Population Pharmacokinetics of Bendamustine and Metabolites in Patients With Indolent Non-Hodgkin Lymphoma

J. S. Owen,[1] M. Melhem,[1] D. D'Andrea,[2] M. Darwish[2]

1. Cognigen Corporation, Buffalo, NY; 2. Cephalon, Inc., Frazer, PA

Introduction

- Bendamustine is a bifunctional alkylating agent in development as monotherapy and in combination with other agents in the treatment of indolent non-Hodgkin lymphoma (NHL):
  - Synthesized to combine the activities of a purine antimetabolite (benzimidazole) with the alkylating properties of the bifunctional mechlorethamine nitrogen mustard[1,2]
  - Converted in vivo to active metabolites: γ–hydroxy bendamustine (M3) and N-desmethyl bendamustine (M4)
- The precise mechanism of action of bendamustine in humans has not been fully characterized, although it differs from other alkylating agents.

Methods

Objectives

- Develop separate population pharmacokinetic models for bendamustine, M3, and M4 to describe the pharmacokinetic disposition of each analyte in patients with NHL
- Perform covariate analysis of selected patient factors and laboratory values to explore sources of interpatient variability in bendamustine pharmacokinetic parameters and to assess the pharmacokinetic disposition of bendamustine in special population groups
- Evaluate the dose proportionality of bendamustine pharmacokinetics within the administered dose range

Study Design

- Data were obtained from a phase III study in patients with relapsed indolent B-cell NHL refractory to rituximab treatment.
- Treatment:
  - Bendamustine 120 mg/m^2 I.V. over 60 minutes on days 1 and 2 of 6 consecutive 3-week treatment cycles
  - Dose reductions to 90 or 60 mg/m^2 were allowed in subsequent cycles for observed drug-related adverse events
- Pharmacokinetic sampling groups:
  - General Clinical Research Center (GCRC) group (at selected centers)
  - Groups A, B, C, and D at all centers
- Blood samples were collected in the GCRC Group before start of the infusion (predose), at the midpoint of the infusion, at the end of the infusion, and at 15, 30, and 45 minutes, and 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the end of the infusion. In addition, pharmacokinetic samples were collected on day 1 of cycle 2 at the following times: predose, between 0.25 and 0.5 hour after the start of the infusion, and between 1 and 3 hours after the start of the infusion. In the non-GCRC group, sparse data were collected from the non-GCRC patients (up to 4 samples per patient).
- Separate population pharmacokinetic models were developed for bendamustine, M3, and M4.
- Patient covariates explored were sex, age, race, weight, body surface area (BSA), alanine aminotransferase level, aspartate aminotransferase level, total bilirubin level, creatinine clearance, and serum albumin level.
- Development of base models for bendamustine, M3, and M4 were performed using an index data set:
  - Models were evaluated using a smaller test data set.
  - Parameters in each of the 3 models were reestimated using a total data set.
- Individual patient exposures were estimated based on individual Bayesian model parameter estimates; these parameter values were used to compute appropriate measures of bendamustine drug exposure for each patient.
- A dose proportionality assessment was performed using exposure values based on individual Bayesian parameter estimates using regression of the log-transformed data.[3]

Data Analysis

- Population pharmacokinetic analysis was completed using NONMEM® software, Version 6, Level 1.0.[4] Model parameters were estimated using the first order conditional estimation method with interaction.

Results

Bendamustine Data Description

- There were 347 bendamustine concentrations from 78 patients.

