

Nick Holford¹, Sarapee Hirankarn², Erin Dombrowsky², Dimple Patel², Jeffrey S. Barrett²

1. University of Auckland, New Zealand, 2. The Children’s Hospital of Philadelphia, USA

Objective

- To identify the between and within subject sources of unpredictable variability in methotrexate clearance

Conclusions

- Unpredictable variability of methotrexate clearance is similar between subjects (65%) and between occasions (56%)
- Between occasion variability should be estimated using all structural parameters when they are correlated

Introduction

- Methotrexate**
- Methotrexate (MTX) is a folic acid antagonist and a potent inhibitor of dihydrofolate reductase
 - Component of many effective chemotherapeutic regimens for a diverse range of pediatric malignancies such as osteosarcoma, acute lymphocytic leukemia (ALL), non Hodgkin’s lymphoma (NHL), and some brain tumors
 - Previous reports of between subject (BSV) and between occasion (BOV) variability have ranged from 13 to 44% and 8 to 17% respectively
 - Target concentration intervention using Bayesian estimated clearance increases 5 year survival [1]

Methods

- Subjects**
- 56 children with cancer who had received methotrexate on multiple treatment cycles.
- Models**
- Full PK model (Figure 2) is described elsewhere [2] Each cycle is considered an occasion for estimation of between cycle variability (BOV). Three models were used for a simulation study:
- BSV and BOV with covariance (Full model) (Figure 1)
 - BOV only on CL and without any covariance as used in literature reports (BOVCL model)
 - BOV for CL, V1, Q and V2 but without covariance between BSV or BOV parameters (BOV4 model)
- Population modeling**
- The full model MTX parameters including BSV and BOV and their correlations was used to simulate 100 data sets using the same covariates and sampling times as in the original data.
 - A parametric bootstrap was performed with each of these data sets by fitting the Full model and the two simpler models (BOVCL and BOV4).
 - NONMEM 7.2 FOCE with INTERACTION

References

- [1] Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med 1998; 338: 499-505.
- [2] Hirankarn, S., Holford, N.H.G., Dombrowsky, E., Patel, D. & Barrett, J.S. Pharmacokinetics of high-dose methotrexate in children with cancer: A mechanism-based evaluation of clearance prediction. PAGE, (2012).

Results

Table 1 Methotrexate clearance and sources of predictable and unpredictable variability reported in the literature

Patient Group	Design	Predictable variability	Population Clearance	Units	BSV _{CL}	BOV _{CL}	BOV/Total	Reference
Adult osteosarcoma	Every 24 h from end of 24 h infusion until MTX<0.2 uM	Allometric weight 70kg , normal serum creatinine	13.6	L/h/70kg	0.13	0.12	46 %	Johansson et al. 2012
Children and adolescents; ALL or myeloid leukaemia	Every 12 h from end of inusion until 48h then every 6 h until MTX<0.25 uM	Empirical allometric weight	11.8	L/h	0.297	0.166	24%	Kotnik, Grabnar et al. 2011
Adults; CNS lymphoma	Every 24 h from end of 24 h infusion plus earlier sample in some until MTX<0.05 uM	Creatinine clearance 95 mL/min; BSA 1.75 m2	10.8	L/h	0.339	0.133	13%	Joerger, Ferrieri et al. 2011
Children osteosarcoma	At 1, 2, 4h during and 24 and 48 h from end of 4 h infusion then every 12 h until MTX<0.2 uM	Weight 70 kg, age 30 y	9	L/h/70kg	0.119	0.082	32%	Colom et al 2009
Adult, various malignancies	At 24 and 48 h after 3h infusion and some others until MTX < 0.1 uM	Normal creatinine clearance 87 mL/min	8.85	L/h	0.196	0.133	32%	Joerger, Huitema et al. 2006
Children; ALL	At 24, 48, 72 h after start of 24 h infusion until MTX <0.2 uM	None	8.8	L/h	0.428	0.132	9%	Piard, Bressolle et al. 2007
Adult; ALL, lymphoma	At 8, 12, 24 and 48 h after a 1 to 6 h infusion then every 24 h until MTX < 0.05 uM	Age 62 y; serum creatinine 67 umol/L	7.1	L/h	0.22	0.17	37%	Faltaos, Hulot et al. 2006
Children, adult, lymphoid malignancies	At 6, 12, 18, 24, 30, 36, 44, 50, 56, 68, 74, 80, 92 h (N=15), others at 20 h, after a 24 h infusion then every 24 h until MTX<0.2uM	Serum creatinine 0.89 mg/dL	7.45	L/h	0.506	Not significant	NA	Min, Qiang et al. 2009

