Population pharmacokinetic modeling of bortezomib after bolus intravenous injection in cancer patients

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BACKGROUND

- Bortezomib is a proteasome inhibitor that is indicated for the treatment of multiple myeloma, and, in the United States, for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.
- Bortezomib is administered as either a 3–5 second bolus intravenous (IV) injection or a subcutaneous injection.
- Noncompartmental pharmacokinetic analyses revealed greater than expected accumulation in bortezomib systemic exposure after repeated bolus IV dosing in patients using a twice-weekly schedule in 21-day cycles.[1]
- The apparent time-dependence in drug disposition could not be convincingly explained by including between-occasion typical value differences or between-occasion random effects in the submodels for disposition parameters.
- Bortezomib is not an inhibitor or inducer of enzymes responsible for its metabolism, but displays concentration-dependent binding to the proteasome; its primary pharmacologic target protein.
  - Therefore, the apparent time-dependence in pharmacokinetics can be hypothesized to stem from saturable distribution/redistribution kinetics, as opposed to nonlinearities in clearance.

OBJECTIVE

- To further understand the observed differences in bortezomib pharmacokinetics after first and repeated IV dosing through the population modeling approach.

METHODS

Data collection

- Adult cancer patients received bortezomib as a bolus IV injection in 5 clinical phase 1 studies (Table 1).
- Serial blood samples were collected before and after dosing at selected visits during the first 3 cycles.
- Bortezomib concentrations were determined in plasma using liquid chromatography with tandem mass spectrometry methods (Table 1).

Table 1. Study information

Study	N	Bortezomib dose (mg/m^2)	Dosing schedule (cycle length)	Pharmacokinetic sampling timepoint(s)	Assay LLOQ (ng/mL)
1	18	1.45, 1.6, 1.8, 2.0	Days 1, 8, 15, 22 (35-day)	Day 1, cycle 1	0.78, 0.25, 0.5
2	40	1.0, 1.3	Days 1, 4, 8, 11 (21-day)	Days 1 and 11, cycles 1 and 3	0.5
3	16	1.3	Days 1, 4, 8, 11 (21-day)	Day 8, cycle 1 or 2	0.5
4	24	1.0	Days 1, 4, 8, 11 (21-day)	Day 8, cycle 1 or 2	0.1
5	44	1.3	Days 1, 4, 8, 11 (21-day)	Day 11, cycles 2 and 3 (subset)	0.1

N, number of patients.
LLOQ, the lower limit of the assay's quantification.

Model development

- Population models were fitted to the concentration-time data from bortezomib-only treatments using NONMEM version 7.2.
- Various disposition models were examined including:
  - Linear (1, 2, 3, 4 compartment) or nonlinear (3, 4 compartment) elimination
  - Empirical time-dependent systemic clearance (3, 4 compartment)
  - Saturable binding (3, 4 compartment)
  - Concentration-dependent intercompartmental clearance (3 compartment)
  - Combined linear and nonlinear distribution for a peripheral compartment (3, 4 compartment)
- A log-transform, both-sides approach was used to model residual variability.
  - Concentrations below the lower limit of the assay's quantification (BLQs) were handled using a modified version of the M3 method.[2]
    - Unlike M3, the likelihood was maximized for BLQs only with respect to the model parameters.
- The final model was achieved using the full Markov Chain Monte Carlo (MCMC) Bayesian analysis (BAYES) method.[3]
  - NONMEM's termination test was used during burn-in for model convergence.
  - Post-burn-in convergence testing and summarization of posterior parameters were performed using R package CODA.

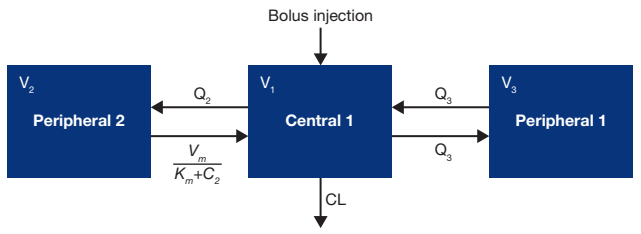
Model evaluation

- Model goodness-of-fit was evaluated by standard diagnostic plots.
- Normalized prediction distribution error (NPDE) was output to construct a distribution for normality testing.[4]
- Visual predictive check (VPC), based on 100–300 simulations under the final model, was used for internal validation.[5]

RESULTS

- 142 patients provided 3004 observations.
- A 3-compartment model, with nonlinear distribution from a peripheral compartment to the central compartment, was considered most adequate (Figure 1).
  - ADVAN 13 TOL=5 subroutine was used.
  - Pharmacokinetic parameters were transformed exponentially to ensure non-negative estimates.
  - Residual variability in quantifiable concentrations consisted of a common parameter for all the assays and a shift parameter for the most sensitive assay.
- Nonconvergence of V_m, K_m, and V_2 was encountered during initial runs and could be best resolved by fixing V_m to 0.0926 ng/mL/hr.
- The final model converged after 500 iterations in the first burn-in phase. In the second stationary distribution phase, its parameters achieved the desired posterior starting from the iteration 5001.