Table 1. Patient Characteristics

	Patients (%)	Mean ± SD
Male	64%	–
Caucasian	88%	–
Age	–	59.1 ± 11.0 years
Weight	–	86.432 ± 20.463 kg
Body Surface Area	–	2.001 ± 0.274 m^2
Creatinine Clearance	–	93.75 ± 33.42 mL/minute
Alanine Aminotransferase Level	–	27.205 ± 15.649 U/L
Aspartate Aminotransferase Level	–	27.000 ± 17.858 U/L
Total Bilirubin Level	–	9.970 ± 5.079 mol/L

Bendamustine Model

- The final-population pharmacokinetic model for bendamustine was a 3-compartment open model with 0-order input, first-order elimination, and interindividual variability (IIV) terms estimated with exponential error structure on clearance, V_c, V_{p1}, and V_{p2}. Residual variability (RV) was expressed with a proportional error model:
  - The final pharmacokinetic model was applied to the test data set to assess the predictive capabilities of the model. Pharmacokinetic parameters were reestimated using data from the total data set.
  - The model adequately described the central tendencies in the bendamustine concentration time data.
  - Estimates of α, β, and γ half-lives for bendamustine were 0.29 hour, 0.7 hour, and 110 hours, respectively. Because the area under the curve (AUC) for the terminal phase accounted for < 1% of the total AUC, the half-life of the β phase was considered to be reflective of bendamustine elimination half-life.

Bendamustine Exposures

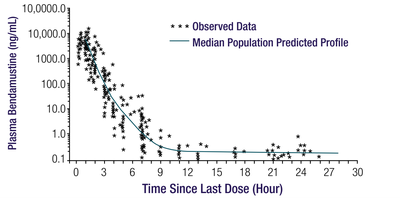
- Median bendamustine AUC was 13,635 ng·hr/mL.
- Sex and age had no significant effect on exposure measures of bendamustine.
- A trend of increasing exposure with increasing BSA category was observed.

Table 2. Parameter Estimates and Standard Errors From the Bendamustine Final Model: Total Data Set

	Final Parameter Estimate		Magnitude of IIV (% CV)	
	Population Mean	SEM	Final Estimate	SEM
Central Clearance	31.7 L/hour	7%	33.32	22%
Central Volume of Distribution	14.1 L	6%	15.56	69%
Peripheral Volume of Distribution 1	0.920 L	8%	22.29	41%
Peripheral Volume of Distribution 2	25.2 L	34%	66.78	52%
Intercompartmental Clearance 1	0.989 L/hour	9%	NE	NA
Intercompartmental Clearance 2	0.159 L/hour	25%	NE	NA
Residual Variability (% CV)	36%	18%	NA	NA

Minimum value of the objective function = 3009.938
Abbreviations: CV = coefficient of variation; IIV = interindividual variability; NA = not applicable; NE = not estimated;

Figure 1. Measured Plasma Bendamustine Concentrations Compared to Time Since Last Dose Overlaid With the Typical Value Median Population Predicted Profile From the Bendamustine Final Model: Total Data Set



- Within the narrow range of 1.61-2.40 m^2, 80% of the BSA values retained a flat relationship with AUC.
- Mild hepatic dysfunction was not a significant predictor of pharmacokinetic variability.
- Mild or moderate renal dysfunction were not significant predictors of pharmacokinetic variability.

Bendamustine Dose Proportionality

- Prespecified criteria for dose proportionality of bendamustine were not met; the relationship of bendamustine dose across the full dose range with AUC and C_{max} was less than proportional.
- Although single doses ranging from 145 mg to 296 mg (2-fold) were administered, 80% of the doses fell within the single dose range of 176 mg to 262 mg (1.5-fold), as would be expected based on the narrow range of BSA values. This narrow range of doses resulted in inadequate power to conclusively determine dose proportionality.

M3 Results

- The pharmacokinetic profile of 302 M3 plasma concentrations from 77 patients declined from peak in a biphasic manner.
- The final-population pharmacokinetic model for M3 was a 2-compartment model with 0-order input, first-order elimination, and a formation lag time. Residual variability was expressed with a proportional error structure.
  - Interindividual variability terms were estimated on apparent clearance (CL/F) (347 L/hour), apparent central volume of distribution (Vc/F) (209 L), apparent peripheral volume of distribution (Vp/F) (26.1 L), apparent intercompartmental clearance (Q/F) (6.60 L/hour), duration of 0-order M3 formation (1.07 hours), and lag time of metabolite formation (0.198 hour).
  - The magnitude of IIV on M3 CL/F and Vc/F were small (< 20% CV), and the magnitude of IIV on Vp/F was moderately larger (39% CV).
  - Residual variability for M3 (37% CV) and bendamustine were similar.
- The estimates of α and β half-lives of M3 in the current analysis were 0.408 hour and 2.8 hours, respectively.
- Exposure to M3 was approximately 10% of the exposure to bendamustine.

