2476 An Open-Label Phase I Pharmacokinetic Study of [^{14}c] Bendamustine in Patients with Relapsed or Refractory Malignancy

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Background: Bendamustine is a unique alkylating agent which combines a nitrogen mustard moiety of mechlorethamine with a benzimidazole. This study was conducted to characterize the distribution, metabolism, and elimination of [^{14}C] bendamustine and its metabolites (M3, M4, and dihydroxy bendamustine [HP2]) and to assess the roles of renal and hepatic pathways in the drug's metabolism and excretion. A secondary objective was to further characterize the safety profile of single-agent bendamustine.

Methods: This open-label, phase I study enrolled 6 patients, age ≥18 years, with confirmed relapsed or refractory malignancy. The study was divided into 2 assessment periods: period A, during which the mass balance and pharmacokinetics of [^{14}C] bendamustine were investigated, and period B, an extended-use period of up to 6 cycles with non-labeled bendamustine, during which safety continued to be assessed. Patients received intravenous (IV) bendamustine (120 mg/m^2), containing 80-95 µCi of [^{14}C] bendamustine, on day 1 of cycle 1 and non-labeled IV bendamustine (120 mg/m^2) on day 2 of cycle 1 (period A). Pharmacokinetic parameters of bendamustine and metabolites M3, M4, and HP2 were calculated through plasma and urine concentrations, which were determined through 24 hours following administration of bendamustine on day 1. Total radioactivity (TRA) levels were measured in plasma, urine, and feces collected prior to drug administration and at time points through 168 hours after patients received [^{14}C] bendamustine. Collection of excreta could continue (after the 7-day period) on an outpatient basis: if radiolabeled bendamustine ≥1% of dose was measurable in the 144- to 168-hour urine or feces collection, collection continued until the recovery in each 24-hour urine or feces collection was <1% of dose.

Results: Six patients (3 males; 3 females) with a median age of 66 (48-75) years were enrolled and completed the pharmacokinetic portion of the study. For bendamustine, the decline from peak plasma concentration was characterized by an initial rapid distribution phase, followed by a somewhat slower intermediate phase. The pharmacologically relevant half-life ($t_{½}$) was approximately 40 minutes. The plasma concentrations of M3, M4, and HP2 were very low relative to the bendamustine concentrations.

Of the TRA dose administered, approximately half of the dose was recovered in the urine and approximately a quarter of the dose was recovered in the feces. Less than 5% of TRA dose was recovered in the urine as unchanged bendamustine. Mean recovery of TRA in excreta was approximately 76% of the radiochemical dose. Total recovery was incomplete due to continued slow excretion of TRA at the end of the collection period. The sustained levels of radioactivity in the plasma as compared with plasma

concentrations of bendamustine suggest that, despite the rapid clearance of bendamustine, 1 or more longer-lived [^{14}C] bendamustine-derived materials remain in the plasma. These longer-lived materials likely include by-products of alkylation. As previously noted, bendamustine volume of distribution was small (V_{ss}~20 L). The steady-state volume of distribution for TRA was ~50 L. These results confirm previous data and provide evidence that neither bendamustine nor TRA are extensively distributed into the tissues. All 6 patients withdrew prior to completion of period B due to disease progression (n = 4), an adverse event (n = 1), or refusal to continue treatment (n=1). Bendamustine was well tolerated when administered at a dosage of 120 mg/m^{2}for 2 to 3 cycles. The most frequent treatment-related adverse events were fatigue (50%) and vomiting (50%). A grade 3/4 absolute lymphocyte count decrease occurred in all patients at some point during the study. There were no other grade 3/4 hematologic adverse events.

Conclusions: Bendamustine was extensively metabolized via multiple metabolic pathways, with subsequent excretion in both urine and feces. Bendamustine accumulation is not anticipated in cancer patients with renal or hepatic impairment due to the dose administration schedule and short intermediate half-life. Adverse events and hematologic changes were consistent with the known safety profile of bendamustine.

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Disclosures: Darwish: *Cephalon, Inc.:* Employment. **D'Andrea:** *Cephalon, Inc.:* Employment. **Bond:** *Cephalon, Inc.:*Employment. **Hellriegel:** *Cephalon, Inc.:* Employment.

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