Figure 1. Schematic diagram of final model



CL, systemic clearance; K_m, Michaelis constant for clearance from Peripheral 2 to Central 1; Q_2, clearance from Central 1 to Peripheral 2; Q_3, intercompartmental clearance for Peripheral 3; V_1, volume of distribution of Central 1; V_2, volume of distribution of Peripheral 2; V_3, volume of distribution of Peripheral 3; V_m, maximum velocity for clearance from Peripheral 2 to Central 1.

- A total of 28,157 iterations were used for graphical and statistical convergence tests and parameter summarization.
  - Trace and density plots revealed no trends in sampled values and no multimodal posterior distributions for the parameters, respectively.
  - Geweke's diagnostic and Heidelberger and Welch's diagnostic confirmed stationarity of the posterior parameter distribution.
- All the estimated parameters except for V_2 are estimated with good precision, as evidenced by small coefficients of variation and narrow sampling distributions (Tables 2 and 3).

Table 2. Summary of estimated population parameters

Parameter	Mean	SD	CV (%)	Time-series Naïve SE	Time-series SE	IIV (%)
CL (L/hr)	10.8	0.51	5	0.003	0.022	43
V_1 (L)	14.1	1.34	10	0.008	0.094	81
Q_2 (L/hr)	46.3	4.40	9	0.026	0.267	93
Q_3 (L/hr)	51.7	3.66	7	0.022	0.218	70
V_2 (L)	349	528	151	3.15	77.5	304
V_3 (L)	895	104	12	0.620	6.29	114
K_m (ng/mL)	0.06	0.008	13	0.000	0.001	93
RV_{Common}	42%	1%	2	0.000	0.000	–
RV_{Shift}	20%	1%	5	0.000	0.000	–
MCMCOBJ	–4255	72.1	–2	0.430	3.39	–

CV, coefficient of variation; IIV, inter-individual variability reported as CV; MCMCOBJ, objective function displayed during BAYES analysis; RV, residual variability; SD, standard deviation; SE, standard error.

Table 3. Quantiles of the sampling distribution for estimated population parameters

Parameter	2.5%	25%	50%	75%	97.5%
CL (L/hr)	9.83	10.5	10.8	11.1	11.8
V_1 (L)	11.7	13.1	14.0	14.9	17.0
Q_2 (L/hr)	38.6	43.2	46.0	49.1	55.8
Q_3 (L/hr)	45.3	49.1	51.5	54.1	59.5
V_2 (L)	60.8	133	210	353	1490
V_3 (L)	702	824	891	962	1110
K_m (ng/mL)	0.05	0.05	0.06	0.06	0.08
MCMCOBJ	–4394	–4303	–4256	–4207	–4110
IIV for CL	0.13	0.16	0.18	0.21	0.27
IIV for V_1	0.42	0.56	0.65	0.75	1.01
IIV for Q_2	0.60	0.76	0.85	0.95	1.19
IIV for Q_3	0.34	0.43	0.48	0.54	0.67
IIV for V_2	0.92	1.14	1.28	1.43	1.77
IIV for V_3	5.31	7.31	8.74	10.6	15.9
IIV for K_m	0.44	0.67	0.83	1.02	1.50
RV_{Common}	–0.44	–0.43	–0.42	–0.42	–0.41
RV_{Shift}	0.18	0.19	0.20	0.20	0.22

- The final model could describe the observed data reasonably well, as evidenced by reasonable goodness-of-fit (Figure 2) and a near normal distribution of NPDE (Figure 3).

