

Population pharmacokinetic model for individualized busulfan dosing in children: Annexation to the existing vast list of PopPK models for performance evaluation.

CRS Uppugunduri ^{1,2}, D.J.A.R. Moes ³, Patricia Curtis Huezco-Diaz ^{1,2}, Nava T ^{1,2}, Kuntzinger M ⁴, Doffey-Lazeyras F ⁴, Youssef Daali ⁴, Marc Ansari ^{1,2}

¹CANSEARCH Research Laboratory, Department of Pediatrics, Faculty of Medicine, University of Geneva, Geneva, Switzerland.

²Onco-Hematology Unit, Department of Pediatrics, Geneva University Hospitals, University of Geneva, Geneva, Switzerland.

³Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.

⁴Clinical Pharmacology and Toxicology Unit, Geneva University Hospitals, University of Geneva, Geneva, Switzerland.

Introduction

Busulfan (Bu) dosing in children has been improved recently with the development of personalized dosing algorithms based on population pharmacokinetic studies (PopPK). However, performance of these models is not optimal but has significantly improved targeted therapy.^{1,2} Few PopPK models evaluated the impact of GSTA1 genetic variants on inter-individual variability (IIV) of Bu clearance (CL). Since cumulative AUC of Bu is linked to outcomes,³ inter-occasional variability (IOV) in its CL determines the overall cumulative exposure. It is also well known that Bu conjugation is catalyzed predominantly by GSTA1 enzyme. No model has evaluated the effect of covariates such as hematocrit and genetic variants in GSTA1 on IOV in Bu CL.

Objectives

The objective of this study is to develop a PopPK model for intravenous Bu in children and to evaluate dynamic and static covariates such as anthropometric, clinical (hematocrit) characteristics and genetic variants (GSTA1 functional diplotypes) that might explain IIV and IOV of Bu CL.

Materials & Methods

- 22 Pediatric patients receiving four times daily Busulfan (Bu) were included
- Dataset consisted out of 327 plasma concentration measurements (53% on 1st day, 16% on 2nd day, and 28% on 3rd day) determined with LC-MS/MS.³
- Covariate analysis with demographic covariates such as Weight, Height, Age, Hematocrit, BSA, Sex, and pharmacogenetic covariates GSTA1 functional diplotypes⁴
- Analysis was performed using NONMEM 7.2, R-Statistics and Pirana.⁵

Results

$$\checkmark \text{IOV} = \text{DAY1} * \text{ETA}(5) + \text{DAY2} * \text{ETA}(6) + \text{DAY3} * \text{ETA}(7)$$

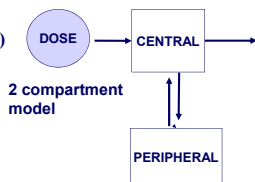
$$\checkmark \text{TVCL} = \text{THETA}(1) * \text{EXP}(\text{IOV}) * (\text{BSA}/0.86) ** (\text{THETA}(5))$$

$$\checkmark \text{CL} = \text{TVCL} * \text{EXP}(\text{ETA}(1))$$

$$\checkmark \text{K} = \text{CL}/\text{V}$$

$$\checkmark \text{K12} = \text{Q}/\text{V}$$

$$\checkmark \text{K21} = \text{Q}/\text{V2}$$



	N	Mean	SD	Median	Range
Male	12	-	-	-	-
Female	10	-	-	-	-
Conditioning (BU-CY/ CY-BU/ BU-Fludarabine)	11 / 4 / 7	-	-	-	-
Diagnosis (Malignancies / Non-malignancies)	17 / 5	-	-	-	-
Age (Y)	6.9	3.96	7.5	0.3 – 13.9	
Weight (kg)	26.5		24.1	5.5 – 68.2	
Height (cm)	118.0	28.4	120.0	61.0 – 169.0	
Body surface Area (m2)	0.9	0.4	0.9	0.3 – 1.8	
Busulfan Dose (cumulative "mg")	320.1	155.6	291.0	72 – 654	
Hematocrit (L/L) Day 1/Day3	0.29 / 0.27	0.04 / 0.03	0.26 / 0.26	0.2 – 0.4 / 0.2 – 0.3	
Fat free mass (FFM)	21.2	11.1	20.9	4.0– 53.0	

PK Parameter	Base Model		Final Model		1000 Bootstrap runs		
	Mean	Shr, %	Mean	RSE (%)	Shr, %	Median	95 %CI
CL (L/h)	2.8		2.94	11		2.82	2.0 – 3.8
V _c (L)	8.42		10.5	26		10.37	6.8 – 15.0
Q (L/h)	0.943		0.98	35		1.02	0.4 – 2.4
V _p (L)	44.2		50.7	92		52.7	17.2 – 476.0
Scaling BSA	-		1.24	12		1.25	0.9 – 2.5
Interindividual variability							
IIV CL (CV%)	39.6	0	22	59	6	22.5	9.5 – 40.0
IIV V _c (CV%)	108.2	0	110.9	44	0	108.1	27.6 – 164.5
IIV V _p (CV%)	100	3	86.8	74	0	99.9	50.3 – 232.7
IIV Q (CV%)	126.9	19	61.9	66	10	59.4	27.9 – 150.6
IOV CL (CV%)	21.5	17	21.8	33	22.5	3.8 – 30.3	
Random residual variability							
σ ² (proportional error)	12.3		12.7	13.3		12.6	10.2 – 15.1

