Model-informed precision dosing of high-dose IV busulfan in Thai pediatric patients

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Context

- Busulfan is used in conditioning regimens for pediatric hematopoietic stem cell transplantation. Target : AUC of 16,000 or 18,000 µM.min over 4 or 5 days.
- Currently at Ramathibodi Hospital (Bangkok, Thailand): TDM with 7 samples/day
- Objectives: Use the population approach (NONMEM) to:
  1. Predict clearance from a **formula based on demographic and pharmacogenetics covariates** to predict the dose and possibly replace TDM
  2. Identify **the best TDM strategy** (days, number of samples, Bayesian analysis)

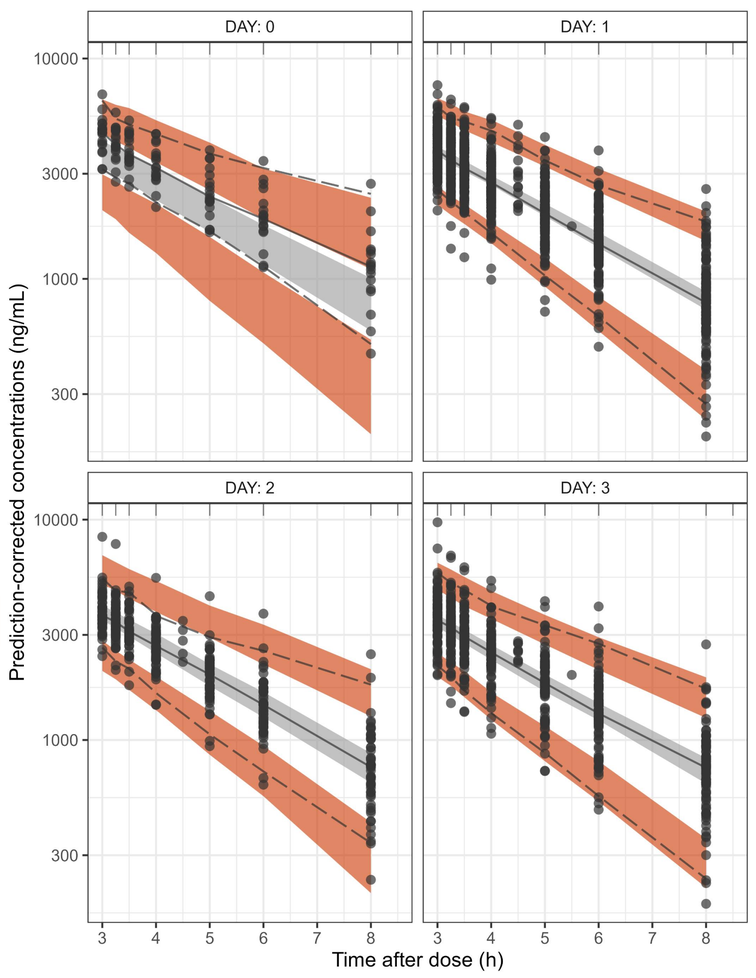
Characteristic	Full cohort, N = 135[1]	Genetics cohort, N = 114[1]
Age (y.o.)	8.0 (4.0, 12.0)	8.0 (5.0, 12.0)
Body Weight (BW, kg)	25 (15, 40)	25 (18, 39)
Height (cm)	126 (102, 146)	127 (105, 147)
Body Surface Area (kg/m²)	0.93 (0.66, 1.28)	0.94 (0.72, 1.27)
Sex		
Female	62 (46%)	51 (45%)
Male	73 (54%)	63 (55%)
Diagnosis		
Hematologic malignancy (MALIGN)	38 (28%)	29 (25%)
Non-hematol malignancy (MALIGN)	17 (13%)	14 (12%)
Hematologic benign disease	68 (50%)	62 (54%)
Metabolic disease	5 (3.7%)	5 (4.4%)
Primary immunodeficiency	7 (5.2%)	4 (3.5%)
Fludarabin Conditioning Regimen	104 (77%)	89 (78%)
Duration of Busulfan Regimen (days)		
4	116 (86%)	100 (88%)
5	19 (14%)	14 (12%)
Number of PK explorations		
1	7 (5.2%)	0 (0%)
2	107 (79%)	99 (87%)
3	20 (15%)	15 (13%)
4	1 (0.7%)	0 (0%)
PK explorations at Day 0	18 (95%)	14 (100%)
PK explorations at Day 1	133 (99%)	113 (99%)
PK explorations at Day 2	50 (37%)	45 (39%)
PK explorations at Day 3	83 (61%)	71 (62%)
PK explorations at Day 4	1 (0.7%)	0 (0%)
GSTM1 Copy Number Variations (0 / 1 / 2 / 3)		78 / 33 / 2 / 1 (68% / 29% / 2% / 1%)
GSTP1 variant carriers (WT / HET / HOM)		65 / 46 / 3 (57% / 40% / 3%)
GSTA1 variant carriers (WT / HET / HOM)		90 / 19 / 5 (79% / 17% / 4%)

[1]Median (IQR); n (%)

