INFLUENCE OF CYCLOSPORIN INFUSION DURATION ON EFFICACY IN PAEDIATRIC BONE MARROW TRANSPLANTATION: ANALYSIS BY A PBPK MODEL

C. Gérard (1), N. Bleyzac (2), P. Girard (1), B. Tranchand (1), G. Freyer (1), Y. Bertrand (2), M. Tod (1).

(1) EA 3738 Ciblage Thérapeutique en Oncologie, Faculté de médecine Lyon Sud, Oullins, France.
(2) Institut d'Hématologie et d'Oncologie Pédiatrique, Lyon, France.

Objectives

In bone marrow transplantation (BMT), cyclosporin is used to prevent the graft versus host disease (GVHD). In our hospital, more frequent and severe GVHD were observed with continuous infusion than with twice daily infusion (2 h every 12 h), given the same daily dose (mg/kg) **(table I)**. The team of Rowland has built a physiologically based pharmacokinetic (PBPK) model of cyclosporin in rats **(fig. 1)** and clearly showed that cyclosporin distribution presents several sources of non-linearity [1]. Our hypothesis is that the difference of efficacy of cyclosporin between both types of infusion is linked to a difference of tissue distribution of the target organs of GVHD (skin, intestine and liver). The objective of this study was to compare, with a global PBPK model, exposure of these organs to cyclosporin for each type of infusion.

Methods

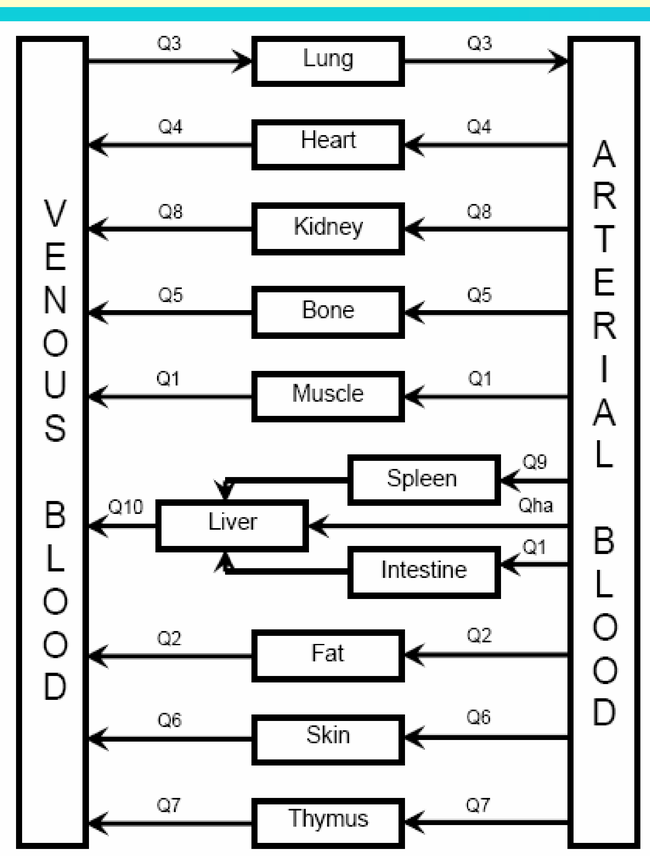
The rat PBPK model of Rowland was scaled up to human adult and adjusted to children. The scaling was based on physiological data and allometric equations. The model was implemented in ADAPT II. The paediatric PBPK model was fitted individually (bayesian MAP estimator) to cyclosporin blood concentrations from 61 paediatric patients (31 and 30 with intermittent and continuous infusion, respectively). Both groups were comparable for demographics, BMT indication **(table II)** and initial dosing regimen. Using the adjusted PBPK model, the AUCs in blood and target organs were calculated for each child.

Results

Kinetic profiles simulated in blood and all organs with the rat PBPK model were similar to the experimental data [1].

Table I. aGVHD characteristics in both groups.
NS: no statistically significant difference (*Mann-Whitney test, alpha = 5%)

	Intermittent infusion	Continuous infusion	p value*
n	31	30	
Presence of aGVHD (%)	51.6	60.0	NS
GVHD grade			
I (%)	56.2	33.3	
II (%)	43.8	50	NS
III et IV (%)	0	16.7	
Location			
Cutaneous only (%)	87.5	44.4	
Digestive or hepatic locations associated or not with cutaneous (%)	12.5	55.6	< 0.01
Cutaneous associated or not with other locations (%)	100	93.3	NS



The model in children was improved by modifying the mean value of CLint.

With the final model, weighted residuals were normally distributed, with 100 % in the range [-3;+3] **(fig. 2)**.

