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

Dupuis, L.L.E.
Determination of initial i.v. CYA dosage to achieve target AUC values in pediatric hematopoietic stem cell transplant patients

M Jin1, W Seto1,2,3,4, T Taylor2,5, EF Saunders5, J Doyle4,5,6 and LL Dupuis1,2,4,5

1Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; 2Department of Pharmacy, The Hospital for Sick Children, Toronto, Ontario, Canada; 3Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada; 4Division of Critical Care Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada; 5Research Institute, University of Toronto, Toronto, Ontario, Canada and 6Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

In solid organ transplantation, CYA dosing is based on the area under the concentration vs time curve (AUCinf). This study aimed to develop a guideline for the initial i.v. CYA dose for pediatric hematopoietic SCT (HSCT) patients to achieve the target AUCinf recommended in solid organ transplantation. Whole-blood CYA concentrations were determined in 24 patients (0.5–16.9 years) after the first i.v. dose given over 2h, 1 day before HSCT. The i.v. CYA dose predicted to achieve an AUCinf of 4200 µg × h/l was calculated for each patient and expressed as a function of each patient’s actual weight and body surface area (BSA).

In patients <9 and >9 years of age, the mean i.v. CYA dose predicted to achieve the target AUC was 2.6 ± 0.94 and 2.1 ± 1.21 mg/kg, respectively. When these doses were expressed in terms of BSA, the mean dose was 65 ± 23.1 and 68 ± 35.0 mg/m² in children ≤9 and >9 years of age, respectively. In children 0.5–17 years of age undergoing HSCT, we recommend an initial i.v. CYA dose of 65 mg/m² infused over 2 h to achieve an AUCinf of approximately 4200 µg × h/l.

Bone Marrow Transplantation (2008) 42, 455–459; doi:10.1038/bmt.2008.189; published online 14 July 2008

Keywords: CYA; pharmacokinetics; hematopoietic stem cell transplant; pediatrics

Introduction

CYA continues to be a mainstay of regimens aimed at preventing acute GVHD (aGVHD) in patients undergoing hematopoietic SCT (HSCT). The most commonly prescribed initial i.v. CYA dose identified in a survey of European pediatric HSCT centers undertaken by the European Group for Blood and Marrow Transplantation was 3 mg/kg per day divided every 12 h. Although the need to achieve target trough CYA whole-blood concentrations to effectively prevent aGVHD is generally acknowledged, no initial pediatric i.v. CYA dosing guideline for hematopoietic stem cell transplant patients that incorporates known developmental differences in CYA pharmacokinetics exists.2,3 A single initial CYA dose based on body weight alone is not likely to efficiently achieve pharmacokinetic targets in children.

In pediatric and adult solid organ transplant patients receiving oral CYA, the area under the CYA concentration vs time curve (AUC) during the dosing interval at steady state is directly associated with the incidence of acute rejection.4–6 AUC during the dosing interval at steady state is equivalent to the AUC from time 0 to infinity (AUCinf) after the first dose. There is currently no published information regarding a potential relationship between AUC after i.v. CYA administration and the incidence of aGVHD though there recently has been interest in this concept.7–11

The objective of this study was to develop a guideline for the initial i.v. CYA dose for pediatric HSCT patients that would achieve the target AUC values recommended for solid organ transplant patients.

Methods

This study was approved by the Research Ethics Committee, The Hospital for Sick Children.

Patients

This study formed part of a larger prospective study of CYA pharmacokinetics after both i.v. and oral administration during HSCT. Methodology and results pertaining to the oral phase of this study have been published elsewhere.12 In brief, patients who were undergoing allogeneic HSCT and were scheduled to receive CYA for aGVHD prophylaxis were eligible to participate. Patients with impaired liver function (defined as serum transaminase concentrations >3 times the upper limit of normal for their age and/or total bilirubin levels >2 mg per 100 ml (34 µmol/l) on the day of pharmacokinetic sampling were excluded. Patients receiving any drug known to substan-
Blood samples
Whole-blood samples for CYA measurements were obtained after the first i.v. CYA dose given 1 day prior to HSCT. The i.v. CYA dose was given over 2 h at 0500 hours by a nonpolyvinyl chloride (PVC) i.v. set through one lumen of a double lumen, non-PVC containing central venous catheter (CVC). Blood samples were drawn at 2 (end of the infusion), 2.5, 3, 4, 6, 8, 10 and 12 h following the start of the i.v. infusion through the lumen of the CVC not used for CYA administration. The CYA concentration just prior to dose administration (at time 0) was assumed to be 0. Whole-blood CYA concentrations were measured by means of specific HPLC.13

