Initial dosage optimization of ciclosporin in pediatric Chinese patients who underwent bone marrow transplants based on population pharmacokinetics

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Abstract. Bone marrow transplants (BMT) are an established therapeutic strategy for patients with severe aplastic anemia, acute lymphoblastic leukemia, acute myeloid leukemia or chronic myeloid leukemia. However, the successful application of BMT is limited by graft-vs.-host disease (GVHD). Ciclosporin has been widely used for treating GVHD in pediatric patients who underwent BMT. The present study aimed to optimize the dosage of ciclosporin for safety and effectiveness based on population pharmacokinetics. A non-linear mixed-effects model was used to analyze the clinical data of pediatric patients who underwent BMT between September 2016 and September 2019 at the Children's Hospital of Fudan University. Monte Carlo simulations were used to identify the optimal dose of ciclosporin. The final population pharmacokinetic model indicated that body weight and days post-transplant influenced the clearance of ciclosporin in pediatric patients who underwent BMT. The present study indicated that the optimal initial dose of ciclosporin for pediatric patients weighing 5-30 kg who underwent BMT was 6 mg/kg/day split into 2 doses.

Introduction

Bone marrow transplants (BMT) are used to treat patients with severe aplastic anemia (1), acute lymphoblastic leukemia (2), acute myeloid leukemia (3) and chronic myeloid leukemia (4,5). However, the clinical application of BMT is limited by graft-vs.-host disease (GVHD) (6). Acute GVHD is a common complication which results in severe morbidity and mortality following BMT and has an occurrence rate of 30-50% (7-9). Acute GVHD primarily occurs in the skin, intestines and liver (10). Cytokine dysregulation resulting from an allogeneic interaction causes tissue injury that is characteristic of acute GVHD (11,12). Therefore, identifying a novel therapeutic strategy for GVHD is required.

Ciclosporin, an immunosuppressant drug, has been widely used as a treatment strategy for GVHD in pediatric patients who have undergone BMT (12-14); however, the therapeutic range is relatively narrow (15) and the drug exhibits wide inter-individual pharmacokinetic variability (16-18). Identifying the optimal dose regimen of ciclosporin to achieve and maintain the target concentration of the drug is crucial (19,20).

Population pharmacokinetics is a tool that can be used to collect sparse clinical data in order to model and simulate approaches to assess dosing regimens in specific patients (16,18). Numerous studies have established population pharmacokinetics of ciclosporin. For example, Ni *et al* (21) established population pharmacokinetics of ciclosporin in Chinese children with aplastic anemia, Fanta *et al* (22) and Irtan *et al* (23) in patients receiving pediatric renal transplants and Wilhelm *et al* (24) in patients receiving hematopoietic allogeneic stem cell transplants. Therefore, the present study aimed to optimize the initial dosage of ciclosporin for safety and effectiveness in pediatric Chinese patients who underwent BMT based on population pharmacokinetics.

Materials and methods

Patients and data collection. Pediatric patients who underwent BMT between September 2016 and September 2019 at the Children's Hospital of Fudan University (Shanghai, China) were retrospectively recruited to the present study. The criteria for inclusion were as follows: i) Age, <16 years; ii) treated with cyclosporin; and iii) full set of therapeutic drug monitoring (TDM) data for cyclosporin. Patients with other transplant statuses, including liver or kidney transplants were excluded. Ciclosporin concentrations and clinical data were gathered via TDM records and from medical records, respectively. The present study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University

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[approval no. (2019)021]. A total of 18 patients were included in the current study (male/female ratio, 13/5; mean age, 1.60±1.15 years; age range, 0.29-6.49 years).

Drug administration and concentration detection. The initial ciclosporin dosage range was 14-100 mg/day. The dose was later adjusted based on clinical efficacy, adverse events and the trough concentration based on TDM. TDM was measured twice per week or more frequently if required, especially in suspected cases of intolerance or adverse events, using the Emit® 2000 Cyclosporin Specific assay (cat. no. 6R079UL; Siemens Healthcare Diagnostics, Inc.) according to the manufacturer's protocol. Blood samples (≥100 μl) were collected from the elbow vein immediately before the next drug administration.