Haplotype	-52(G>A)	-69(C>T)	-513(A>G)	-631(T>G)	-1142(C>G)
*A1	G	C	A	T	G
*A2	G	C	A	G	C
*A3	G	C	A	T	G
*B1a	A	T	A	G	G
*B1b	A	T	G	G	G
*B2	A	T	A	G	C

GSTA1 diplotype groups	N (%)
Rapid metabolizers (G1)	3 (13.6)
Normal and intermediate metabolizers (G2)	14 (63.6)
Poor metabolizers (G3)	5 (22.7)

Figure 1: GSTA1 functional diplotype groups included

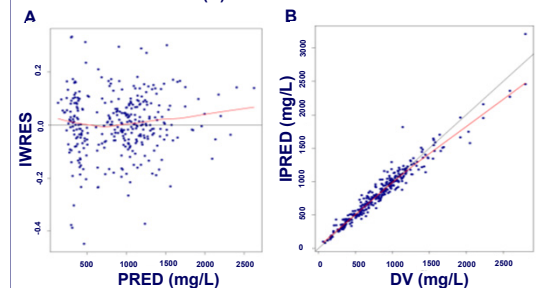
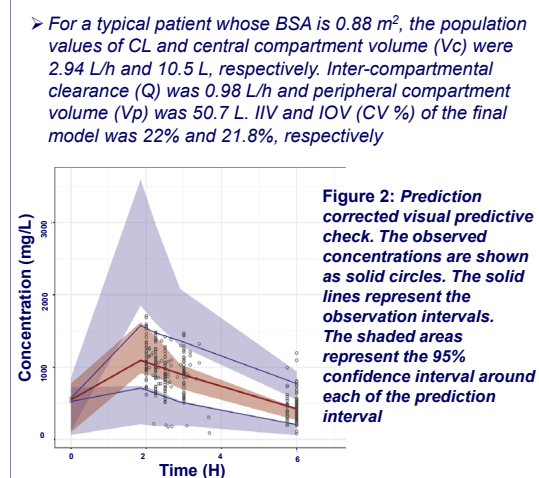


Figure 3: Diagnostic plots A) Individual weighted residuals (IWRES) versus predicted concentrations (PRED) B) Observed concentrations (DV) versus individual predicted values (IPRED)

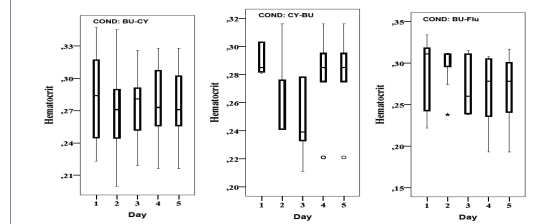


Figure 4: Haematocrit in relation to day and the type of conditioning regimen used.

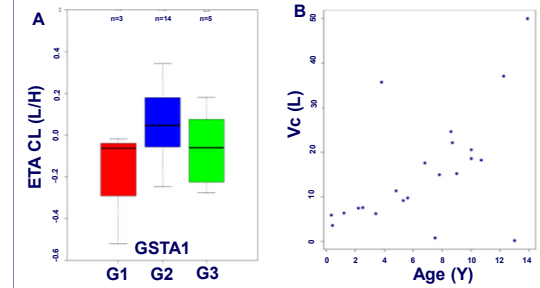


Figure 5: A) Estimated random effects on CL in relation to GSTA1 groups B) Vc in relation to Age

Conclusion

- BSA showed slightly more significant influence on CL (reduced variability from 48.1% to 22%) and V_c compared to bodyweight
- Hematocrit and functional haplotype groups of GSTA1 did not have a significant effect on both IIV and IOV (trend seen of 11%) in this data set
- Small number of patients (Posterior Power analysis showed 49% Power in detecting a 25% difference in clearance (0.05)) and use of various conditioning regimens may have influenced the results of the covariate analysis, and this model performance must be evaluated in a larger dataset.

References

- Zao, J.H., Schechter, T., Liu, W.J. et al. Performance of busulfan dosing guidelines for pediatric hematopoietic stem cell transplant conditioning. *Biol Blood Marrow Transplant.* 2015; 21: 1471–1478.
- Nava T, Rezgui MA, Uppugunduri CRS, et al. GSTA1 genetic variants and conditioning regimen: missing key factors in dosing guidelines of Busulfan in pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2017; 23:1918-1924.
- Bartelink IH, Lalmohamed A, van Reij EM, et al. Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis. *Lancet Haematol.* 2016; 3(11):e526-e536.
- Ansari M., Uppugunduri, C.R., Déglon, J. et al. A simplified method for busulfan monitoring using dried blood spot in combination with liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom.* 2012; 26: 1437–1446.
- Ansari M, Curtis PH, Uppugunduri CRS, et al. GSTA1 diplotypes affect busulfan clearance and toxicity in children undergoing allogeneic hematopoietic stem cell transplantation: a multicenter study. *Oncotarget.* 2017; 8(53):90852-90867.
- Keizer RJ, van Bentem M, Beijnen JH, Schellens JHM, Huijten ADM, Piraña and PCluster: A modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed [Internet].* 2010 Jun.