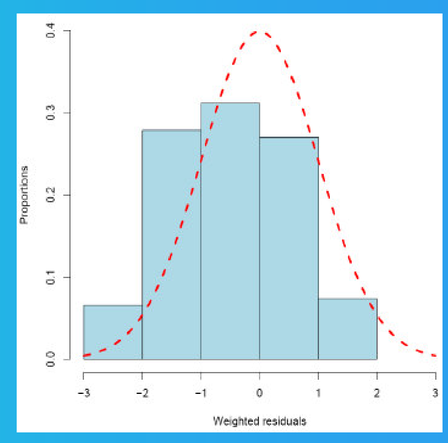


Fig. 2. Distribution of weighted residuals

Fig. 1. (on the left) Schematic representation of the global PBPK model

The study showed that mean AUCs were significantly greater for the blood and GVHD targeted organs at the beginning of the treatment (0-24 hours) when cyclosporin was administered by intermittent rather than continuous infusion ($p < 0.05$ in each case) **(fig. 3).** The ratio of mean AUCs 0-24h (intermittent / continuous) was 1.25 (blood), 1.42 (skin), 1.10 (intestines), 1.25 (liver).

Table II. Patients characteristics.
NS: No statitiscal difference (*Mann-Whitney test, alpha = 5%)

	Intermittent infusion	Continuous infusion	p value*
n	31	30	
Median age (range), years	7.58 (0.62-17.0)	5.73 (0.48-15.8)	NS
Median body weight (range), kg	22.4 (5.62-63.0)	19.8 (7.18-58.6)	NS
Sex (% male)	51.6	56.7	NS
Hematocrit (range)	0.26 (0.14-0.32)	0.25 (0.16-0.31)	NS
Disease			
Acute lymphoblastic leukemia (%)	25.8	26.7	
Acute myeloid leukemia (%)	22.6	33.3	NS
Other malignant haematological diseases (%)	16.1	10.0	
Non malignant haematological diseases (%)	35.5	30.0	
Donor type			
Related (%)	61.3	43.3	NS
Unrelated (%)	38.7	56.7	
Treatment			
Median delay from graft to aGVHD apparition (range), days	11 (8-38)	15.5 (8-32)	NS
Median dosage regimen at day 1 (range), mg/kg	3.16 (2.64-5.51)	3.12 (2.21-5.26)	NS

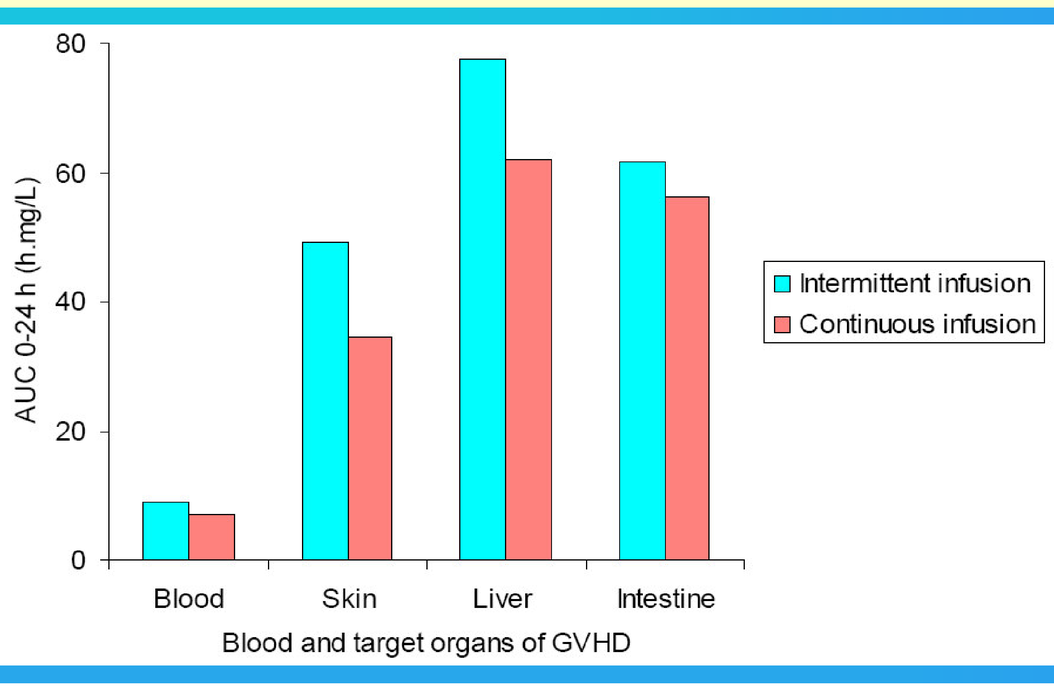


Fig. 3. Comparison of the AUC between the 2 types of infusion

Conclusion

The PBPK model in children showed that the day 1 exposure to cyclosporin was more important in the GVHD target organs when it was administered by intermittent infusion, which is consistent with the greater efficacy of intermittent infusion in prevention of GVHD.

[1] Tanaka C, Kawai R, Rowland M. J Pharmacokinet Biopharm 1999;27(6):597-623.