Table 3. Summary Statistics of Exposure Measurements From the Bendamustine Final Model Stratified by Covariate: Total Data Set

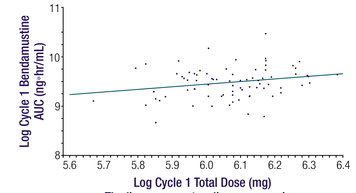
	Number of Patients	Bendamustine	
		Mean Area Under the Curve ± SD	Mean C_{max}, ± SD
Gender			
Male	50	13,496 ± 3915 ng × hour/mL	5963 ± 1348 ng/mL
Female	28	14,235 ± 5567 ng × hour/mL	5798 ± 1478 ng/mL
Age			
16-64 years	54	13,650 ± 4910 ng × hour/mL	5928 ± 1474 ng/mL
65-74 years	15	14,131 ± 4446 ng × hour/mL	5905 ± 1485 ng/mL
≥ 75 years	9	13,815 ± 2255 ng × hour/mL	5752 ± 543 ng/mL
Body Surface Area			
Minimum-25th percentile	19	12,618 ± 4064 ng × hour/mL	5167 ± 1181 ng/mL
25th-50th percentile	22	13,258 ± 3979 ng × hour/mL	5616 ± 1067 ng/mL
50th-75th percentile	23	14,806 ± 6013 ng × hour/mL	6299 ± 1679 ng/mL
75th-maximum percentile	14	14,387 ± 2930 ng × hour/mL	6706 ± 993 ng/mL
Hepatic Function[5]			
Normal function*	52	13,346 ± 3773 ng × hour/mL	5792 ± 1318 ng/mL
Mild dysfunction†	26	14,592 ± 5813 ng × hour/mL	6127 ± 1524 ng/mL
Renal Function[6]			
Normal function‡	47	14,132 ± 4584 ng × hour/mL	6180 ± 1357 ng/mL
Mild impairment§	23	12,679 ± 3976 ng × hour/mL	5435 ± 1320 ng/mL
Moderate impairment‖	8	14,697 ± 5894 ng × hour/mL	5626 ± 1522 ng/mL
Total Data Set	78	13,761 ± 4555 ng × hour/mL	5903 ± 1389 ng/mL

* Normal total bilirubin, aspartate aminotransferase, and alkaline phosphatase ranges
† Total bilirubin ≤ upper limit of normal, aspartate aminotransferase level elevated to a maximum of 2.5 times the upper limit of normal, and/or alkaline phosphatase elevated to a maximum of 5 times the upper limit of normal
‡ Creatinine clearance of > 80 mL/minute
§ Creatinine clearance of 49-80 mL/minute
‖ Creatinine clearance of 31-50 mL/minute

M4 Results

- The pharmacokinetic profile of 254 M4 plasma concentrations from 73 patients declined from the peak in a monoexponential manner.
- The final-population pharmacokinetic model for M4 was a 1-compartment model with 0-order input and first-order elimination. A proportional error structure expressed RV.
  - Interindividual variability terms were estimated on CL/F (3890 L/hour), apparent volume of distribution (V/F) (3490 L), and duration of 0-order M4 formation (1.27 hours). Covariance between IIV on CL/F and IIV on V/F was 0.527.
  - The magnitudes of IIV on M4 CL/F and V/F were moderately large (< 90% CV).
  - Residual variability for M4 (35% CV) and bendamustine were similar.
- The half-life estimate for M4 was 0.622 hour, which was similar to that of the β phase of bendamustine.
- Exposure to M4 was approximately 1% of the exposure to bendamustine.

