almost all experience CINV despite receiving antiemetic prophylaxis. When antiemetic prophylaxis is provided to adult cancer patients according to the recommendations of evidence-based guidelines, CINV control is improved. Similarly, our pediatric guidelines aim to improve CINV control in children by providing evidence-based recommendations for antiemetic prophylaxis. The performance of these guidelines requires prospective evaluation.

2.1 FUTURE DIRECTIONS

Symptom management in children with cancer will be improved when a symptom screening tool is available for routine use by children themselves. We have developed a prototype of such a tool that is currently undergoing refinement. The final version will be converted to an electronic platform. This tool will screen for approximately 15 symptoms and may be completed in hospital, in clinic and/or at home. We anticipate that children will complete the tool prior to an interaction with a health care provider and that their responses will serve to focus the dialogue with the health care provider on the symptoms of most importance to the child. Responses can be captured and tracked in the health record. Ideally, each symptom
included in the screening tool will be linked to guidelines regarding its prevention and/or management with recommendations aimed at both parents/patients and health care providers. In this way each member of the care circle will be focused on symptoms that are most important to the child and will have access to evidence-based recommendations regarding their management. The impact of the final screening tool on patient and family satisfaction, symptom burden and quality of life will require prospective evaluation.

Similarly, the degree to which CINV is controlled when the recommendations of the current CINV guidelines are followed needs to be determined. Patient-related factors that may influence an individual’s risk of developing CINV need to be identified in children and incorporated into recommendations for CINV prevention. Factors identified in adults that increase CINV risk include: chemotherapy regimen, age, sex, prior receipt of chemotherapy and history of alcohol use. Adult guidelines recommend a higher level of prophylaxis for patients with these factors. The only risk factor for CINV definitively identified in children is the chemotherapy regimen. Genetic polymorphisms which convey an increased risk of CINV or variability in the response to antiemetic agents are beginning to be identified in adult cancer patients. The influence of such polymorphisms on CINV control also needs to be evaluated in children and incorporated into the recommendations of evidence-based guidelines.

Of course, novel antiemetic agents such as acupressure, olanzapine, palonosetron and rolapitant must be rigorously evaluated in children using validated patient-reported outcome tools. We are now undertaking a multi-centre trial of the contribution of acupressure to CINV control in children and a feasibility study of the use of olanzapine in children receiving highly emetogenic chemotherapy. The development of palatable and bioavailable pediatric dosage forms (e.g. oral liquids, patches and oral dissolving tablets) of novel antiemetic agents should be a priority for pharmaceutical manufacturers and pharmacists.

Surprisingly, even antiemetic agents that are widely considered to be the standard of care require systematic study in children. For example, the currently recommended antiemetic dose of dexamethasone for children receiving highly emetogenic chemotherapy (6 mg/m²/dose every 6 hourly) is effective but likely higher than necessary. Elegant dose-finding studies have established the minimum effective dexamethasone dose in adult cancer patients. Similar studies must be undertaken in children so that the most effective and safest prophylaxis can be provided.

The list of research gaps in the evidence base available to inform guidelines to prevent CINV in children is lengthy. Meeting these gaps will improve our ability to control CINV and reduce the symptom burden of children receiving chemotherapy. Not only is improved CINV control
expected to improve quality of life but, in children undergoing HSCT, it is possible that the risk of aGVHD may be reduced. The impact of improved CINV control on morbidity beyond the period of chemotherapy administration requires evaluation.

3.2 IMPLICATIONS FOR RESEARCH
Significant progress in the supportive care of children with cancer and those undergoing HSCT would stem from research focusing on the following elements:

- Tools that can be used by children to systematically communicate their symptom experience to care-givers need to be developed, validated and implemented in routine clinical practice.
- Supportive care guidelines which address subjects which are the most bothersome to children as assessed by children themselves, should be prioritized by guideline developers.
- Information regarding the patient-related factors (e.g. sex, age, pharmacogenetics, history of motion sickness) which predispose children to CINV need to be identified and incorporated into guidelines for CINV prevention.
- Pediatric clinicians must lobby pharmaceutical manufacturers to increase the probability that innovations in the supportive care of adults with cancer are evaluated in children.
- The optimal pediatric doses and dose schedules of older antiemetic agents (e.g. dexamethasone, ondansetron, granisetron, aprepitant) must be determined through controlled trials.
- Where pediatric drug formulations are not marketed, pharmacists must develop stable, extemporaneous formulations.
- Measurement of the clinical impact of systematic, patient-reported screening of symptom burden and of evidence-based guidelines that address these symptoms is the key to further improvements in the supportive care of children with cancer.
REFERENCES