Population pharmacokinetic modeling. A Nonlinear Mixed-Effects Modeling tool (NONMEM®; version VII; ICON Development Solutions Ltd.) was used to analyze the clinical data of pediatric patients who underwent BMT. The absorption phase was described by a one-compartment model with first-order elimination, where pharmacokinetic parameters included apparent oral clearance/bioavailability (CL/F) and apparent volume of distribution (V/F). Based on published literature, the absorption rate constant (Ka) of the model was 0.68 h^{-1} (16,21,25).

Random effect model. Equation A was used to calculate inter-individual variability: $P_i=T(P) \times \exp(\eta_i)$, where P_i represented the individual parameter value, T(P) was the typical individual parameter value and η_i was the symmetrical distribution, which was a zero-mean chance variable with variance term. Equation B was used to calculate random residual variability: $Y=F \times (1+\varepsilon_1) + \varepsilon_2$, where Y was the observation, F was the individual predicted concentration, and ε_1 and ε_2 were symmetrically distributed, zero-mean random variables with variance terms.

Covariate model. The relationship between weight and pharmacokinetic parameters was calculated using Equation C: $P_i=P_{norm} \times (WT_i/WT_{norm})^{POW}$, where P_i represented the i^{th} individual pharmacokinetic parameter, WT_i represented the i^{th} individual weight, WT_{norm} represented the standard weight of 70 kg, P_{norm} represented the typical individual parameter whose weight was WT_{norm} and POW represented the allometric coefficient (0.75 for CL/F; 1 for V/F) (26).

The relationship between continuous covariates or categorical covariates and pharmacokinetic parameters was calculated by Equations D and E, respectively. Equation D: $P_i=T(P) \times (Cov_i/Cov_{median})^{\theta}$. Equation E: $P_i=T(P) \times (1+\theta \times Cov_i)$. P_i represented the individual parameter value, T(P) was the typical individual parameter value, θ was the parameter to be estimated, Cov_i was the covariate of the ith individual and Cov_{median} was the population median for the covariate.

To explain the variability of pharmacokinetic parameters, the correlations between covariates were investigated and the pharmacokinetic parameters were estimated. The potential covariates, which were obtained from the medical records, included sex, age, weight, days post-transplant (POD), albumin, alanine transaminase, aspartate transaminase, creatinine, urea, total protein, total bile acid, direct bilirubin, total bilirubin, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and co-medications (glucocorticoids, mycophenolate mofetil, omeprazole, phenobarbital and tacrolimus).

Statistical analysis. Alterations to the objective function values (OFV) were generated using covariate inclusions and a decrease in OFV of >3.84 [χ^2; α=0.05; degrees of freedom (df)=1] was considered sufficient for inclusion of the base model. After establishing a full regression model, the model was further assessed by eliminating covariates from each pharmacokinetic parameter to obtain the final model. An increase in OFV of >6.64 (χ^2; α=0.01; df=1) was considered to indicate a statistically significant difference.

Model validation. The reliability and stability of the final parameters were assessed by bootstrap, an internal validation method, which was performed using Wings for NONMEM (version VII; ICON plc) and repeated 1,000 times using different random draws. The medians and 2.5-97.5% percentiles of the bootstrap results were compared with the final pharmacokinetic parameter estimates and the absolute threshold of bias was set at <15% which was calculated using the following formula: Bias = (median-estimate)/estimate x100%. The final model was evaluated using goodness of fit plots and prediction-corrected visual predictive check plots, which were used to analyze model precision and predictability, respectively.