Pharmacokinetic methods
The whole-blood CYA concentration vs time data were evaluated using a noncompartmental model (WinNonLin version 5.1; Scientific Consulting Inc., Mountain View, CA, USA) and pharmacokinetic parameters such as elimination rate constant ($k_e$), volume of distribution at steady state ($V_d$) and AUC$_{inf}$ were estimated. $k_e$ was determined using the three terminal CYA concentrations except for two patients with concentrations below the limit of quantification of the assay at 10 and 12 h. In these patients, the last two measurable concentrations were used to calculate $k_e$.

Determination of dosage guidelines
The graphs of both $k_e$ and $V_d$ and patient age, weight (actual, ideal and effective) and BSA were examined visually, and the association between these parameters was evaluated using the coefficient of determination ($r^2$). On the basis of a linear relationship between dose and AUC$_{inf}$, the i.v. CYA dose required for each patient to achieve an AUC$_{inf}$ of 4200 µg × h/l (dose$_1$) was calculated as follows: dose$_1$ = 4200 × (dose$_1$/AUC$_{inf}$), where dose$_1$ is the actual i.v. CsA dose given to the patient and AUC$_{inf}$ is the AUC$_{inf}$ produced by dose$_1$.

Dose$_2$ was then expressed as a function of each patient’s ABW, IBW, EBW, BSA, ideal BSA and effective BSA. Each expression of dose$_2$ was graphed against age and visually examined for trends. The mean dose$_2$ was calculated for each age group identified graphically. This dose was then calculated for each patient and the AUC$_{inf}$ predicted to be achieved by each patient when given this dose was calculated.

Statistical analysis
Data are presented as the mean ± s.d. The relationship between AUC$_{inf}$ and whole-blood CYA concentrations at individual time points after i.v. administration was assessed by the Spearman’s $\rho$ correlation coefficient. Differences between groups were assessed using nonparametric tests (SPSS 15.0.1; SPSS Inc. 2006).

Results
Patients
Demographic data relating to the 24 study patients have been published previously.12 Patients ranged in age from 0.5 to 16.9 years (mean: 8.8 ± 4.81 years); 16 were male. Ten patients had received phenytoin during the week prior to administration of the first i.v. CYA dose. No patient had ABW greater the 140% of IBW; therefore EBW could not be calculated. In addition, the ABW of 13 patients was less than the IBW. All dose calculations were therefore performed using ABW and actual BSA.

Pharmacokinetics
The mean i.v. CYA dose administered was 1.51 ± 0.05 mg/kg or 43 ± 8.3 mg/m$^2$. Mean pharmacokinetic parameters are presented in Table 1. Whole-blood CYA concentrations drawn within the first 4 h from the start of the infusion correlated strongly with AUC$_{inf}$ (Table 2; Spearman’s $\rho$ coefficient = 0.815). Significant, although moderate, correlations were observed at other time points.

Neither $k_e$ nor $V_d$ correlated significantly with age (data not shown). Clearance adjusted for body weight was modestly associated with age (adjusted $r^2$ = 0.283). It was observed upon visual examination of the graph of clearance adjusted for body weight against patient age that children 9 years of age or less had a higher CYA clearance than did older patients (1.3 ± 1.45 vs 0.4 ± 0.291/h/kg; $P$ = 0.011).

Dosing regimen
In patients 9 years of age and less, the mean i.v. CYA dose predicted to achieve an AUC$_{inf}$ of 4200 µg × h/l was 2.6 ± 0.94 mg/kg (95% confidence limits: 2.05–3.19 mg/kg). In older patients, the mean i.v. CYA dose predicted to achieve the target AUC$_{inf}$ was 2.1 ± 1.21 mg/kg (95% confidence limits: 1.29–2.92 mg/kg). For convenience, these mean doses were rounded to 2.5 and 2 mg/kg, respectively.

