POPULATION PHARMACOKINETIC MODELING OF BUSULFAN IN PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

Soy D[1], *Clopés A*[2], *Farré R*[3], *Mangues MA*[3]

Pharmacy Department, [1]Hospital Clinic; [2]Institut Català d'Oncologia; [3]Hospital de la Santa Creu i Sant Pau. Barcelona. (Spain)

AIMS

- To assess the Pharmacokinetics of busulphan (BU) in Autologous Stem Cell Transplantation (ASCT) patients.
- To look for relationships between covariates and BU Pharmacokinetics.

METHODS

• Patients:

– This prospective study was performed in 23 patients undergoing an ASCT. Their main diagnose was Myeloma Multiple in first response after chemotherapy.

• Conditioning regimen:

BU: Initial dose: 0.75mg/Kg/6h x 16 doses oral
day -6 to day -3
Following doses were adjusted according to blood levels.

Melphalan: 140mg/m^2 IV day -2

• Blood samples:

– After first dose: 0.5h, 1h, 3 h, 4 h, 6h.

– Sparse samples along treatment were also available for some patients.

• Analytical technique:

– Duplicate analysis was performed by HPLC.

• Target BU systemic exposure:

– The dose of BU was adjusted after 3rd dose performing an individual Pharmacokinetic study (USC Pack).

– Exposure target: $C_{average}^{ss}$ = 850 ng/mL

• Population PK (PopPK) Modeling:

– Data was analyzed on the basis of the population approach (NONMEM-VI).

– Demographic, clinical and biochemistry data were collected for each patient and tested as covariates.

• Validation:

– A validation was conducted in new individuals (n=21) by predicting and comparing the concentrations at the same time (IPRED) than observed (OBS).

– Bias (MPE) and precision (MAPE) were computed. Statistics were performed using S-Plus5.

RESULTS

• Basic popPK model:
One-compartment model with first-order absorption and elimination.

• Parameter estimation:
FOCE with INTERACTION

• Interindividual variability (IIV): (Lognormal)
Clearance (Cl/F) → 30%
Volume of distribution (V/F) → 27%

• Interoccasion variability (IOV): (Lognormal)
It was only retained for Cl/F → 19%

• Measurement error variability:
Proportional normal distribution → 16%

• Model covariates:
- **weight** and **age** for **Cl/F**
- **sex** and **weight** for **V/F**

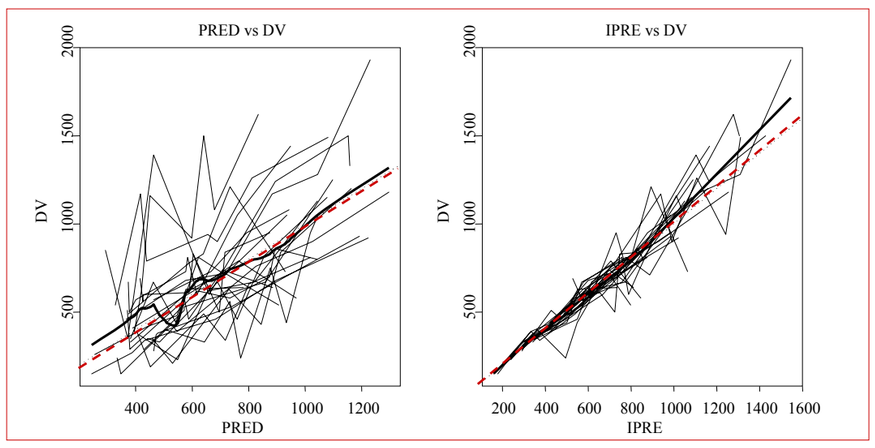
• Final model:
A 4% and 7% reduction in unexplained IIV was found for Cl/F and V/F, respectively.

Final estimates of the population PK parameters for BU

Parameter	Estimate	Parameter	Estimate
$\theta_{CL/F}$ (L/h)	10.6 (11.1)	θ_{V3}	0.328 (56)
$\theta_{V/F}$ (L)	46.8 (11)	$\omega^2_{CL/F}$ (%)	25.2 (21)
$\theta_{Ka/F}$ (h^{-1})	1.68 FIX	$\omega^2_{V/F}$ (%)	19.7 (51)
θ_{CL2}	-2.06 (60)	$\omega^2_{IOV\text{-}CL/F}$ (%)	19.1 (41.6)
θ_{CL3}	0.418 (68)	σ^2 (%)	16.3 (24)
θ_{V2}	-10.2 (63)		

