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Blood distribution of bortezomib and its kinetics in multiple myeloma patients

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ABSTRACT

Objectives: Pharmacokinetic disposition of bortezomib in the blood has not been fully characterized in humans. This study aimed to evaluate the blood distribution of bortezomib and its kinetics in multiple myeloma patients.

Design and method: Eighteen multiple myeloma patients receiving bortezomib–dexamethasone combination therapy were enrolled. Blood specimens were drawn just before bortezomib administration on days 1 and 8 in the second and third cycles and after discontinuation. The relationships between bortezomib concentration and blood components were evaluated.

Results: Bortezomib concentration in the blood on day 1 was higher than that on day 8 in the second cycle. No difference was observed in bortezomib blood concentrations between day 8 in the second and third cycles. The bortezomib concentration in the blood and blood cells was 3- and 7-fold higher than that in plasma. Bortezomib concentration in the blood was correlated with the red blood cell count. The half-life of bortezomib in the blood was 23 days.

Conclusion: Bortezomib was taken up into red blood cells to only a limited extent and eliminated in parallel to the red blood cells' lifespan. The turnover of red blood cells can affect the pharmacokinetic disposition of bortezomib in multiple myeloma patients.

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Introduction

The proteasome inhibitor bortezomib is used for the treatment of multiple myeloma. Bortezomib selectively blocks the chymotryptic activity of 26S proteasome and induces apoptosis of the tumor cells [1,2]. In patients with relapsed multiple myeloma following 1–3 prior therapies (APEX trial), bortezomib showed superior efficacy against high-dose dexamethasone in terms of response rate, time to progression and overall survival [3]. For some patients, bortezomib has poor therapeutic effects or causes serious adverse effects including critical pulmonary damage, peripheral neuropathy and thrombocytopenia [4]. The efficacy and adverse effects associated with bortezomib are quite diverse in multiple myeloma patients.

The plasma pharmacokinetic profile of bortezomib is characterized by a two-compartment model with a rapid initial distribution phase followed by a longer elimination phase and a large volume of distribution [5]. Bortezomib is distributed in the adrenal gland, liver and prostate gland in monkeys. Intravenous bortezomib is principally metabolized by liver and excreted into the urine and feces [5]. *In vitro* studies showed that the primary route of bortezomib metabolism was oxidative deboronation by cytochrome P450 (CYP) 2C19, CYP1A2 and CYP3A4 with contribution from CYP2D6 and several other CYP450 enzymes in the liver [6]. In a pharmacokinetic study of intravenous bortezomib, the terminal half-life of bortezomib in plasma was approximately 15 h [5].

Bortezomib is alternatively and reversibly bound with the chymotrypsin-like part of 26S proteasome. The 26S proteasome consists of a 20S proteasome with a 19S proteasome attached at one end only, or a 20S proteasome with one 19S proteasome attached at each end [7]. Bortezomib reversibly binds to the β5-subunit and to a lesser extent to the β1-subunit of the 20S proteasome. Proteasomes isolated from mature red blood cells displayed 20S activity *in vitro* [8].

Abbreviations: CYP, cytochrome P450; LC-MS/MS, liquid chromatography-tandem mass spectrometry; IQR, interquartile range; RSD, relative standard deviation.

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After an intravenous administration of ^{14}C-bortezomib, its concentration in whole blood was twice as high as that in plasma in rats and monkeys [9]. However, the blood distribution of bortezomib and its kinetics in humans remain to be clarified.

The pharmacokinetic parameters of bortezomib reflecting its efficacy and adverse effects are still not clear. Reliable and stable pharmacokinetic parameters of bortezomib are difficult to obtain in clinical settings because bortezomib disappears rapidly from the plasma. In addition, the dose adjustment of high blood distribution drugs such as calcineurin inhibitors is commonly based on the whole blood concentration. The plasma concentration of bortezomib may be overestimated due to hemolysis and to fluctuations in the temperature of the blood [10,11]. Pharmacokinetic data for bortezomib, more specifically concerning its blood disposition and elimination, are needed in order to ensure its safe and effective use. However, the blood distribution of bortezomib has not yet been fully evaluated in multiple myeloma patients.

Assessment of the blood disposition of bortezomib can contribute to the dose optimization for patients with multiple myeloma. The aim of this study was to evaluate the blood distribution of bortezomib and its kinetics in multiple myeloma patients.

Materials and methods

Ethics

The study was performed in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Hamamatsu University Hospital. The patients received information about the scientific aim of the study, and each patient provided written informed consent for participation in the study.

