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Population Pharmacokinetic Analysis of Bortezomib in Pediatric Leukemia Patients: Model-Based Support for Body Surface Area-Based Dosing Over the 2- to 16-Year Age Range

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Abstract

This population analysis described the pharmacokinetics of bortezomib after twice-weekly, repeat-dose, intravenous administration in pediatric patients participating in 2 clinical trials: the phase 2 AALL07P1 (NCT00873093) trial in relapsed acute lymphoblastic leukemia and the phase 3 AAML1031 (NCT01371981) trial in de novo acute myelogenous leukemia. The sources of variability in the pharmacokinetic parameters were characterized and quantified to support dosing recommendations. Patients received intravenous bortezomib 1.3 mg/m^2 twice-weekly, on days 1, 4, and 8 during specific blocks or cycles of both trials and on day 11 of block 1 of study AALL07P1, in combination with multiagent chemotherapy. Blood samples were obtained and the plasma was harvested on day 8 over 0-72 hours postdose to measure bortezomib concentrations by liquid chromatography-tandem mass spectrometry. Concentration-time data were analyzed by nonlinear mixed-effects modeling. Covariates were examined using forward addition ($P < .01$)/backward elimination ($P < .001$). Data were included from 104 patients (49%/51% acute lymphoblastic leukemia/acute myelogenous leukemia; 60%/40% aged 2-11 years/12-16 years). Bortezomib pharmacokinetics were described by a 3-compartment model with linear elimination. Body surface area adequately accounted for variability in clearance (exponent 0.97), supporting body surface area-based dosing. Stratified visual predictive check simulations verified that neither age group nor patient population represented sources of meaningful pharmacokinetic heterogeneity not accounted for by the final population pharmacokinetic model. Following administration of 1.3 mg/m^2 intravenous bortezomib doses, body surface area–normalized clearance in pediatric patients was similar to that observed in adult patients, thereby indicating that this dose achieves similar systemic exposures in pediatric patients.

Keywords

multiple myeloma, bortezomib, pediatric pharmacokinetics, proteasome inhibitor, population pharmacokinetics, leukemia

Bortezomib is a dipeptidyl boronic acid that selectively inhibits the ubiquitin proteasome pathway, which is involved in the degradation of many intracellular proteins.[1] Bortezomib disrupts the ubiquitin proteasome pathway by inhibiting the 26S proteasome, which is a multisubunit protein that degrades proteins involved in multiple cellular processes, including cell cycle regulation, transcription factor activation, and apoptosis.[2–5] Important regulatory proteins affected by inhibition of the ubiquitin proteasome pathway system include nuclear factor κB, p53, Bax, and other cell cycle regulatory proteins, including the cyclin-dependent kinase inhibitors p27 and p21.[6] Proteasome inhibition is thought to alter the ratio of proapoptotic and antiapoptotic proteins within cells, resulting in an increased sensitivity to apoptosis.[7]

In the United States, bortezomib is approved for the treatment of adult patients with multiple myeloma (MM) or mantle cell lymphoma.[5] The recommended dose and schedule for bortezomib is 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle. Pharmacokinetic

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(PK) data from adult patients with MM have shown that bortezomib PK is time dependent. Specifically, bortezomib plasma clearance is reduced after repeat-dose administration as compared with the first dose of the first treatment cycle, resulting in an associated increase in systemic exposures and terminal half-life.[8]

In the pediatric patient population, 2 phase 1 studies have determined the maximum tolerated dose and preliminary PK and pharmacodynamic characteristics of bortezomib when administered as a single agent. The phase 1 ADVL0015 study enrolled pediatric patients with refractory solid tumors and investigated 1.2 and 1.6 mg/m^2 intravenous (IV) doses of bortezomib administered on days 1, 4, 8, and 11 of 21-day cycles. Dose-dependent inhibition of blood 20S proteasome activity was observed, with maximal inhibition occurring within 1 hour of dosing. The maximum tolerated dose was determined to be 1.2 mg/m^2 following the observation of 2 dose-limiting toxicities of thrombocytopenia at the 1.6 mg/m^2 dose level.[9] The phase 1 ADVL0317 study enrolled pediatric patients with refractory/recurrent leukemias and investigated twice-weekly (days 1, 4, 8, and 11 of 21-day cycles) IV bortezomib treatment at dose levels of 1.3 or 1.7 mg/m^2. After administration of the first dose, bortezomib concentrations decreased in a multiphasic manner. Plasma bortezomib exposures (ie, area under the concentration-time curve) increased with an increase in dose from 1.3 to 1.7 mg/m^2. Additionally, the limited PK data obtained from 5 patients in this study[10] (aged 11 to 17 years; data on file) suggested that the first-dose PK of bortezomib was similar in adult and pediatric patients. Two dose-limiting toxicities (grade 3 confusion and grade 4 hypotension with fever) were observed in patients who received the 1.7 mg/m^2 dose level; therefore, the maximum tolerated dose was established at 1.3 mg/m^2 in children with refractory/recurrent leukemias.[10] The data collected in studies ADVL0015 and ADVL0317 enabled the further evaluation of the safety and efficacy of bortezomib when used in combination with multiagent chemotherapy backbone regimens in pediatric patient populations with hematologic malignancies.