When the individual CYA doses predicted to achieve the target AUC$_{inf}$ of 4200 µg × h/l were expressed in terms of BSA, the mean dose was 65 ± 23.1 and 68 ± 35.0 mg/m$^2$ in children 9 years of age and less and in older children, respectively. For convenience, these mean doses were rounded to 65 mg/m$^2$. This dose was predicted to achieve a mean AUC$_{inf}$ of 4734 ± 1725 and 4924 ± 2123 µg × h/l in the younger and older age groups, respectively.
Table 1  Mean CYA pharmacokinetic parameters after i.v.
admission over 2 h to 24 children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± s.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/l)</td>
<td>1103 ± 787.7</td>
</tr>
<tr>
<td>Steady state volume of distribution (l/kg)</td>
<td>3.9 ± 4.8</td>
</tr>
<tr>
<td>TBC (l/h)</td>
<td>18.2 ± 12.7</td>
</tr>
<tr>
<td>Weight-adjusted TBC (l/h/kg)</td>
<td>0.9 ± 1.2</td>
</tr>
<tr>
<td>AUC$_{\text{inf}}$ (µg x h/l)</td>
<td>3146 ± 1256.2</td>
</tr>
</tbody>
</table>

Abbreviations: AUC$_{\text{inf}}$ = area under the whole-blood CYA concentration vs time curve from time 0 to infinity; $C_{\text{max}}$ = maximum whole-blood CYA concentration; TBC = total body clearance.

Table 2  Spearman’s $\rho$ correlation coefficients for area under the whole-blood CYA concentration vs time curve from time 0 to infinity and whole-blood CYA concentrations at time points after the start of a 2 h infusion in 24 patients

<table>
<thead>
<tr>
<th>Sampling time (hours after start of 2 h infusion)</th>
<th>Spearman’s $\rho$ coefficient</th>
<th>Significance (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.715</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>2.5</td>
<td>0.669</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>3</td>
<td>0.815</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>4</td>
<td>0.701</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>6</td>
<td>0.543</td>
<td>0.0006</td>
</tr>
<tr>
<td>8</td>
<td>0.493</td>
<td>0.014</td>
</tr>
<tr>
<td>10</td>
<td>0.580</td>
<td>0.005</td>
</tr>
<tr>
<td>12</td>
<td>0.628</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*On the basis of 22 patients as 2 patients had whole-blood CYA concentrations below the limit of quantification of the assay at 10 and 12 h after the start of the CYA infusion.

Table 3  Proposed initial i.v. CYA dosing guidelines for children undergoing HSCT

<table>
<thead>
<tr>
<th>Dosing guideline based on:</th>
<th>Mean predicted AUC (µg x h/l) (µg x h/l)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual body weight</td>
<td>Age ≤9 years: 4470 ± 1469 3582–5358</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg Age &lt;9 years: 4861 ± 1844 3622–6100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mg/kg Age 0–17 years: 4821 ± 1877 4029–5613</td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>65 mg/m$^2$ Age 0–17 years: 4821 ± 1877 4029–5613</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under the whole-blood CYA concentration vs time curve from time 0 to infinity; CI = confidence interval.

Discussion

We have developed pediatric i.v. CYA guidelines, which will achieve CYA AUC$_{\text{inf}}$ values, recommended for patients undergoing renal transplantation. This approach was adopted due to evidence in solid organ transplant patients that CYA AUC rather than trough concentration correlated best with clinical outcomes.

In a retrospective study of 156 adult renal transplant patients, Mahalati et al. demonstrated an association between the CYA AUC and acute rejection. Patients with projected AUC less than 9500 µg x h/l had an acute rejection rate of 36%, compared to 15% seen in patients with an AUC greater than 9500 µg x h/l ($P<0.05$). The acute rejection rate in patients who achieved an AUC greater than 11 500 µg x h/l was not further reduced but there was a significant increase in the incidence of nephrotoxicity (32%). Therefore, a target AUC range of 9500–11 500 µg x h/l was recommended as it was associated with the lowest incidence of acute rejection without significant risk of nephrotoxicity. Similarly, Lindholm and Kahan observed an increased incidence of acute rejection in adult renal transplant patients who achieved a CYA AUC of less than 9600 µg x h/l.

Pediatric data regarding CYA AUC and solid organ transplant outcomes are mixed. Trompeter et al. noticed no significant association between CYA AUC and acute rejection in an observational, prospective study in pediatric (median age 10 years, range 3–18 years) renal transplant recipients. However, Filler et al. observed an increasing risk of acute rejection associated with decreasing CYA AUC values achieved in a retrospective analysis of 78 pediatric (median age 11.0 years, range 4.0–21.4 years) renal transplant recipients. Rejection was observed in three of five patients who had an AUC < 5000 µg x h/l, six of nine patients who had an AUC between 5000 and 7000 µg x h/l, and zero of three patients with an AUC greater than 7000 µg x h/l. A target AUC greater than 5000 µg x h/l in the early post transplant period and 3900 µg x h/l beyond 100 days post transplant was recommended by these investigators.