Simulation of dosing regimens. The dosage regimen simulations were performed using the parameter estimates obtained from the final model. The probability to achieve the target concentration was investigated using Monte Carlo simulations (NONMEM®; version VII; ICON plc), based on the established model. According to previous studies, the target concentrations were determined as 50-350 ng/ml (27-29). A total of 1,000 virtual patients were simulated in each of the four weight groups (5, 10, 20 and 30 kg) and for seven initial dosage regimens (2, 3, 4, 5, 6, 7 and 8 mg/kg/day ciclosporin split into 2 doses). Due to the large differences between individuals, the simulation results were presented with 70% confidence interval.

Results

Data collection. Clinical data of 18 pediatric patients who underwent BMT (13 male and 5 female) were collected for the present study. Patient characteristics and co-medications are presented in Table I.

Modeling. The final covariate models were displayed by equations F and G: i) Equation F, $CL/F=\theta_{CL/F} \times (WT/70)^{0.75} \times (POD/51.5)^{\theta POD}$; and ii) Equation G: $V/F=\theta_{V/F} \times (WT/70)$. $\theta_{CL/F}$ and $\theta_{V/F}$ represented the typical population values of CL/F and V/F, respectively, whilst θ_{POD} represented the coefficient of the POD. From Table II, the value of $\theta_{CL/F}$ was found to be 29.200, $\theta_{V/F}$ was 6550.000 and θ_{POD} was 0.749. Using these two models, WT and POD were included as the covariates of CL/F, whilst WT was included as the covariate of V/F.

Table I. Demographic data of patients and co-medications (n=18).

Characteristic	Mean ± SD	Median (range)
Sex, male/female	13/5	n/a
Age, years	1.60±1.15	1.22 (0.29-6.49)
Weight, kg	8.40±3.28	7.60 (5.20-25.60)
POD	61.16±40.16	51.50 (1.00-188.00)
Albumin, g/l	34.07±5.51	34.40 (1.20-45.20)
Alanine transaminase, IU/l	51.26±65.97	30.00 (1.00-439.00)
Aspartate transaminase, IU/l	56.00±57.58	36.30 (5.80-392.00)
Creatinine, μmol/l	17.59±5.23	16.00 (8.00-38.00)
Urea, mmol/l	3.62±1.86	3.45 (0.60-11.10)
Total protein, g/l	57.74±8.49	58.80 (38.40-77.80)
Total bile acid, μmol/l	21.62±32.09	10.85 (0.40-201.20)
Direct bilirubin, μmol/l	20.73±45.60	4.60 (0.10-301.90)
Total bilirubin, μmol/l	33.30±64.46	11.60 (1.30-384.20)
Hematocrit, %	30.64±6.76	30.40 (10.50-44.30)
Hemoglobin, g/l	101.16±21.86	101.00 (35.00-149.00)
Mean corpuscular hemoglobin, pg	29.78±3.30	29.70 (20.40-42.00)
Mean corpuscular hemoglobin concentration, g/l	331.48±19.62	333.00 (273.00-396.00)
Comedication, n		
Glucocorticoids	15	n/a
Mycophenolate mofetil	7	n/a
Omeprazole	16	n/a
Phenobarbital	2	n/a
Tacrolimus	2	n/a

SD, standard deviation; POD, days post-transplant.

Table II. Parameter estimates of the final model and bootstrap validation.

Parameter	Estimate	SE (%)	Bootstrap median	95% confidence interval	Bias (%)
CL/F (l/h)	29.200	15.3	28.700	(20.000, 38.300)	-1.71
V/F (l)	6,550.000	29.9	6,620.000	(3,500.000, 11,800.000)	1.07
Ka (h^{-1})	0.680 (fixed)	-	-	-	-
θ_{POD}	0.749	25.4	0.730	(0.330, 1.120)	-2.54
$\omega_{CL/F}$	0.627	16.5	0.611	(0.338, 0.826)	-2.55
$\omega_{V/F}$	0.998	20.1	0.955	(0.522, 1.367)	-4.31
σ_1	0.447	15.6	0.442	(0.296, 0.597)	-1.12
σ_2	70.071	30.2	67.749	(14.765, 104.403)	-3.31

95% confidential interval is presented as (2.5th, 97.5th percentile) of bootstrap estimates. Bias=(median-estimate)/estimate x100%. SE, standard error; CL/F, apparent oral clearance; V/F, apparent volume of distribution; Ka, absorption rate constant; θ_{POD} was the coefficient of days post-transplant; ωCL/F, inter-individual variability of CL/F; $\omega_{V/F}$, inter-individual variability of V/F; σ_1, residual variability, proportional error; σ_2, residual variability, additive error; bias, prediction error; -, not applicable.