Although bortezomib has been investigated in pediatric cancers, a systematic evaluation of the sources of PK variability (eg, age, body size) to support dosing recommendations has not been conducted. Accordingly, a pediatric population PK analysis for bortezomib after repeat-dose administration was conducted using sparse PK samples collected from patients aged 2 to 16 years with acute leukemias who were participating in 2 Children's Oncology Group studies: study AALL07P1, a phase 2 trial in pediatric patients with relapsed acute lymphoblastic leukemia (ALL), and study AAML1031, a randomized phase 3 trial in pediatric patients with de novo acute myelogenous leukemia (AML). The aims of this population PK analysis were to describe the PK of bortezomib following twice-weekly, repeat-dose, IV administration in pediatric patients and to quantify and characterize the sources of variability in PK parameters in order to support dosing recommendations. The results of this analysis were subsequently used to support the requirements of a Pediatric Written Request from the US Food and Drug Administration.[5,11]

Methods

Human Subject Protection

The PK data used to develop the population PK model were collected in 2 Children's Oncology Group studies (studies AALL07P1 [NCT00873093][12] and AAML1031 [NCT01371981][13]). The final study protocol, any amendments, and informed consent documentation were reviewed and approved by the institutional review board(s) or by the pediatric central institutional review board according to Children's Oncology Group procedures. Written informed consent was obtained from a parent or guardian of each patient at the time of the patient's enrollment. Patients aged 2 to 16 years had the option of participating in the bortezomib PK portion of each study. Both studies were conducted in compliance with their protocol, Good Clinical Practice, applicable regulatory requirements, and International Conference on Harmonization guidelines as well as any local institutional regulations concerning research in children.

Study Design

In study AALL07P1, patients with relapsed ALL received a 3-block reinduction chemotherapy regimen with bortezomib integrated into blocks 1 and 2 (block duration of 35 days). Bortezomib 1.3 mg/m^2 was administered IV on days 1, 4, 8, and 11 of block 1 and on days 1, 4, and 8 of block 2. In study AAML1031, patients with AML received a 4-course chemotherapy backbone (denoted as induction 1, induction 2, intensification 1, and intensification 2), with patients randomized to arm B of the study receiving 1.3 mg/m^2 IV bortezomib on days 1, 4, and 8 of induction 1, induction 2, intensification 1, and intensification 2 (Figure 1).

In study AALL07P1, the use of anticonvulsants that induced CYP3A activity was not allowed. Administration of inhibitors or inducers of CYP1A2, CYP2C19, or CYP3A was to be avoided, if possible, and every attempt was to be made to switch patients to an acceptable alternative medication. In study AAML1031, coadministration of strong CYP3A inducers was to be avoided throughout therapy with bortezomib. Additionally, coadministration of strong or clinically relevant moderate CYP3A inhibitors was

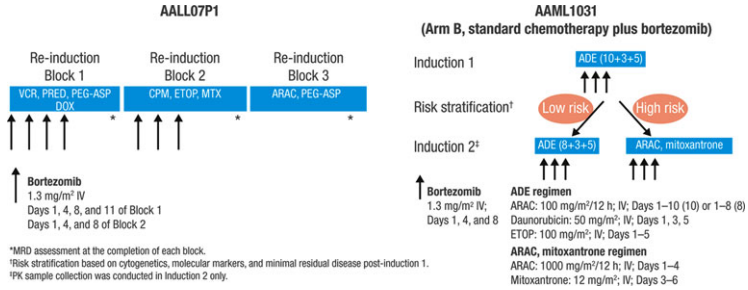

Figure 1. Bortezomib administration in Children's Oncology Group (COG) studies AALL07P1 and AAML1031. ADE, cytarabine/daunorubicin/etoposide; ARAC, cytarabine; CPM, cyclophosphamide; DOX, doxorubicin; ETOP, etoposide; MRD, minimal residual disease; MTX, methotrexate; PEG-ASP, pegylated asparaginase; PRED, prednisone; VCR, vincristine.

to be avoided until 72 hours after the administration of the day 8 dose of bortezomib. Similarly, administration of strong or clinically relevant moderate CYP3A inhibitors was to be stopped 72 hours prior to the day 1 bortezomib dose in all courses.

Assessments

In consenting patients aged 2 to 16 years, blood samples were obtained, and the plasma was harvested for the measurement of plasma concentrations of bortezomib after the day 8 dose of bortezomib. On day 8 of block 1 of study AALL07P1, samples were collected predose (within 1 hour prior to the day 8 dose) and at 5 to 15 minutes, 30 to 60 minutes, 4 to 8 hours, and approximately 72 hours postdose. One predose sample was also collected within 1 hour prior to the day 8 bortezomib dose in block 2. During induction 2 of study AAML1031, samples were collected within 1 hour prior to the day 8 dose (predose) and at 5 to 15 minutes, 30 to 60 minutes, 4 to 8 hours, 18 to 30 hours, and approximately 72 hours postdose. Plasma concentrations of bortezomib were measured using a previously published method.[14] The dynamic range of the assay was 0.1 to 25.0 ng/mL.

