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Bayesian Estimation of Methotrexate Pharmacokinetics in Children with Acute Lymphoblastic Leukaemia and Prediction of Folinic Acid Rescue

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Objectives

Acute lymphoblastic leukaemia is the most common childhood cancer and high dose-methotrexate (MTX) is still the mainstay in the chemotherapy. Due to high variability in pharmacokinetics and well established relationship between treatment toxicity and MTX exposure, TDM and adaptive folinic acid rescue are essential for clinical management of patients. We have previously studied the association of genetic polymorphism in the folate metabolic pathway with MTX pharmacokinetics and toxicity [1,2]. The aim of the present study was to evaluate Bayesian predictions of MTX concentrations in the elimination phase based on scarce samples to develop an adaptive rescue strategy based upon the early detection of patients with impaired MTX elimination.

Methods

Routine TDM data from 64 patients were used for development of a population pharmacokinetic model. Four courses of MTX treatment were infused over 24 hours and blood samples were collected at 24, 36, 42 and 48 hours. Additional samples were obtained, if MTX concentration at 48 hours was above 0.5 µmol/L. This extra sampling procedure was continued until the MTX plasma concentration was less than 0.25 µmol/L.

Pharmacokinetic parameters of MTX were estimated by NONMEM VI. MTX plasma concentration data were fitted by a two-compartment model with first-order elimination, which was specified by NONMEM subroutines ADVAN3 and TRANS4. The first-order conditional method was used to estimate total plasma clearance (CL), volume of distribution of the central (V_1) and peripheral (V_2) compartment and distribution clearance (Q). Inter-individual variability in pharmacokinetic parameters was described by an exponential variance model. Additive, proportional and combination error models were evaluated to describe residual variability of MTX concentration. Additionally, inter-occasion variability of clearance was estimated as there were samples from four different courses available. First order conditional estimation (FOCE) method was used. The covariates investigated were patient's age, weight, sex and body surface area.

The population model was used for Bayesian estimation of MTX concentration at 48h in the independent data set from 37 patients based on only two concentration measurements at 24 and 42 h. Predictive performance of the model was evaluated by comparisson with the measured MTX concentrations. Additionally, forecasted folinic acid dosage was compared to the actual dosage to assess if Bayesian estimates can guide adaptive rescue strategy.

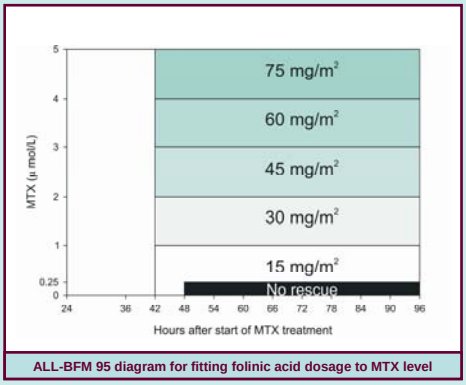
Results

Pharmacokinetic data from 252 courses and 919 MTX concentration measurements were available for analysis. MTX concentration profiles were fitted with a two compartment model. In a typical patient CL was estimated at 7.12 L/h, volumes of the central and peripheral compartment were 9.73 and 3.61 L, respectively and distribution clearance was 0.134 L/h. IOV in CL was estimated 14.8%. Residual variability was estimated at 0.0642 µmol/L (additive component) and 68.1% (proportional component).

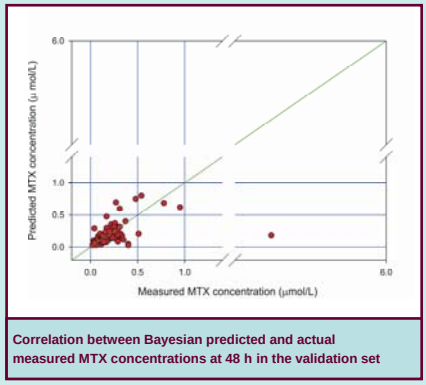
In the independent group of patients bias of the predicted concentrations at 48 h was 10.3% with precision of 77.0%. Dosage adjustment of folinic acid rescue based on predicted MTX concentration was accurate in 81% of courses.

Model parameters

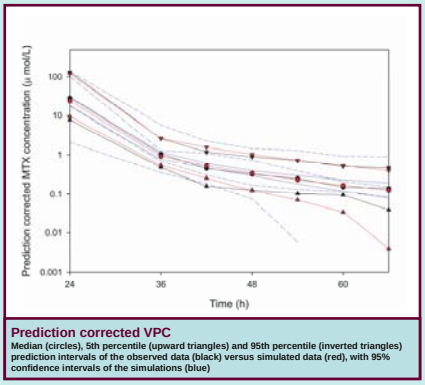
Parameter	Estimate	Bootstrap	
		Median	(95% CI)
Fixed effects			
CL (L/h/20 kg)	7.12	7.06	(6.08-8.32)
Exponent of WT on CL	0.434	0.433	(0.224-0.680)
V_1 (L/20 kg)	9.73	9.32	(6.87-11.5)
V_2 (L)	3.61	3.48	(1.96-6.18)
Q (L/h)	0.134	0.141	(0.0931-0.265)
Inter-individual variability			
IIV_{CL} (CV %)	30.7	29.7	(14.8-40.0)
IIV_{V1} (CV %)	6.1	3.0	(0.1-31.4)
IIV_{V2} (CV %)	62.7	58.3	(0.6-101.2)
IIV_{Q} (CV %)	64.5	63.4	(0.6-107.7)
Inter-occasion variability			
IOV_{CL} (CV %)	14.8	15.1	(12.7-17.7)
Residual variability			
Proportional component (CV %)	68.1	67.6	(60.9-75.1)
Additive component (µmol/L)	0.0642	0.0637	(0.0121-0.125)



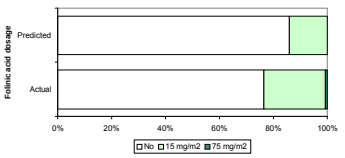
ALL-BFM 95 diagram for fitting folinic acid dosage to MTX level



Correlation between Bayesian predicted and actual measured MTX concentrations at 48 h in the validation set



Prediction corrected VPC
Median (circles), 5th percentile (upward triangles) and 95th percentile (inverted triangles) prediction intervals of the observed data (black) versus simulated data (red), with 95% confidence intervals of the simulations (blue)



Prediction correct	81%
Prediction to low	14%
Prediction to high	5%

Acuracy of folinic acid dosage based on predicted MTX concentration at 48 h

Conclusions

We found that 23% of patients needed special rescue management with prolonged folinic acid administration. We believe that Bayesian estimation is a useful tool for prediction of MTX concentration in the elimination phase and can be used for adjustments of folinic acid dosage.

Bias and precision of Bayesian predicted MTX concentrations at 48 h in the validation set

	Bias	Precision (RMSE)
Absolute difference (µmol/L)	-0.0476	0.492
Relative difference (%)	10.3	77.0

References

[1] Faganel Kotnik B, Dolzan V, Grabnar I, Jazbec J. Relationship of the reduced folate carrier gene polymorphism G80A to methotrexate plasma concentration, toxicity, and disease outcome in childhood acute lymphoblastic leukemia. Leuk Lymphoma 2010; 51(4):724-6.

[2] Faganel Kotnik B, Grabnar I, Bohanec Grabar P, Dolžan V, Jazbec J. Association of genetic polymorphism in the folate metabolic pathway with methotrexate pharmacokinetics and toxicity in childhood acute lymphoblastic leukaemia and malignant lymphoma. Eur J Clin Pharmacol (*in press*).

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