If the potential influencing factors could be included in the model as covariates, it indicated that there was an influence on ciclosporin. Conversely, if not, it indicated that there was no influence on ciclosporin. In the final models co-medications (glucocorticoids, mycophenolate mofetil, omeprazole, phenobarbital and tacrolimus) were could not be included into the final covariate models, suggesting that there was no significant drug interaction with ciclosporin.

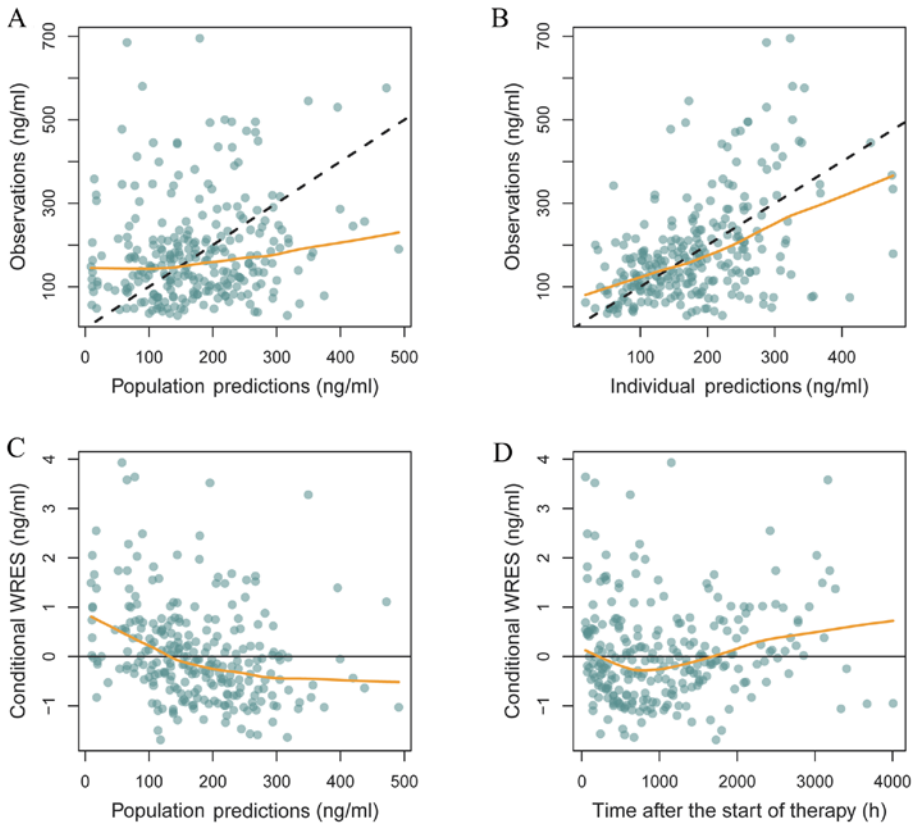

Figure 1. Goodness of fit plots of the final population model. (A) Observations vs. population predictions. (B) Observations vs. individual predictions. Black dashed lines (y=x) represent the line of unity, where the predictions matched the observed values. Smooth yellow line represents the trend of the data. The closer the smooth yellow line to the black dashed line, the more predictive the model. (C) WRES vs. population predictions. (D) WRES vs. time after the start of therapy. Smooth yellow line represents the trend of the data, where the closer the yellow smooth line is to the line of unity (y=0), the more predictive the model. WRES, conditional weighted residuals.