Population PK Modeling

A population PK model was developed using the sparse PK data collected in studies AALL07P1 and AAML1031. The plasma concentration-time data collected in these studies were analyzed using nonlinear mixed-effects modeling methods as implemented by NONMEM (version 7, level 2, ICON Development Solutions, Dublin, Ireland).[15] Diagnostic graphics, exploratory analyses, and postprocessing of NONMEM output were performed using R version 3.02 and XPOSE version 4.[16]

The available bortezomib concentration-time data were used (1) to estimate population PK parameters and associated interindividual variability (IIV) using an exponential error model; (2) to estimate residual error using a proportional error model; and (3) to predict potential covariates that affected the PK parameters. Modeling was performed using the first-order conditional estimation method and the log-transform both sides approach for residual variability. Model selection was based on evaluation of the change in the objective function value (OFV) between nested models, the magnitude of the interindividual and residual variance, and examination of diagnostic plots. Model stability was tested through the evaluation of the condition number, which was calculated only if the covariance step of NONMEM completed successfully.

Covariate analysis was conducted using the base model. The following covariates were examined: age, weight, body surface area (BSA), race, disease type (ALL or AML), risk group within the AML population (study AAML1031), and treatment plan stratum within the ALL population (study AALL07P1). Continuous covariates were modeled as power models using the following equation:

$$\mathrm{TVP} = \mathrm{P_{pop}} \cdot \prod_{i=1}^{n} \mathrm{cov_i}^{\theta_i}.$$

In this equation, TVP represents the model-predicted PK parameter for the "typical" individual with covariate value $\mathrm{cov_i}$, $\mathrm{P_{pop}}$ represents the population central tendency for the PK parameter TVP, $\mathrm{cov_i}$ represents the individual value for the covariate normalized for the population mean, and θ_i represents a scaling factor. Categorical covariates were modeled as a linear proportional change using the following equation:

$$\mathrm{TVP} = \mathrm{P_{pop}} \cdot \prod_{i=1}^{n} \theta_i^{\mathrm{cov}_i}.$$

In this equation, θ_i is a direct proportionality constant that is fixed to 1 for the reference subgroup (eg, $\mathrm{cov_i}$ value of 0 for males) and is estimated for other subgroups (eg, $\mathrm{cov_i}$ value of 1 for females). All body size metrics were referenced to the size of an average adult (weight, 70 kg; BSA, 1.8 $\mathrm{m^2}$).

Table 1. Demographic and Disease Information for Patients in the Population Pharmacokinetic Analysis Data Set

	Study AALL07P1 (N = 51)	Study AAML1031 (N = 53)	Total (N = 104)
Age group, n (%)			
2-11 years	36 (71)	26 (49)	62 (60)
12-16 years	15 (29)	27 (51)	42 (40)
Mean age, y (range)	8.5 (2-16)	11.4 (3-16)	10 (2-16)
Mean BSA, m^2 (range)	1.20 (0.60-2.21)	1.40 (0.61-2.53)	1.30 (0.60-2.53)
Mean weight, kg (range)	40.6 (14.3-100.2)	49.6 (13.9-139.7)	45.2 (13.9-139.7)
Sex, n (%)			
Male	31 (61)	29 (55)	60 (58)
Female	20 (39)	24 (45)	44 (42)
Race, n (%)			
White	33 (65)	34 (64)	67 (65)
Black	9 (18)	10 (19)	19 (18)
Other	9 (18)	9 (17)	18 (17)
Risk group (Study AAML1031 only), n (%)			
Low-risk AML	–	40 (75)	–
High-risk AML	–	13 (25)	–
Treatment plan stratum (Study AALL07P1 only), n (%)			
Pre-B ALL, relapse within 18 months of diagnosis	20 (39)	–	–
Pre-B ALL, relapse 18-36 months from diagnosis	26 (51)	–	–
T-cell ALL and T-cell lymphoblastic lymphoma	5 (10)	–	–

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BSA, body surface area.

After development of the base model, covariate vs η plots were inspected visually for trends. Covariates with trends that significantly decreased the OFV ($P < .01$, corresponding to a $\geq$6.6 point decrease in the OFV using the likelihood ratio test for nested models) were pooled into a full model. The full model with all included covariates was then subjected to backward elimination. If the removal of a covariate increased the OFV by <10.8 points (corresponding to a *P*-value of .001 for nested models), then that covariate was removed from the model. This was repeated until all the covariates that remained in the model resulted in an increase of the OFV by at least 10.8 points when individually removed.

Visual predictive check (VPC) plots, stratified by age group (2–11 years vs 12–16 years) and study, were constructed using simulated data from the final model and were used to evaluate the predictive performance of the model. Nonparametric bootstrapping (N = 5000 runs), stratified by study, was used to evaluate parameter precision. Shrinkage values were also estimated for parameters for which IIV was included in the model.

Estimates of the α, β, and γ (terminal/elimination) disposition phase half-lives were also calculated as described previously.[17] Volume of distribution at steady-state was calculated as the sum of the central compartment volume (V1), peripheral volume 1 (V2), and peripheral volume 2 (V3). Individual patient PK parameters were summarized using descriptive statistics.