Subjects

Eighteen multiple myeloma patients receiving intravenous bortezomib (Velcade® injection, Janssen Pharmaceutical K.K., Tokyo, Japan) at Hamamatsu University Hospital between January 2010 and November 2012 were enrolled. All patients had previously received the combination regimen of melphalan or cyclophosphamide with prednisolone. Bortezomib (1.3 mg/m^2) and dexamethasone sodium phosphate (20 mg/m^2, Decadron® phosphate injection, MSD K.K., Tokyo) were administered intravenously on days 1, 4, 8 and 11 of each cycle (withdrawal on days 12–21). All patients with multiple myeloma were treated with the above regimen for at least 3 cycles. Blood specimens from a forearm were drawn into tubes containing ethylenediaminetetraacetic acid disodium salt (EDTA-2Na) just before the bortezomib administration on days 1 and 8 in the second and third cycles and after discontinuation. Clinical laboratory values including red blood cell count, hemoglobin, white blood cell count, platelets, hematocrit, and serum albumin were obtained from routine laboratory tests.

Materials and solutions

Bortezomib was obtained from Toronto Research Chemicals Inc. (North York, Ontario, Canada). Diazepam as an internal standard, zinc sulfate heptahydrate, MS-grade acetonitrile, HPLC-grade methanol and ammonium acetate were obtained from Wako Pure Chemicals (Osaka, Japan). All other chemicals were reagent grade. Stock solutions of bortezomib (100 μg/L) and diazepam (100 μg/L) were prepared with methanol. Zinc sulfate solution (0.4 M) was prepared with distilled water. Standard solutions of bortezomib were obtained by the dilution of stock solution with methanol. Calibration standards were prepared with drug-free pooled whole blood (Abbott Japan, Tokyo). The final bortezomib concentrations were 5, 10, 20, 40, 60, 80 and 100 μg/L. Quality control samples were spiked to bortezomib concentrations of 10, 40 and 80 μg/L in drug-free whole blood.

Sample preparation

Blood specimens collected into tubes containing EDTA-2Na were kept at −80 °C before the sample preparation. Whole blood (100 μL), 950 μL of methanol, 100 μL of diazepam solution, and 50 μL of zinc sulfate solution were mixed for 30 min and then the mixture was ultrasonicated for 30 min. After cooling at −35 °C for 30 min, the samples were centrifuged at 17,900 ×g at 4 °C for 30 min, and then 900 μL of the supernatant was evaporated to dryness. The residue was reconstituted in 100 μL of methanol and the supernatant was injected onto the analytic column.

Chromatographic and mass spectrometer conditions

The Agilent 1100 HPLC System (Agilent Technologies, Palo Alto, CA, USA) consisted of a G1312A binary pump, G1367A autosampler, G1379A degasser, and G1316A thermostatted column compartment. Separation was performed using a 3-μm particle size octadecylsilyl column (TSKgel ODS-100 V, 150 × 2.0 mm I.D., Tosoh, Tokyo). The mobile phase consisted of 50% acetonitrile containing 5 mM ammonium acetate at pH 3.5. The flow rate was 0.3 mL/min and the column oven temperature was set at 60 °C. The injection volume was 10 μL. The analyses were performed using a Finnigan model TSQ®-7000 triple–quadrupole MS (Thermo Fisher Scientific, Waltham, MA, USA) with an electrospray ionization interface to the LC. Data were collected and analyzed using Xcaliber software (version 1.2, Thermo Fisher Scientific). The ion spray voltage was set at 4.5 kV with 68 psi of sheath gas, and the capillary temperature was 300 °C. Collision-induced dissociation was achieved using argon as the collision gas at 3 mTorr. The electrospray ionization source was operated in positive ion mode. Bortezomib and diazepam were monitored by the respective transitions of m/z 367.0 to 226.0 and 285.1 to 153.9 with collision energy of −20 eV, respectively.

Method validation

Calibration curves were obtained by plotting the measured peak area ratios of bortezomib to diazepam. Linearity was observed at concentration ranges of 5–100 μg/L for bortezomib in human whole blood. The accuracy and precision were calculated for three quality control samples. Accuracy was determined by evaluation of the analytical recovery of known amounts of standard whole blood specimens. The intra- and inter-assay precisions were expressed as relative standard deviation (RSD). The lower limit of quantification was defined as the concentration at which the RSD does not exceed 20%. Preparation recovery was assessed by three replicates of spiked human whole blood at 40 μg/L of bortezomib. The stability of bortezomib in whole blood at 40 μg/L was evaluated by comparing peak areas after 1, 2, 4, 8 and 24 h of storage at 4 °C and room temperature (25 °C) with initial peak area. Long-term stability in whole blood at −80 °C was determined after one month.

Deamination of plasma and blood cell concentrations

Plasma specimens were obtained by centrifugation of blood collected into EDTA-2Na tubes at 1670 ×g at 37 °C for 10 min and then stored at −80 °C until sample preparation. Plasma concentrations of bortezomib were determined by the above mentioned sample preparation and analytical procedure for whole blood. Bortezomib concentrations in blood cells were estimated with the following equation: (whole blood concentration − plasma concentration × (1 − % hematocrit/100))/(% hematocrit/100).

Statistical and pharmacokinetic analysis

All statistical analyses were performed using SPSS 15.0J (SPSS Japan Inc., Tokyo). All values are expressed as the median and interquartile

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