Figure 2. Diagnostic plots for final model

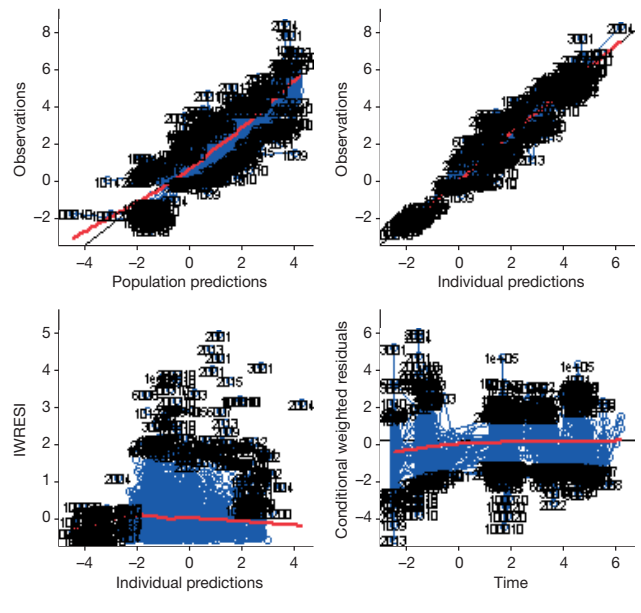
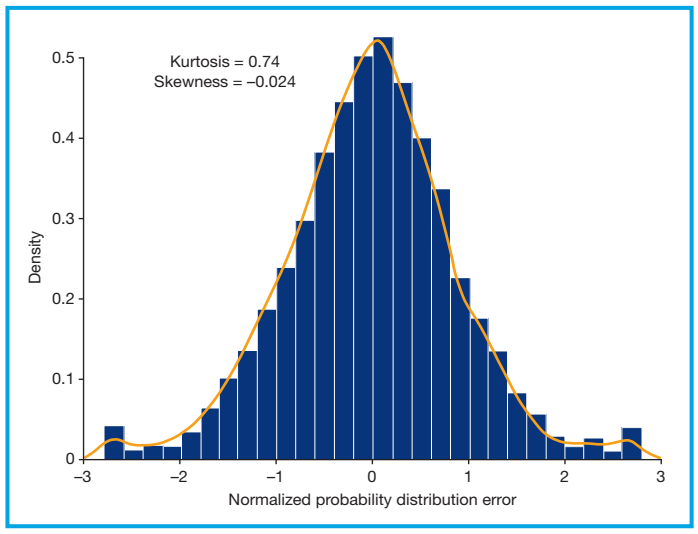


Figure 3. NPDE histograms and normality evaluated by kurtosis and skewness



- VPCs showed that the 95% prediction interval contained the 2.5th and 97.5th percentiles of the observed data on day 1 of cycle 1 (Figure 4) and of the observed data excluding those on day 1 of cycle 1 (Figure 5).

Figure 4. Predicted and observed concentrations versus time (day 1, cycle 1)

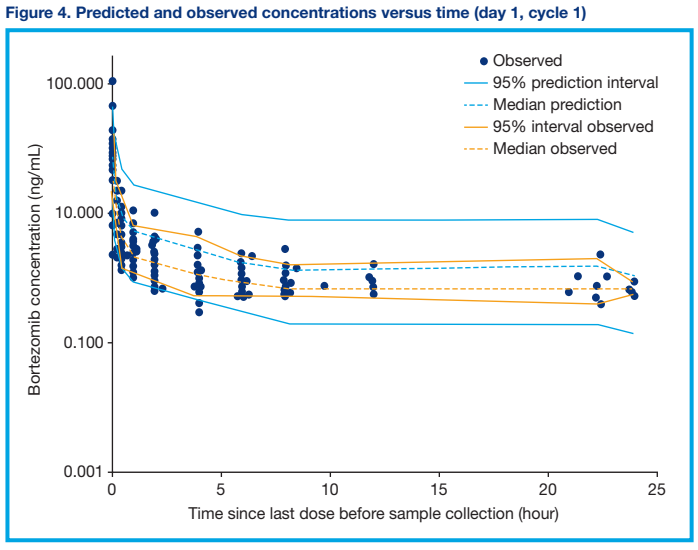
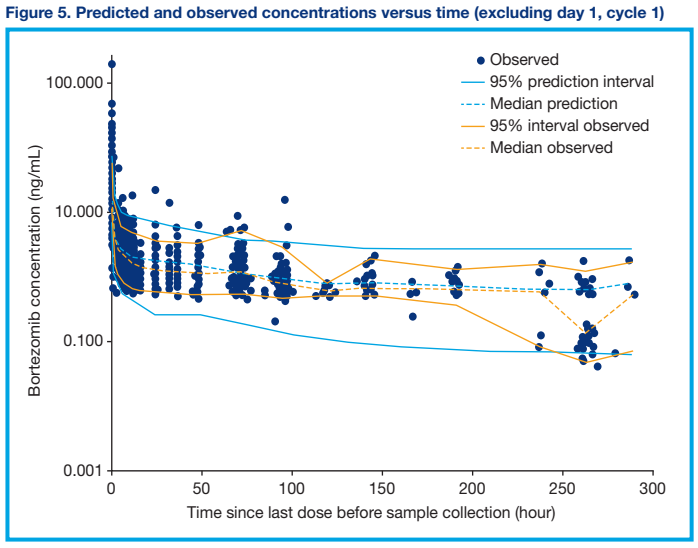


Figure 5. Predicted and observed concentrations versus time (excluding day 1, cycle 1)



CONCLUSIONS

- The final model attributes previously reported time-dependence in bortezomib disposition to saturable distribution from a peripheral compartment (Peripheral 2) to the central compartment (Central 1).
  - This is likely explained by saturable binding to the proteasome, a ubiquitously expressed cellular protein that represents the pharmacologic target of bortezomib.
- The model describes the observed data reasonably well, and its predictive performance is demonstrated through VPCs.
  - Accordingly, the model may be used to predict bortezomib plasma exposure following alternative dosing schedules.

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