Results

Data from 104 pediatric patients diagnosed with ALL (study AALL07P1, N = 51) or AML (study AAML1031, N = 53) contributed to this population PK analysis. The final analysis data set included 571 concentration values. None of the concentrations were reported as below the limit of quantification (<0.1 ng/mL). The median number of concentrations per patient was 6 (range 1–6). The demographics and baseline characteristics of patients included in the population PK analysis data set are summarized in Table 1. The patient age range was 2 to 16 years (2–11 years, N = 62; 12–16 years, N = 42), with a mean of 10 years. Accordingly, PK data were available from patients over a wide range of BSA values (0.60–2.53 m^2) and body weights (13.9–139.7 kg). Fifty-eight percent of patients were male, and 65% were white.

After twice-weekly IV bolus repeat-dose administration, plasma concentrations of bortezomib declined in a multiexponential manner indicative of a multicompartmental PK model (Figure 2). Additionally, bortezomib disposition in pediatric patients appeared similar to that previously observed in adult patients with MM after repeat-dose administration.[8]

After evaluation of 1-, 2-, 3-, and 4-compartment PK models, a 3-compartment model was selected as the base model based on the OFV, condition number, and goodness-of-fit considerations. The base model included IIV terms on clearance (CL), the central volume of distribution (V1), and intercompartmental

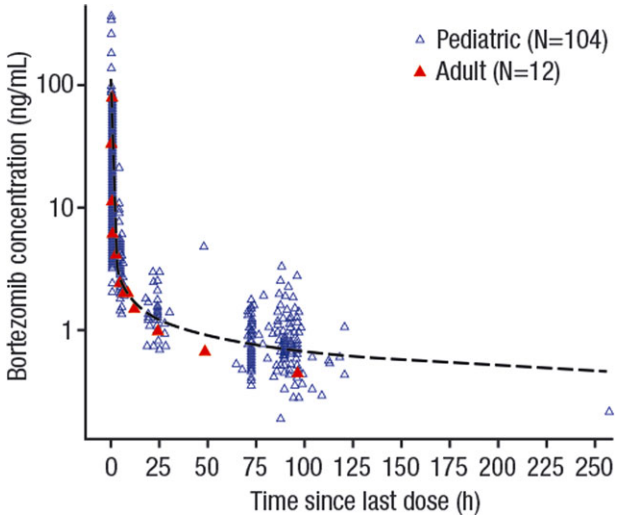

Figure 2. Concentration-time profile of bortezomib after repeat dosing of 1.3 mg/m^2 intravenously. Blue triangles represent individual concentration data from the 104 pediatric patients included in the population pharmacokinetic analysis data set. The black dashed line represents a LOESS curve for the observed data. Red triangles denote mean concentrations from 12 adult multiple myeloma patients on day 11 of cycle 1.[8]

clearance between the central and second peripheral compartment (Q3). The residual error model was a homoscedastic model on the log scale, proportional after back transformation. Evaluation of the base model showed that, in general, there was acceptable concordance between the population and the individual predicted concentrations with the observed concentrations. There was no apparent trend in the individual weighted residuals, indicating that the residual error model was appropriate. The plot of the conditional weighted residuals vs the relative time since the last dose also did not show any trends. Overall, the model fit was considered adequate for a base model.

Final model development included the examination of covariate influences on the parameters with IIV terms. Because this was a pediatric population PK analysis, and the patient population spanned a wide range of ages and body sizes (ie, body weight, BSA), the first step in covariate analysis was to evaluate the contribution of these patient-specific factors to IIV in PK parameters. Univariate analysis showed that an effect of BSA on CL resulted in the largest decrease in the OFV. Age and weight also decreased the OFV. On the basis of the lowest OFV for an effect of BSA on CL and examination of covariate vs η plots, which showed that many of the trends in the plots (eg, between weight or age and η_{CL}) were removed when this effect was added, an effect of BSA on CL was included in the model. At this stage, BSA effects on V1 and Q3 were also evaluated, and it was shown that the effect on Q3 was statistically significant ($P < .01$). Therefore, a BSA effect was included on both CL and Q3. In order to account for the difference in the sparse PK sampling scheme between studies AALL07P1 and AAML1031 (ie, lack of the 18 to 30 hours postdose sample in study AALL07P1), separate residual variability parameters were estimated for each study. This resulted in a large (>52 point) decrease in the OFV.

After the base model was updated to include BSA effects on CL and Q3, and the residual error model was updated to account for the sparser sampling scheme in study AALL07P1, the effects of additional covariates were examined by forward addition ($P < .01$) and backward elimination ($P < .001$). No additional statistically significant covariates were identified. Therefore, the final model was the base model with a BSA effect on CL and Q3, and a study effect on residual variability. The IIV percentage coefficient of variation (CV) for all 3 parameters in the final model (CL 29.7%, V1 34.6%, Q3 29.8%) decreased relative to those in the base model (CL 41.2%, V1 50.7%, Q3 38.3%). The condition number for the final model was 6.37, indicating an adequately parameterized model without unacceptable colinearity between the parameters. The shrinkage on CL was reasonable at approximately 14%. Shrinkage on V1 and Q3 were approximately 30% each. Parameter estimates for the final model based on bootstrap analysis (N = 5000 runs) are summarized in Table 2.

Goodness-of-fit plots for the final model demonstrated that there was acceptable concordance between the model-predicted population concentrations and the model-predicted individual patient concentrations with the observed concentration data (Figure 3). Additionally, there was no apparent trend in the individual weighted residuals, thereby indicating adequacy of the residual error model. The plot of conditional weighted residuals vs the relative time since last dose also did not show any trends, supporting an appropriate structural model.

