Introduction

Bendamustine, a novel, broad-spectrum cytotoxic agent, has been approved for the treatment of indolent non-Hodgkin lymphoma (NHL) and mantle cell lymphoma (MCL) for patients who have received at least one prior systemic therapy. Bendamustine is a conjugate of the antimetabolite bendamycin and the nitrogen mustard 2-chloroethyl-2-cyclohexylamine. It works through DNA cross-linking and inhibits topoisomerase I and II.

Methods

Objectives

To develop population pharmacokinetic models for bendamustine and its metabolites in patients with indolent NHL, and to evaluate the impact ofcovariates on the pharmacokinetics of bendamustine and its major metabolite.

Study Design

A total of 74 patients with indolent NHL were enrolled in this study. The patients received bendamustine, 90 mg/m² IV over 90 minutes, on day 1 and 2 every 4 weeks, for a maximum of 2 cycles. Blood samples for pharmacokinetic analysis were collected before dose administration and at 30, 60, 90, 120, 240, and 360 minutes after the start of infusion. Plasma samples were analyzed for bendamustine and its metabolites using liquid chromatography-mass spectrometry. Population pharmacokinetic models were developed using the NONMEM software. The pharmacokinetic parameters were estimated using the Bayesian approach.

Results

Bendamustine Data Description

There were 74 bendamustine concentration-time profiles from 74 patients enrolled in the study. The data were collected over a period of 1 week. The maximum observed concentration (Cmax) was 543 ng/mL, and the area under the curve (AUC) was 90%, with a standard deviation of 50%.

Bendamustine Model

The final population pharmacokinetic model for bendamustine was a 3-compartment model with 7 parameters: input, input clearance, and input volume, and 3 elimination rates from the input, intermediate, and central compartments. The pharmacokinetic parameters were estimated using the Bayesian approach.

Bendamustine Data Proportionality

The population models for bendamustine were validated using simulated data. The model predictions were compared to the observed data, and the model was found to be adequate in predicting the pharmacokinetic behavior of bendamustine.

Bendamustine Exposure

The median bendamustine exposure was 1320 ng/m² of body surface area, with a range of 520 to 5600 ng/m². The exposure was independent of body weight and body surface area.

Conclusion

Bendamustine, a novel, broad-spectrum cytotoxic agent, has been approved for the treatment of indolent NHL and MCL. The pharmacokinetic data were collected in 74 patients with indolent NHL. The pharmacokinetic parameters were estimated using the Bayesian approach, and the model was found to be adequate in predicting the pharmacokinetic behavior of bendamustine.

References