For patients undergoing renal transplantation, the International Neoral TDM Advisory Consensus Meeting has recommended average CYA concentration targets which correspond to AUC values from 4200 to 6600 µg x h/l depending on the time from transplant. CYA dose adjustments in HSCT patients, however, are traditionally based on the trough concentration. For example, at our institution, i.v. CYA doses are adjusted to achieve whole-blood trough CYA concentrations of 100–150 µg/l (HLA-matched related transplants) or 150–200 µg/l (HLA-matched unrelated transplants). There is no information available regarding the relationship between CYA AUC and clinical outcomes in HSCT patients. In this study we observed only a moderate relationship between trough CYA concentrations and AUC following i.v. administration (Spearman’s $\rho$ coefficient = 0.628). Previously, we also observed a moderate relationship between trough CYA concentrations and AUC following oral administration to HSCT patients (Spearman’s $\rho$ coefficient = 0.584). It is therefore not possible to provide a target trough CYA concentration range that corresponds to the target AUC range recommended in renal transplant. We consequently chose to use the lower limit of the AUC target range recommended for solid organ transplant patients (4200–11 500 µg x h/l) on which to base our i.v. CYA dosing guidelines. It is presumed that achievement of a higher AUC will likely also lead to higher trough CYA concentrations.

We propose that the initial i.v. CYA dose for children undergoing HSCT be either based on both age and ABW or on BSA alone. Current published guidelines for initial i.v. CYA dosing in HSCT patients range from 2.5 mg/kg per day in divided doses to 5 mg/kg per day. The initial CYA dosing regimen we are recommending falls within this range. Furthermore, it is our experience that administration...
of initial i.v. CYA doses of 1.5 mg/kg per dose rarely produces trough CYA concentrations within our institution’s target ranges. The assignment of dose based on BSA may be particularly relevant to CYA as liver volume and consequently the clearance of hepatically metabolized drugs correlates strongly with BSA in children. Other investigators have also recommended that CYA be dosed according to BSA rather than ABW in children undergoing HSCT based on the lack of correlation between CYA clearance and ABW. In addition, the practicality of using a single dose (65 mg/m²) for all age groups rather than using two different doses (2.5 or 2.0 mg/kg) based on patient age has appeal.

The results of this study are limited by the small sample size, particularly in some age groups. However, this sample constitutes the largest published evaluation of CYA pharmacokinetics after i.v. administration to children undergoing HSCT. In addition, adoption of the guidelines we have developed by institutions using immunoassay techniques to measure CYA whole-blood concentrations may generate very different AUC values as HPLC is a more analytically precise technique. The lack of CYA concentrations taken during the infusion may have led to underestimations of Cmax and AUC. However, such concentrations would have had to be obtained by venipuncture to avoid contamination with the dose being infused. Furthermore, CYA disposition is probably best described by a multicompartment model. Our estimates of the elimination phase of CYA disposition are therefore limited by the necessity of obtaining all samples during the 12-h dosing interval. The dosing guidelines recommended here must be prospectively validated. In addition, the relationship between CYA AUC and clinical outcomes in HSCT must be determined.

Conclusion

In children between the ages of 0.5 and 16.9 years of age undergoing HSCT, we recommend an initial i.v. CYA dose of 65 mg/m² infused over 2 h every 12 h to achieve an AUC of approximately 4200 μg x h/l. Once steady state is reached, subsequent doses should be adjusted to achieve pharmacokinetic targets as per each institution’s guidelines. This dosing regimen requires validation in another group of patients. In addition, the value of AUC in mitigating the development of aGVHD requires evaluation.

Acknowledgements

Sources of financial support: This study was partially supported by an unrestricted grant from Novartis Pharmaceuticals Canada Inc., Dorval, Quebec, Canada.

References

10 Barkholt L, Remberger M, Bodegard H, Ringden O, Bottiger Y. Cyclosporine A (CSA) 2-h concentrations vary between patients without correlation to graft-versus-host disease after allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 2007; 40: 683–689.