Inclusion of BSA alone as a covariate in the final model was sufficient to eliminate any observed trends in the base model between CL and age or body weight (Figure 4). Similar results were observed for V1 (Supplementary Figure S1) and Q3 (Supplementary Figure S2). Collectively, these model evaluations demonstrate that any trends observed vs age or body size metrics in the base model are no longer observed in the final model. This indicates that incorporation of BSA effects on CL and Q3 adequately accounts for the variability in the PK parameters of bortezomib across the age range (2–16 years) evaluated in this analysis. Of note, the estimated exponent for the BSA effect on clearance was 0.97, indicating an approximately linear BSA-clearance relationship in the pediatric patient population across the 2 to 16 years age range.

Table 2. Parameter Estimates for the Final Population Pharmacokinetic Model

Parameter	Population Median (95%CI)[a]	%CV Interindividual Variance Mean (95%CI)[a]
CL, L/h	9.59 (8.79-10.37)	29.7 (23.1-36.8)
BSA effect on CL	0.97 (0.72-1.25)	–
V1, L	10.0 (6.09-13.4)	34.6 (13.5-59.9)
Q2, L/h	25.8 (18.9-31.9)	–
V2, L	32.5 (23.1-43.1)	–
Q3, L/h	26.6 (21.3-30.7)	29.8 (14.3-43.3)
BSA effect on Q3	0.75 (0.43-0.99)	–
V3, L	975 (792-1190)	–
Residual error for study AALL07P1, %CV	46.8% (37.5-57.7)	–
Residual error for study AAML1031, %CV	21.9% (16.0-29.1)	–

BSA, body surface area; CL, clearance; CV, coefficient of variation; Q2, intercompartmental clearance 1; Q3, intercompartmental clearance 2; V1, central volume; V2, peripheral volume 1; V3, peripheral volume 2.

[a]Determined by bootstrap analysis from 4665 of the 5000 bootstrap model runs that converged successfully.

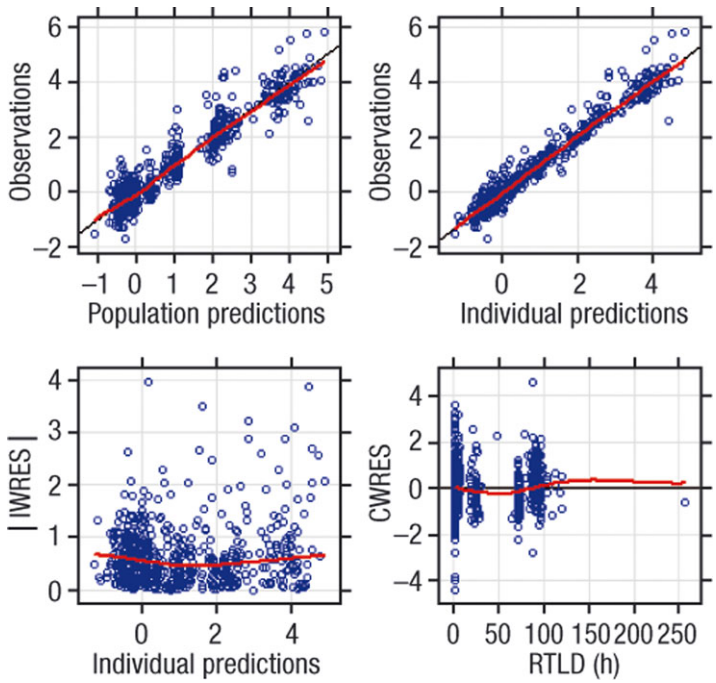

Figure 3. Basic goodness-of-fit plots for the final population PK model. CWRES, conditional weighted residual; IWRES, individual weighted residual; RTLD, relative time since last dose.

The final population PK model was evaluated by VPC. Figure 5 presents the VPC plots for all data (left panel) and by age group (middle and right panels). VPC plots stratified by study are shown in Supplementary Figure S3. Overall, the simulated concentrations from the final model appear to be reasonably consistent with the observed concentrations, with no systematic bias. Furthermore, neither age group (2–11 years vs 12–16 years) nor patient population (ALL vs AML) represented sources of meaningful PK heterogeneity that were not adequately accounted for by the final population PK model.