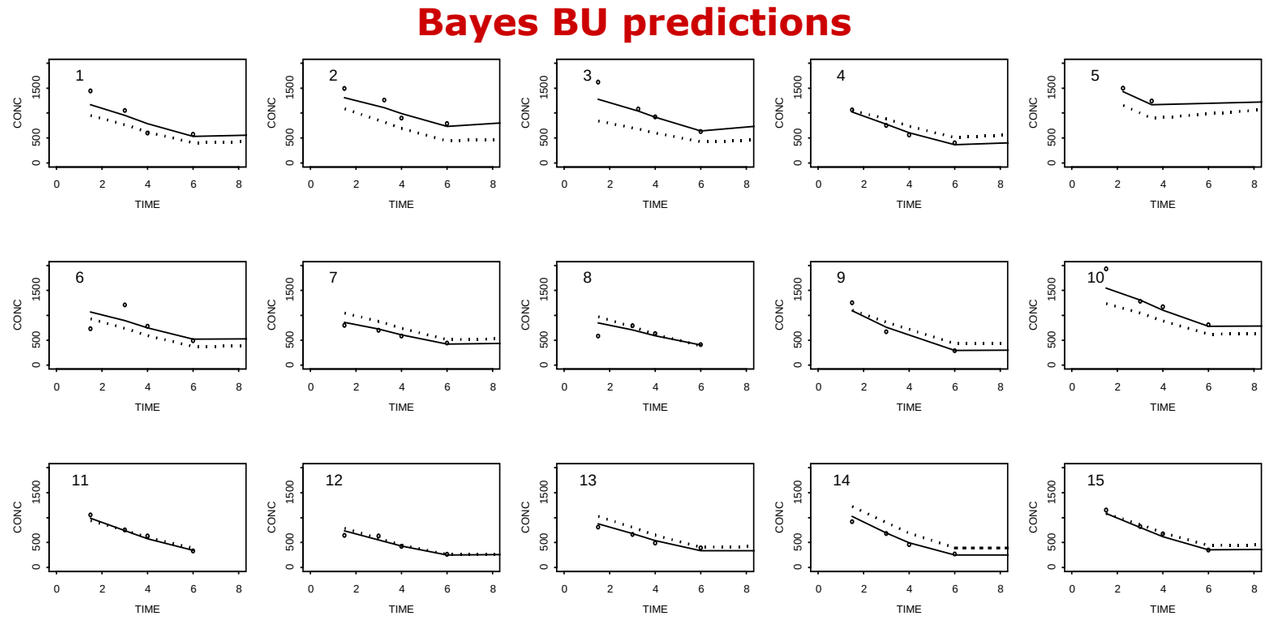
$\theta_{CL/F}$ = BU clearance for an individual with average age and weight; $\theta_{V/F}$ = BU volume of distribution for a male with average weight; $\theta_{Ka/F}$= absorption rate constant; θ_{CL2} = multiplier of BU clearance for the rate (age/mean population age); θ_{CL3} = power of weight in power function predicting BU clearance; θ_{V2} = multiplier of BU volume of distribution for a female; θ_{V3} = power of weight in power function predicting BU V/F; ω^2_p = inter-individual PK parameter variance (P = CL/F, V/F); $\omega^2_{IOV\text{-}P}$ = inter-occasion PK parameter variance; σ^2 = residual error variance.
Precision (standard error) of the estimates is expressed as fraction of estimate (in parenthesis).

Goodness of fit plots for the final population PK model



DV: observed BU concentrations; PRED: population BU predictions; IPRE: individual BU predictions. Red dashed line: line of identity; black thick line: data smooth.
Bu concentrations (DV, PRED and IPRE) are in ng/mL.

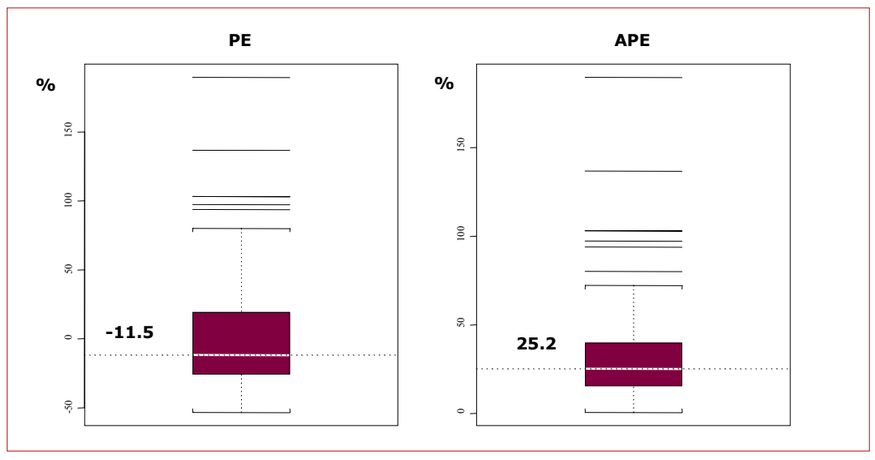
PK model and Individual *Maximum a Priori* Bayes BU predictions



Individual MAP Bayes BU predictions (solid line), population predictions (dashed line) and observed concentrations (dots), after the first dose of BU.
BU concentrations are in ng/mL; time is in hours.

• Validation:

Bias (MPE) and precision (MAPE) were 11.5 % and 25 %, respectively.



The white band in each error box marks the 50th percentile (dashed line); the box boundaries are at the 25th and 75th percentiles, and the limits of the whiskers are at the 10th and 90th percentiles. Other horizontal lines are "outliers", i.e. Values outside the 10-90-percentile range.

CONCLUSIONS

- BU pop-PK parameters were consistent with those previously published.
- Body weight, sex and age were important determinants on Cl/F and V/F.
- Results from this study could be used to optimize the initial and maintenance oral BU dosage in daily prac-tice.

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