Validation. Goodness of fit plots, representing the observed and predicted drug concentrations in the blood, are presented in Fig. 1, including observations vs. population predictions, observations vs. individual predictions, conditional weighted residuals (WRES) vs. population predictions and WRES vs. time after the start of therapy. In Fig. 1A and B, the black dashed lines represent the line of unity, where the predictions matched the observed values and the smooth yellow line represents the trend of the data. Hence, the closer the yellow smooth line is to the black dashed line, the more accurate the predictive the model. In Fig. 1C and D, the yellow smooth line represents the trend of the data such that the closer the yellow smooth line is to the line of unity, the more accurate the predictive model. Therefore, the final model exhibit higher precision and predictability. The parameter estimates of the final model and bootstrap validation are presented in Table II, where the median values of the parameter estimates of bootstraps were close to the respective values of the final population model. The absolute value of bias was found to be <5, <15% of the standard, which indicated that the final population model was accurate and reliable. The prediction-corrected visual predictive check plots of the final model are presented in Fig. 2. The majority of the observations were within the 95% prediction intervals of the simulation data, which suggested that the prediction-corrected concentrations were well predicted by the final model.

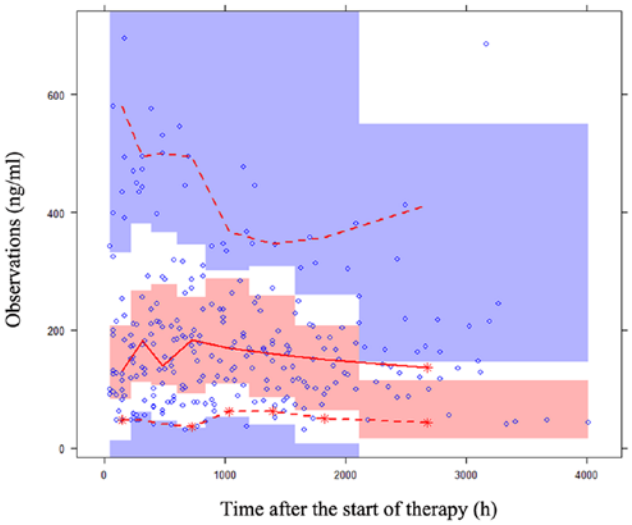

Figure 2. Prediction-corrected visual predictive check of the final model. The middle solid line represents the median of the prediction-corrected concentrations. The lower and upper dashed lines are the 2.5 and 97.5th percentiles of the prediction-corrected concentrations, respectively. The blue points are observed concentrations (measured concentrations). The pink area indicates the confidence interval of the middle solid line and the purple area indicates the confidence interval of the lower and upper dashed lines.

Simulation. Weight and POD influenced the clearance of ciclosporin in pediatric patients who underwent BMT (Fig. 3). Specifically, ciclosporin clearance was found to be increased as POD increased, whilst ciclosporin clearance was reduced

Table III. Predicted median (15th percentile-85th percentile) concentrations (ng/ml) of ciclosporine in each group.

Dose[a]	5 kg	10 kg	20 kg	30 kg
2 mg/kg/day	41.5 (15.05-104.81)	41.41 (15.07-105.82)	41.49 (15.09-107.50)	41.54 (15.11-108.09)
3 mg/kg/day	61.72 (22.57-157.22)	62.11 (22.61-158.74)	62.23 (22.63-161.25)	62.31 (22.67-162.14)
4 mg/kg/day	82.30 (30.10-209.65)	82.82 (30.14-211.65)	82.98 (30.18-215.00)	83.08 (30.22-216.20)
5 mg/kg/day	102.87 (37.63-262.02)	103.52 (37.68-264.56)	103.72 (37.72-268.75)	103.85 (37.77-270.24)
6 mg/kg/day	123.45 (45.15-314.43)	124.22 (45.21-317.47)	124.46 (45.26-322.50)	124.62 (45.32-324.29)
7 mg/kg/day	144.02 (52.68-366.84)	144.93 (52.75-370.39)	145.20 (52.81-376.25)	145.39 (52.88-378.34)
8 mg/kg/day	164.60 (60.20-419.24)	165.63 (60.28-423.29)	165.94 (60.35-430.00)	166.16 (60.43-432.38)

[a]Split into 2 doses.