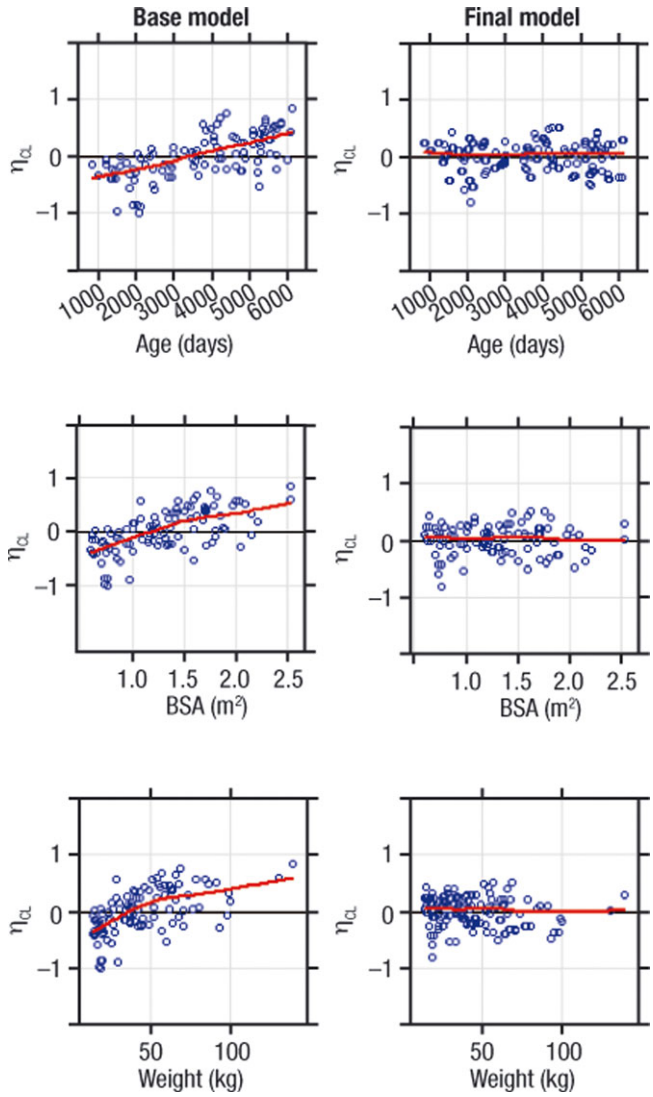

Figure 4. Comparison of covariate vs η plots for the base (left column) and final (right column) population PK model: η_{CL} vs age, BSA, and body weight. BSA, body surface area; η_{CL}, interindividual variability in clearance.

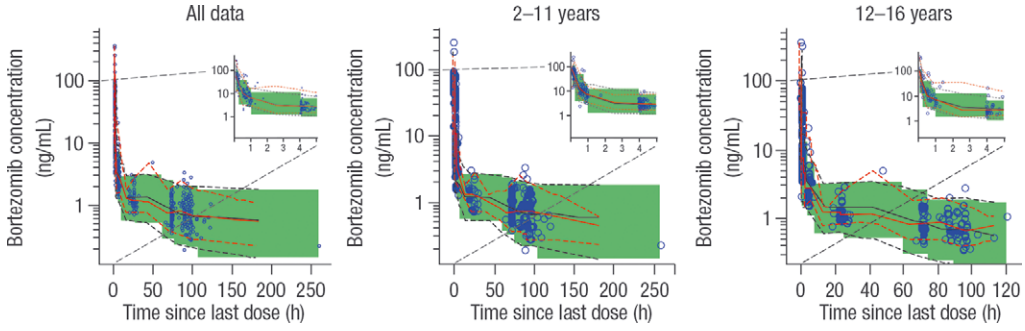

Figure 5. Visual predictive check plots of the final population pharmacokinetic model for all data (left panel) and stratified by age group (middle and right panels). Blue circles represent the observed concentrations. The red solid and dashed lines indicate the 2.5th, 50th, and 97.5th percentiles of the observations. The black solid and dashed lines represent the 50% and 95% prediction intervals for the simulated data. The shaded green area shows the 95%CI of the simulated data. The inset shows the first 5 hours postdose.

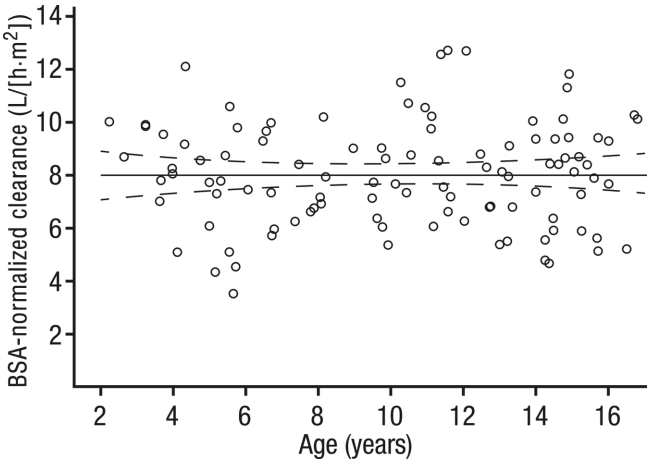

Figure 6. Scatterplot of individual BSA-normalized clearance vs age. The black line represents a linear regression line (slope of 0.0073, 95%CI [–0.087, 0.101]) with the 95% confidence band enclosed by the dashed lines. BSA, body surface area.

Bortezomib PK parameters were estimated for each patient in the analysis data set and summarized descriptively. Across all patients (N = 104), geometric mean (%CV) clearance was 7.79 (25%) L/(h·m^2), the volume of distribution at steady-state was 834 (39%) L/m^2, and half-lives for the α, β, and γ (terminal/elimination) disposition phases of the 3-compartment model were 6.15 (32%) minutes, 1.58 (18%) hours, and 100 (44%) hours, respectively. Of note, BSA-normalized clearance of bortezomib was also similar between the 2 pediatric age groups. For patients 2 to 11 years old (N = 62), BSA-normalized clearance ranged from 3.52 to 12.7 L/(h·m^2), with a mean (%CV) of 8.11 (25%) L/(h·m^2). The mean (%CV) BSA-normalized clearance was 7.94 (25%) L/(h·m^2) and ranged from 4.66 to 12.7 L/(h·m^2) for patients aged 12 to 16 years (N = 42). In addition, no discernible relationship was identified between BSA-normalized clearance and age over the 2 to 16 years age range (Figure 6).

