1857 Bendamustine Combined with Bortezomib Has Efficacy in Patients with Relapsed or Refractory Multiple Myeloma: A Phase 1/2 Study

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Background

Multiple myeloma (MM), the second most common hematologic cancer in the United States, has a 5-year survival rate of 38%.

Bendamustine is a unique alkylating agent with multiple actions leading to cancer cell death in several tumor types. In patients with MM, bendamustine, alone and in combination with prednisone, has been shown to be efficacious, with durable responses.

Bortezomib is a proteasome inhibitor approved as monotherapy for MM. It has been found to sensitize highly chemoresistant MM cell lines to alkylating agents such as melphalan. Subsequent clinical trials have reported anti-MM activity and acceptable safety for bortezomib plus melphalan for relapsed or refractory MM and for bortezomib, ascorbic acid, and melphalan (BAM) for patients with newly diagnosed MM.

The present phase 1/2 study assessed the safety, tolerability, and efficacy of bortezomib plus bendamustine for patients with relapsed or refractory MM.

Methods

All patients were ≥18 years old and had biopsy-confirmed MM, measurable by a serum monoclonal immunoglobulin spike ≥1 gm/dL and/or a urine monoclonal spike ≥200 mg/24 hours. Also, all patients received ≥1 prior MM treatment, not including bendamustine, and showed signs or symptoms of progressive disease, either relapsed (progression following stabilization or response) or refractory (progression during or within 6 months after an antimyeloma regimen).

Patients were enrolled in successive groups of 3 to 5. The groups received open-label bendamustine administered as a 1-hour intravenous (IV) infusion of 50, 70, or 90 mg/m^2 on days 1 and 4 of each 28-day treatment cycle. Each infusion was preceded by bortezomib administered as a 3- to 5-second IV push of 1.0 mg/m^2. Bortezomib was also given on days 8 and 11. Enrollment at each dose level was permitted only if the first 3 patients at the previous level received 1 cycle without unacceptable dose-limiting toxicity (DLT). If not, an additional 3 patients would be treated at the previous level (for a maximum 6 at each level). The maximum tolerated dose was defined as the highest dose at which <33% of recipients had unacceptable DLT. Additional patients were then enrolled and were treated to maximum response plus 2 cycles, for a total of up to 8 cycles without progressive disease. Overall response rate (complete, very good partial, partial, and minimal response rates), duration of response, time to progression, and adverse events (AEs) were assessed by International Myeloma Working Group criteria.

Results

Because no DLT was observed in phase 1, the bendamustine dosage selected for phase 2 was 90 mg/m^2 (plus bortezomib at 1.0 mg/m^2). A total of 40 patients (median age, 67.0 years; range, 43-89) were enrolled and had received a median of 6 (range, 2-20) prior therapies, including bortezomib (75%) and alkylators (70%). Following enrollment, 5 patients received a mean (SD) of 3.0 (1.7) cycles of 50 mg/m^2 of bendamustine, 4 received 4.0 (2.9) cycles of 70 mg/m^2, and 31 received 4.7 (2.8) cycles of 90 mg/m^2.

Among the 39 patients with efficacy data, the overall response rate was 48.7% (n=19); 53.3% in the subgroup of patients receiving 90 mg/m^2 (n=16). Of the 19 responses, 1 was complete (in the 90 mg/m^2 group), 2 were very good partial (both in the 90 mg/m^2 group), 8 were partial, and 8 were minimal. Another 16 patients (41.0% of 39) had stable disease, and the remaining 4 (10.3%) individuals showed progressive disease.

Among all 40 patients, 28 (70.0%) had grade 3 or 4 AEs: 3 of 5 patients (60.0%) receiving 50 mg/m^2, 3 of 4 (75.0%) receiving 70 mg/m^2, and 22 of 31 (71.0%) receiving 90 mg/m^2. There were 3 deaths (unknown/old age, disease progression, and septic shock). Grade 3 or 4 AEs in ≥10% of patients were neutropenia (37.5%), thrombocytopenia (25.0%), anemia (12.5%), and leukopenia (10.0%).

Conclusions

In pretreated patients with relapsed or refractory MM, 28-day cycles of bendamustine 90 mg/m^2 on days 1 and 4 plus bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11 were well tolerated and showed promising efficacy.

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Disclosures: Berenson: *Millennium:* Consultancy, Honoraria, Research Funding; *Cephalon, Inc.:* Research Funding.**Off Label Use:** Bendamustine is FDA-approved for adults with chronic lymphocytic leukemia or indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.. **Boccia:** *Millennium:* Speakers Bureau. **Noga:** *Cephalon, Inc.:* Honoraria; *Janssen Pharmaceuticals:* Honoraria; *Celgene Corporation:* Honoraria; *Millennium:* Honoraria; *Takeda :* Honoraria. **Gravenor:***Cephalon, Inc.:* Research Funding. **Siegel:** *CVS/Caremark:* Consultancy; *Cephalon, Inc.:* Research Funding.**Kewalramani:** *Cephalon, Inc.:* Research

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