Table 2 Final Model Original and Bootstrap Random Effect Parameter Estimates

Parameter	Description	Original Estimate	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
BSV_CL	Between subject variability in total clearance	0.636	0.65	21.3%	0.37	0.91
BSV_V1	Between subject variability in central volume	0.820	0.836	22.3%	0.478	1.192
BSV_Q	Between subject variability in intercompartmental clearance	0.965	1.01	20.4%	0.62	1.38
BSV_V2	Between subject variability in tissue volume	1.21	1.22	21.6%	0.687	1.703
BOV_CL_1	Between occasion variability in total clearance	0.564	0.56	14.9%	0.41	0.74
BOV_V1_1	Between occasion variability in central volume	0.607	0.62	18.1%	0.41	0.85
BOV_Q_1	Between occasion variability in intercompartmental clearance	1.02	1.01	19.7%	0.64	1.41
BOV_V2_1	Between occasion variability in tissue volume	1.07	1.06	19.4%	0.69	1.48
R CL V1 BSV	Correlation of total clearance with V1	0.969	0.97	2.88%	0.90	0.99
R CL Q BSV	Correlation of total clearance with Q	0.835	0.83	14.7%	0.53	0.97
R CL V2 BSV	Correlation of total clearance with V2	0.754	0.76	18.4%	0.41	0.93
R V1 Q BSV	Correlation of V1 with Q	0.761	0.76	18.9%	0.38	0.93
R V1 V2 BSV	Correlation of V1 with V2	0.726	0.73	21.5%	0.32	0.92
R Q V2 BSV	Correlation of Q with V2	0.957	0.966	2.62%	0.905	0.999
R CL V1 BOV	Correlation of total clearance with V1	0.982	0.978	1.3%	0.946	0.996
R CL Q BOV	Correlation of total clearance with Q	0.894	0.886	6.5%	0.747	0.964
R CL V2 BOV	Correlation of total clearance with V2	0.886	0.923	6.1%	0.783	0.994
R V1 Q BOV	Correlation of V1 with Q	0.941	0.873	7.4%	0.713	0.965
R V1 V2 BOV	Correlation of V1 with V2	0.927	0.917	6.6%	0.764	0.997
R Q V2 BOV	Correlation of Q with V2	0.997	0.988	1.3%	0.952	1.00
RUV PROP	Proportional residual error	0.306	0.30	12.1%	0.23	0.37

Table 2 Average and Bias of Parameter Estimates from Parametric Bootstrap of Different Models. Data was simulated using the Full model parameter estimates from the original data.

	Average Estimated Parameter Values			Bias Relative to Full Model Used to Simulate Data		
Model	Full	BOV4	BOVCL	Full	BOV4	BOVCL
CLTUB	21.2	14.9	15.4	11%	-22%	-19%
CLGFR	6.06	4.20	4.25	13%	-22%	-21%
V1	162	98.4	102.6	13%	-32%	-29%
Q	1.03	0.621	0.638	20%	-28%	-26%
V2	23.8	13.3	14.0	12%	-37%	-34%
BSV_CL	0.617	0.270	0.271	-6%	-57%	-82%
BSV_V1	0.799	0.374	0.376	-5%	-54%	-79%
BSV_Q	0.910	0.328	0.350	-11%	-66%	-87%
BSV_V2	1.16	0.516	0.536	-8%	-57%	-80%
BOV_CL	0.569	0.166	0.171	2%	-71%	-91%
BOV_V1	0.596	0.024	.	-3%	-96%	.
BOV_Q	1.01	0.092	.	-2%	-91%	.
BOV_V2	1.07	0.189	.	-1%	-82%	.
RUV_PROP	0.312	0.374	0.405	4%	49%	75%

Figure 1 Sample NM-TRAN code for Full model estimation of BSV and BOV

```
$OMEGA BLOCK(4)
0.404 ; BSV_CL
0.505 0.672 ; BSV_V1
0.512 0.602 0.931 ; BSV_Q
0.581 0.722 1.12 1.47 ; BSV_V2

$OMEGA BLOCK(4)
0.318 ; BOV_CL_1
0.336 0.368 ; BOV_V1_1
0.514 0.582 1.04 ; BOV_Q_1
0.536 0.603 1.09 1.15 ;
BOV_V2_1
$OMEGA BLOCK(4) SAME
;; BOV_CL_2
;; BOV_V1_2
;; BOV_Q_2
;; BOV_V2_2
$OMEGA BLOCK(4) SAME
... etc
```

Figure 2 VPC with censoring of predictions at 0.04 umol/L. Scatterplot shows observed MTX Concentrations (black). 5, 50, and 95 observation percentiles (red) and prediction percentiles (blue) with light blue confidence intervals for predictions.