Discussion

The primary objective of this pediatric population PK analysis was to characterize the PK of bortezomib following twice-weekly repeat dosing in pediatric patients with relapsed ALL or de novo AML aged 2 to 16 years by nonlinear mixed-effects population modeling using data from 2 Children's Oncology Group clinical trials (studies AALL07P1 and AAML1031). Data were also summarized to permit comparisons of bortezomib PK between the 2 to 11 and 12 to 16 years age groups and the adequacy of model performance across both of these age groups, as these age ranges correspond to accepted definitions for children and adolescents, respectively.[18]

After twice-weekly, repeat-dose, IV bolus administration in patients aged 2 to 16 years, bortezomib concentrations declined in a multiexponential manner. This finding of multiexponential disposition is consistent with previous observations following first-dose bortezomib administration in 5 pediatric patients with refractory/recurrent leukemia.[10]

During model development, 1-, 2-, 3-, and 4-compartment linear PK models were evaluated. Although the 4-compartment model had the lowest OFV, the associated condition number was 1581, suggesting that the model was overparameterized. Therefore, the 3-compartment model, which had the next lowest OFV, was selected as the base structural model, which was also supported by goodness-of-fit diagnostic plots. Covariate analysis identified BSA as the only significant covariate (on CL and Q3) in the model. Separate residual variability parameters were estimated for studies AALL07P1 and AAML1031 in order to account for the different sparse PK sampling schemes between studies. Importantly, all of the PK parameters were precisely estimated by the final population PK model. On the basis of bootstrap analysis, the 95% confidence intervals for all clearance and volume parameters were within 60% to 140% of their respective point estimates, thereby fulfilling previously recommended precision criteria for pediatric PK studies.[19]

Bortezomib PK was similar across the ALL and AML patient populations based on patient population/disease type not being identified as a significant covariate, as well as by visual inspection of VPC plots stratified by disease type (ALL vs AML). Of note, the ALL study characterized bortezomib PK in the presence of coadministered vincristine, prednisone, asparaginase, doxorubicin, cyclophosphamide, and etoposide, whereas the AML study characterized bortezomib PK in the presence of coadministered cytarabine, daunorubicin, etoposide, and mitoxantrone.

The pooling of data across these studies was supported by the lack of anticipated drug-drug interactions between bortezomib (as the potential victim drug) and these coadministered chemotherapeutic agents.

Bortezomib undergoes oxidative biotransformation in humans to pharmacologically inactive deboronated metabolites.[20] The hepatic microsomal metabolism of bortezomib is mediated via cytochrome P450 enzymes, with in vitro studies supporting the primary involvement of CYPs 3A4, 2C19, and 1A2, in decreasing order of relative contributions to bortezomib total hepatic microsomal metabolism.[21] In a clinical drug-drug interaction study, the strong CYP3A inhibitor ketoconazole produced a 35% increase in bortezomib area under the concentration-time curve, supporting a role for CYP3A in the clearance of bortezomib in humans.[14] Consistent with the predicted rank order of contributions of individual CYP enzymes to bortezomib metabolism from in vitro studies, CYP2C19-mediated metabolism does not appear to contribute meaningfully to the clearance of bortezomib in humans because coadministration with the potent CYP2C19 inhibitor omeprazole did not alter bortezomib PK.[22] Additionally, varying grades of renal impairment did not alter bortezomib clearance, indicating that renal clearance is not a meaningful contributor to bortezomib clearance in humans.[23] Finally, bortezomib has high apparent permeability and is not a substrate for efflux pumps based on in vitro transport studies (Takeda, data on file). Collectively, these in vitro and clinical PK results suggest that bortezomib clearance is mediated primarily via hepatic metabolism, with CYP3A as an identified partial contributor to overall human clearance, the inhibition of which results in a modest 35% increase in bortezomib exposure.

The chemotherapeutic agents administered as part of the platform regimens in the ALL and AML studies during bortezomib administration/PK characterization are not expected to influence bortezomib PK because these agents are not known to be clinically significant inhibitors or inducers of CYP3A. This enabled pooling of the data from across the 2 pediatric studies for population PK analysis. Consistent with expectations, no readily apparent differences were discernible between the PK of bortezomib in the ALL and AML patient populations, in whom administration was in combination with different chemotherapy regimens, thereby enabling broader conclusions to be drawn regarding the impact of patient-specific characteristics (eg, age, body size) on bortezomib PK without the confounding effects of disease type or coadministered agents.