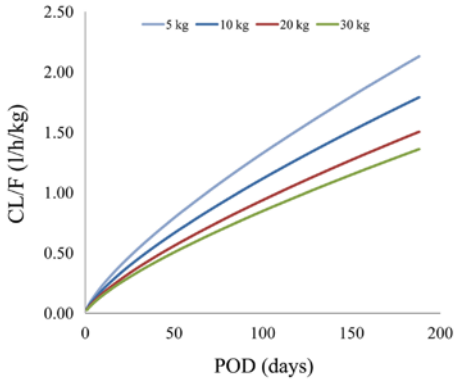

Figure 3. CL/F compared with POD of ciclosporin in pediatric patients who underwent bone marrow transplants. CL/F, apparent oral clearance; POD, days post-transplant.

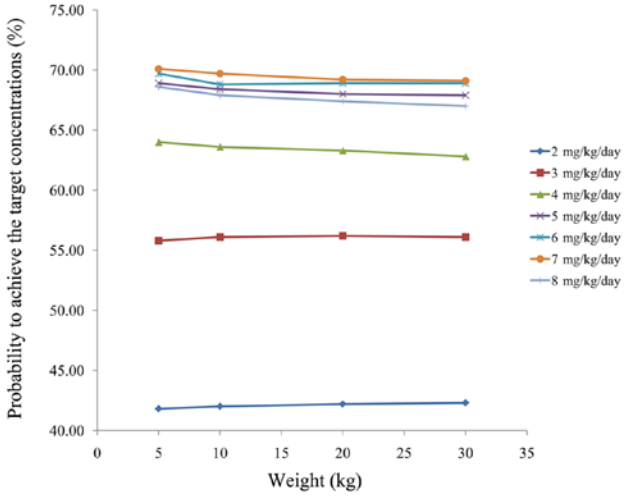

Figure 4. Probability of achieving target concentrations.

with increasing weight. Additionally, lighter weight resulted in higher clearance rates in pediatric patients with the same POD. The initial dosage of 2-5 and 8 mg/kg/day split into 2 doses for pediatric patients weighing 5-30 kg exhibited lower probabilities of achieving the target concentrations, whilst the initial dosage of 6 or 7 mg/kg/day split into 2 doses for pediatric patients weighing 5-30 kg displayed higher probabilities to achieve the target concentrations (Fig. 4). However, the 7 mg/kg/day dose split into 2 doses exceeded the upper limit of the treatment window (350 ng/ml) in all weight groups (Table III). Therefore, an initial dose of 6 mg/kg/day ciclosporin split into 2 doses for pediatric patients weighing 5-30 kg who underwent BMT was identified as the optimal dose.

Discussion

The immunosuppressive drug ciclosporin was initially approved for use to prevent rejection in organ transplants, such as in liver (30,31), kidney (32,33), lung (34) and heart (35,36). Additionally, ciclosporin has been approved by the US Federal Drug Association for severe psoriasis and rheumatoid arthritis treatment (37). It has also been reported that ciclosporin can be used to treat alopecia (38), chronic autoimmune urticaria (39), pyoderma gangrenosum (40), severe atopic dermatitis (41), systemic lupus erythematosus (42), aplastic anemia (43), Crohn's disease (44) and ulcerative colitis (45). Furthermore, ciclosporin has also been used for the treatment of GVHD in pediatric patients who underwent BMT (1,2,13,14).

While ciclosporin has a wide range of clinical applications, the potential risks in numerous conditions have not been fully elucidated (46). Clinically, ciclosporin displays pharmacokinetic challenges which vary considerably between patients receiving the same dose (46). Additionally, ciclosporin has a narrow therapeutic range (47,48). Low doses are closely associated with the risk of graft rejection or loss, and overexposure is associated with acute or chronic toxicity, and irreversible renal damage (48). Therefore, a key challenge for the clinical use of ciclosporin is maintaining constant drug exposure in the narrow therapeutic window for each patient (15,49). While clinical TDM is often used to determine the optimal ciclosporin concentration and to provide reference for subsequent dose adjustments, a concentration reference for the initial dose has not been identified.