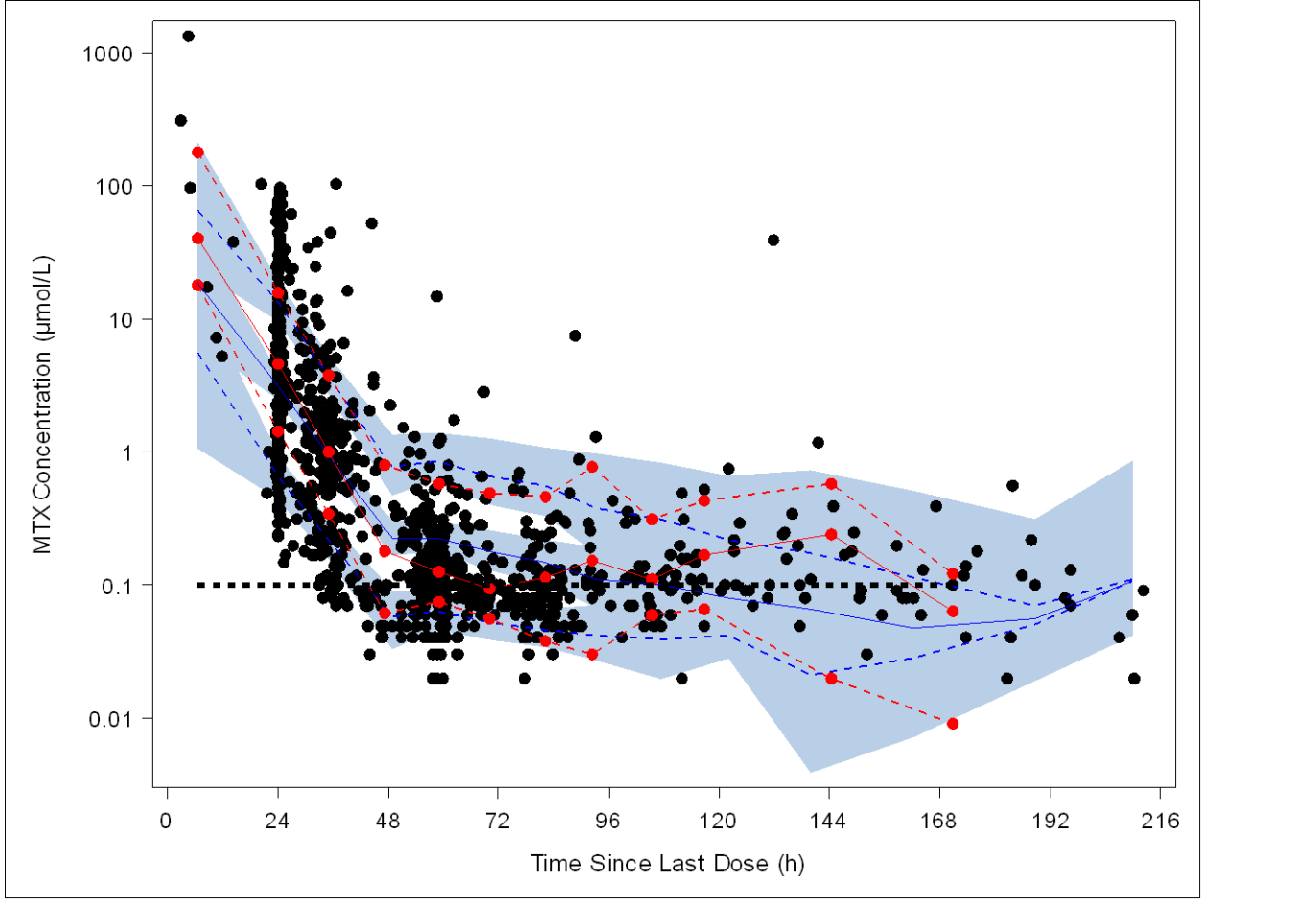


Table 3 Estimates of BSV and BOV using Empirical Bayes (EBE) Parameter Estimates

	Full Model		EBE	
Parameter	BSV	BOV	BSV	BOV
CL	0.64	0.56	0.55	0.36
V1	0.82	0.61	0.60	0.38
Q	0.96	1.02	1.39	0.57
V2	1.21	1.07	2.71	0.59

- The estimate of BOV for CL obtained from the Full model is substantially greater (56%) (Table 2) than the BOV of CL of other studies (0-17%) (Table 1).
- The size of BOV in our study was confirmed by the empirical Bayes estimates (Table 3). As expected these estimates are shrunk and therefore smaller than those from the full mixed effects model, however, they are clearly similar in magnitude and larger than literature estimates.
- It should be noted that the Full model estimated BOV on all parameters. All but one (which also estimated BOV on V) of the other literature studies estimated BOV on CL only.