Bortezomib PK in adult patients with MM following twice-weekly repeat-dose IV administration has been previously reported.[8] Comparison of the adult PK data with the pediatric data from this population PK analysis indicates that the disposition of bortezomib after twice-weekly repeat-dose IV bolus administration is similar between pediatric patients with leukemia and adult patients with MM. In both the pediatric and adult patient populations, plasma bortezomib concentrations declined in a multiphasic manner, with similar mean terminal elimination half-lives of 100 hours for pediatric patients and a range of 40 to 193 hours for adult patients.[8]

Similar to previous observations in adult patients, the volume of distribution for bortezomib in pediatric patients was large.[8] In a recent translational, physiologically-based pharmacokinetic modeling analysis based on tissue distribution studies in mice, whole blood and tissue concentrations of bortezomib were 1 to 2 orders of magnitude greater than concentrations in plasma after IV administration.[24] Furthermore, a rank-order correlation was observed between the model-estimated tissue densities of the target (proteasome) and the respective tissue exposures (area under the concentration-time curve). Therefore, the large volume of distribution observed in the current analysis of bortezomib pediatric PK data collected after repeat-dose administration is likely to be explained by the extensive binding of bortezomib to proteasomes in red blood cells and peripheral tissues.

This population PK analysis characterized the pharmacokinetics of bortezomib after repeat-dose administration. It has been previously demonstrated in adult patients that the plasma clearance of bortezomib is reduced, and the terminal half-life is increased, after repeat-dose administration as compared with the first dose of the first treatment cycle.[8] Accordingly, a limitation of the developed pediatric population PK model is that the model parameters estimated here cannot be directly used to describe systemic exposures following the first bortezomib dose. Furthermore, because patients less than 2 years of age were not included in the analysis, extrapolation of the results of this analysis to younger patients should be done with caution. Nevertheless, this analysis provides valuable prior information to derive initial estimates of the pharmacokinetics of bortezomib in patients less than 2 years of age as opposed to simulations based solely on adult pharmacokinetic data.

As bortezomib is administered using BSA-based dosing, BSA-normalized clearance is the principal PK parameter of interest because it will dictate the total systemic exposure (ie, area under the concentration-time curve) of bortezomib in individual patients. In adult patients, mean (%CV) BSA-normalized clearance values of 12.9 (70%) and 14.9 (63%) L/(h·m^2) were reported after 1.0 mg/m^2 and 1.3 mg/m^2 doses, respectively.[8] The corresponding clearance range for each dose level was 2.75 to 33.4 L/(h·m^2) and 5.06 to 38.4 L/(h·m^2), respectively. For pediatric patients

in the present population PK analysis, the mean BSA-normalized clearance was 8.11 L/(h·m^2) (range 3.52–12.7 L/[h·m^2]) and 7.94 L/(h·m^2) (range 4.66–12.7 L/[h·m^2]) for the 2 to 11 years and 12 to 16 years age groups, respectively. Accordingly, mean values of BSA-normalized clearance of bortezomib in both the 2 to 11 years and 12 to 16 years pediatric age groups were within the range of previously reported values for adult patients with MM, thereby suggesting no readily apparent differences in BSA-normalized clearance between pediatric and adult patients. In turn, this indicates that comparable systemic exposures of bortezomib should be achieved in pediatric patients with leukemia and adult patients with MM after IV administration of 1.3 mg/m^2. Because the 1.3 mg/m^2 dose of bortezomib has been established to be clinically effective in the treatment of MM and mantle cell lymphoma in adults,[5] when taken together with the above discussed results of this pediatric population PK analysis, it follows that the 1.3 mg/m^2 dose in the pediatric population (ages 2–16 years) should provide pharmacologically relevant exposures to enable a robust assessment of the efficacy and safety of bortezomib in pediatric malignancies, based on clinical pharmacology principles for scientifically guided pediatric drug development.[25]

Conclusion

The PK of bortezomib after twice-weekly repeat-dose IV administration in 104 pediatric patients (aged 2–16 years) with ALL or AML was adequately described by a 3-compartment model. All of the PK parameters were precisely estimated by the final model, with 95% confidence intervals for all clearance and volume parameters within 60% to 140% of their respective point estimates based on bootstrap analysis. BSA was the only identified covariate on clearance with no discernible relationship between BSA-normalized clearance and age, supporting BSA-based dosing for clinical development in this pediatric age range without additional considerations of patient age or sex. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adult patients with MM, thereby indicating that the 1.3 mg/m^2 IV dose achieves pharmacologically relevant systemic exposures of bortezomib in pediatric patients with leukemia to enable a robust assessment of the efficacy and safety of bortezomib in pediatric malignancies.

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Author Contributions

Study design was by M.J.H., T.M.H., X.L., and K.V. Patient enrollment was by T.M.H. and R.A. Data analysis was done by M.J.H., D.R.M., T.J.T., N.G., D.L.E., X.L., A.M., and K.V. Data interpretation was done by M.J.H., D.R.M., T.J.T., N.G., K.S., R.N., D.L.E., R.A., T.A.A., A.M., and K.V. All authors wrote or contributed to the writing of this manuscript. All authors approved the final manuscript version for submission.

Declaration of Conflicting Interests

M.J.H., N.G., K.S., R.N., K.V. are employees of Millennium Pharmaceuticals Inc, Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. D.L.E. is an employee of Millennium Pharmaceuticals Inc, Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and is a stock owner in Johnson & Johnson and Takeda Pharmaceutical Company Limited. A.M. is a previous employee of Takeda Pharmaceutical Company Limited. D.R.M. and T.J.T. are paid consultants (Projections Research Inc.). T.M.H. received research funding from Millennium Pharmaceuticals, Inc., Cambridge, MA. R.A., T.A.A., and X.L. have no conflicting interests to declare.

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