1. Base model

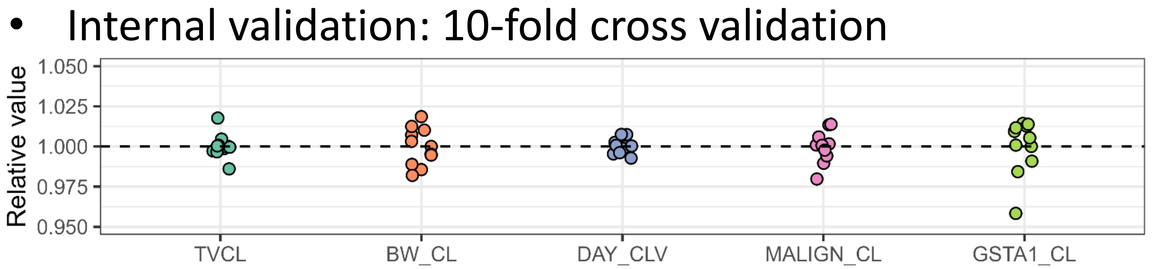
- 2018 conc, 285 courses, 135 patients
- One-compartment model
- Inter-individual (IIV) and inter-occasion (IOV) variabilities on CL and V.
- Correlation between CL and V
- Systematic decrease of CL and V at Day 2-3-4 (- 6%)
- Body size effect: body weight with allometric coefficients on CL and V
- Small residual variability (6.1%)

Parameter	Fixed effects	IIV	IOV
Clearance (L/h)	5.85 (2.52%)	26.0% (8.05%)	14.1% (9.88%)
Volume (L)	18.8 (1.80%)	16.3% (8.41%)	13.8% (8.63%)
Body weight on CL	0.834 (5.45%)	-	-
Body weight on V	0.927 (3.58%)	-	-
DAY234_CLV	0.942 (1.51%)	-	-
Correlation CL~V	-	84.4% (4.83%)	67.9% (13.80%)



2. *A priori* estimation of clearance

- Stepwise covariate modelling
  - Clearance at Day 1 best predicted with
  $$CL = 6.38 \cdot \left(\frac{BW}{25}\right)^{0.768} \cdot 0.896^{MALIGN} \cdot 0.894^{GSTA1}$$
  - RMSE = 1.91 L/h; MPE = +2.4%
- Internal validation: 10-fold cross validation

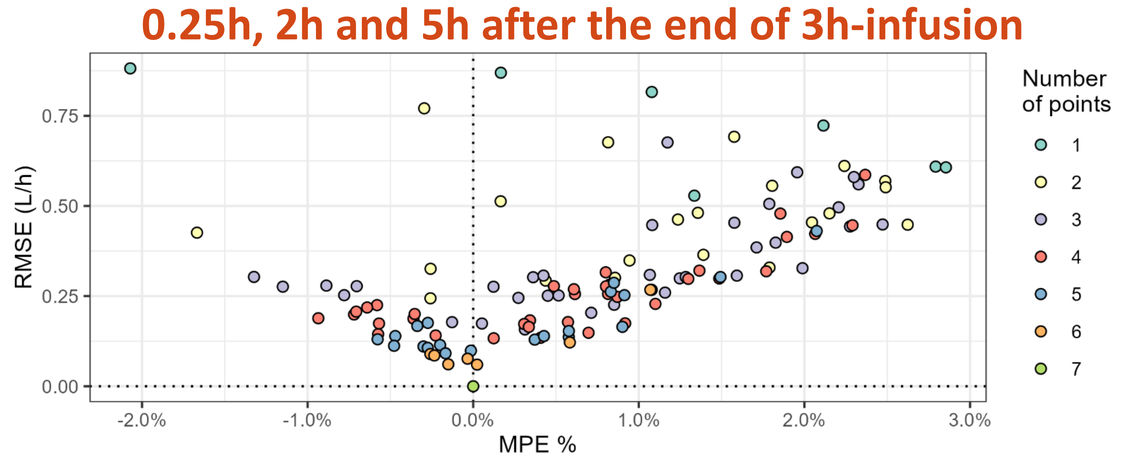


- RMSE = 1.82 L/h, MPE = +2.5%

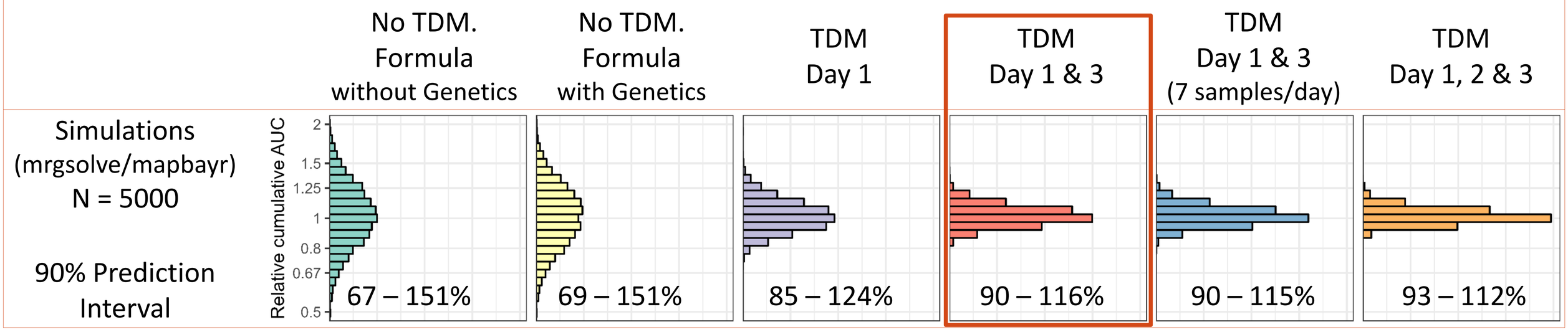
3. Limited Sampling Strategy

- Bayesian analysis with **Base Model**
- Best limited sampling strategy (RMSE = 0.16 L/h, MPE = +0.3%):

0.25h, 2h and 5h after the end of 3h-infusion



4. Evaluation of the best Dosing Strategy



Conclusion

- Formula-based dose calculations perform poorly, **TDM remains essential**
- **Limited perspective for pharmacogenetics** of busulfan
- Performing **TDM on day 1 and 3, with 3 samples**
- Bayesian analysis can be done with **R** with **shiny / mrgsolve / mapbayr** packages