Figure 2. Logarithm of Plasma Bendamustine Area Under the Curve Compared to Logarithm of Cycle 1 Total Dose Overlaid With the Linear Regression: Total Data Set



Abbreviations: AUC = area under the curve

Figure 3. Measured M3 Concentrations Compared to Time Since Last Dose Overlaid With the Typical Value Median Population Predicted Profile From the M3 Structural Model: Total Data Set

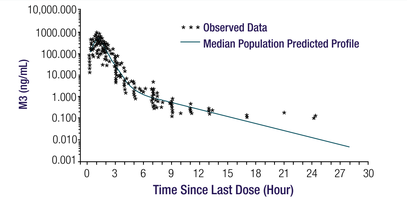
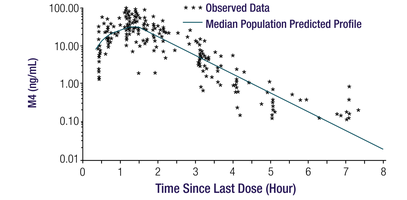


Figure 4. Measured M4 Concentrations Compared to Time Since Last Dose Overlaid With the Typical Value Median Population Predicted Profile From the M4 Structural Model: Total Data Set



Conclusions

- A 3-compartment model with 0-order input and first-order elimination adequately described the data for bendamustine in patients with NHL. Fixed-effect parameters were estimated for clearance (31.7 L/hour), V_c (14.1 L), V_{p1} (0.920 L), V_{p2} (25.2 L), intercompartmental clearance (Q) 1 (Q_1) (0.989 L/hour), and Q_2 (0.159 L/hour). The magnitude of IIV on bendamustine clearance, V_c, and V_{p1} were < 35% CV; IIV on V_{p2} was larger (67% CV). The magnitude of RV was 36% CV. Half-life estimates of α, β, and γ for bendamustine were 0.29 hour, 0.7 hour, and 110 hours, respectively.
- A 2-compartment model with 0-order input, first-order elimination, and a metabolite formation lag time adequately described the data for M3 in patients with NHL. Interindividual variability was estimated on CL/F (347 L/hour), V_c/F (209 L), V_p/F (26.1 L), Q/F (6.60 L/hour), duration of 0-order M3 formation (1.07 hours), and lag time of metabolite formation (0.198 hour). The magnitude of IIV on M3 CL/F and V_c/F were small (< 20% CV); IIV on V_p was moderately larger (39% CV). Residual variability (37% CV) was similar to that of bendamustine.
- A 1-compartment model with 0-order input and first-order elimination described the data for M4 in patients with NHL. Fixed effect parameters were estimated on CL/F (3890 L/hour), V/F (3490 L), and duration of 0-order M4 formation (1.27 hours). Covariance between IIV on CL/F and IIV on V/F was 0.527. The magnitude of IIV on M4 CL/F and V/F were moderately large (< 90% CV). Residual variability (35% CV) was similar to that of bendamustine.
- Based on the corresponding pharmacokinetic models, the IIV of AUC was 33% CV, 17% CV, and 44% CV, for bendamustine, M3, and M4, respectively. Interindividual variability of C_{max} was 24% CV, 17% CV, and 49% CV for bendamustine, M3, and M4, respectively.
- There were no trends for effect of sex, age group, or race on exposure measures of bendamustine.
- With BSA-based dosing, a trend for increasing exposure with increasing BSA category was observed. However, the study data did not allow for a conclusive assessment of the effect of BSA on exposure measures of bendamustine.
- No notable differences were observed:
  - Between patients with normal and those with mild hepatic dysfunction
  - Among patients with normal, mild, and moderate renal dysfunction
- The study data did not allow for a conclusive assessment of dose proportionality.

References

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