Population pharmacokinetics has the potential to aid individualized therapy by integrating different effects of variables on drug exposure (50); therefore, it can be used to determine the initial dose in different diseases. Population pharmacokinetics has been used for dosage optimization of tacrolimus in patients with nephritic syndrome (51,52), oxcarbazepine in pediatric Chinese patients with epilepsy (53), azithromycin in children

with community-acquired pneumonia (54), vancomycin in neonates and young infants (55) and cyclosporin in pediatric patients with hemophagocytic lymphohistiocytosis (16). Therefore, the present study aimed to optimize the initial dosage of ciclosporin in pediatric patients who underwent BMT based on population pharmacokinetics and Monte Carlo simulations.

In the present study, the typical value of CL/F from the final population pharmacokinetic model was 29.200 l/h, which was similar to the previously reported value for pediatric patients receiving stem cell or kidney transplants (23.1-29.3 l/h) (23,27). Weight and POD influenced the clearance of ciclosporin in pediatric patients who underwent BMT. Ciclosporin clearance associated positively and negatively with POD and weight, respectively. A similar previous study demonstrated a non-linear relationship between drug clearance and body weight in pediatric patients (26). The association between body weight and clearance may scale with 0.75 power and a coefficient of 1 for volume (26,56,57). Therefore, in the present study, the following allometric coefficient was selected: 0.75 for CL/F and 1 for V/F. For ease of comparison between studies, body weight is typically standardized to 70 kg and the standardization of weight is particularly important in studies investigating children and neonates (21,56,58,59). Furthermore, in the present study, POD was found to associate positively with ciclosporin clearance, which may be explained by the association between patient recovery and an increased ability to metabolize exogenous drugs (60). Additionally, lighter weight was associated with higher clearance rates in pediatric patients with the same POD.

Subsequently, whether there was a significant difference in initial dose between children with different body weights was investigated. Monte Carlo simulations were used to simulate the optimal initial dose, including four weight groups (5, 10, 20 and 30 kg) and seven initial dosing regimens (2, 3, 4, 5, 6, 7 and 8 mg/kg/day split into 2 doses). According to previous studies, the target concentration range was determined as 50-350 ng/ml (27-29). The results of the present study suggested that the doses of 6 and 7 mg/kg/day split into 2 doses displayed a similar probability to achieve the target concentrations. However, the dose of 7 mg/kg/day resulted in an increased number of cases where the dose exceeded the upper limit of the therapeutic window. Therefore, an initial dose of 6 mg/kg/day ciclosporin split into 2 doses for pediatric patients weighing 5-30 kg who underwent BMT was identified as the optimal dose. Additionally, the present study also considered combination drugs, including glucocorticoid, mycophenolate mofetil, omeprazole, phenobarbital and tacrolimus; however, no significant interaction with ciclosporin was identified.

The present study had an important limitation. Ciclosporin is primarily eliminated via biotransformation by cytochrome P450. Therefore, whether the inclusion of genotyping in the model generated in the present study explains the variability of ciclosporin in pediatric Chinese patients who underwent BMT requires further investigation.

In conclusion, the present study indicated that weight and POD influenced the clearance of ciclosporin in pediatric patients who underwent BMT. Furthermore, the results indicated that the optimal initial dose of ciclosporin was 6 mg/kg/day split into 2 doses for pediatric patients weighing 5-30 kg who underwent BMT.

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Availability of data and materials

The dataset used and/or analyzed during the present study are available from the corresponding authors on reasonable request.

Authors' contributions

ZL and HX conceived and designed the study. XC, XY and DW collected and analyzed the data. XC drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Children's Hospital of Fudan University. Patient consent was waived by the Ethics Committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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