

Bendamustine Therapy in Patients With Relapsed or Refractory Waldenström's Macroglobulinemia

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Abstract

We report the treatment outcome for 30 relapsed/refractory Waldenström's macroglobulinemia (WM) patients following bendamustine-containing therapy. Treatment consisted of bendamustine (90 mg/m² I.V. on days 1, 2) and rituximab (375 mg/m² I.V. on either day 1 or 2) for 24 patients. Six rituximab-intolerant patients received bendamustine alone (n = 4) or with ofatumumab (1000 mg I.V. on day 1; n = 2). Each cycle was 4 weeks, and median number of treatment cycles was 5. At best response, median serum IgM declined from 3980 to 698 mg/dL ($P < .0001$), and hematocrit rose from 31.9% to 36.6% ($P = .0002$). Overall response rate was 83.3%, with 5 VGPR and 20 PR. The median estimated progression-free survival for all patients was 13.2 months. Overall therapy was well tolerated. Prolonged myelosuppression was more common in patients who received prior nucleoside analogues. Bendamustine is active and produces durable responses in previously treated WM, both as monotherapy and with CD20-directed monoclonal antibodies.

Introduction

Bendamustine is a recently approved agent for the treatment of relapsed/refractory indolent non-Hodgkin lymphoma (NHL) with structural similarities to both alkylating agents and purine analogues.^{1,2} Bendamustine given as a single agent every 3 weeks at the dose of 120 mg/m² I.V. on days 1, 2, achieved an overall response rate of 75%, and a median progression-free survival (PFS) of 8-9 months in two studies among rituximab-refractory indolent NHL patients.^{3,4} When given as a salvage treatment to rituximab-naïve NHL patients, an overall response rate of 90% was achieved in two

studies among indolent NHL patients who received bendamustine (90 mg/m² on days 1, 2) and rituximab (375 mg/m² on day 1) every 4 weeks for 4-6 cycles. The median PFS in these studies was about 24 months.^{5,6} The combination of bendamustine plus rituximab (Benda-R) was also compared to CHOP-R in patients with newly diagnosed indolent NHL by Rummel et al.⁷ A total of 546 patients were enrolled in this study, which included 40 patients with WM.⁸ Patients in this study were randomized to receive either 6 cycles of Benda-R or CHOP-R. The overall response rate was 96% for Benda-R, and 94% for CHOP-R treated patients. With a median observation period of 26 months, 20/23 (87%) Benda-R versus 9/17 (53%) CHOP-R treated WM patients remain free of progression. Importantly, Benda-R was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia in this study. The results of this study suggest that Benda-R is active in front-line WM, and may be a preferable option to cyclophosphamide-based therapy in the front-line therapy of WM. Its efficacy however in the relapsed/refractory setting of WM remains to be determined. As such, we examined the outcome of 30 consecutive WM patients who were previously treated, and who received bendamustine-containing therapy.

Patients and Methods

Study Design

We identified all previously treated WM patients at our center who received a bendamustine-containing regimen. Response determinations were made using modified consensus criteria from the Third International Workshop on WM.^{9,10} Time to progression was calculated from the start of therapy using the Kaplan-Meier method. The primary endpoints of this study were best categorical response attainment, PFS, and toxicity. Changes in serum IgM levels and blood counts following bendamustine-based therapy were also assessed at best response. The study was approved by the Dana Farber Cancer Institute/Harvard Cancer Center Institutional Review Board.

Statistical Analysis

Comparison of pre- and post-treatment parameters was performed using a 2-tailed student *t* test on Microsoft Excel™ software. For non-parametric testing of pre- and post-treatment

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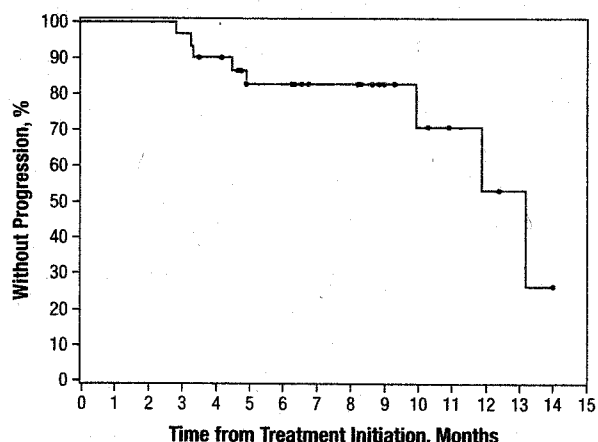
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Figure 1 Kaplan Meier Curve for Time to Progression for All Patients on Study



Circles denote last follow-up for individual patients.

responses, Chi Square test (VassarStats) was used. A *P* value $\leq .05$ was deemed to be significant for the above studies.

Results

Patients Characteristics

Thirty patients met parameters for this study. Their median age was 68 years (range, 44-84 years). Their median number of prior treatments was 2 (range, 1-9), and 16 (53%) patients were refractory to their previous therapy. Prior treatments included nucleoside analogue (*n* = 14; 47%), bortezomib (*n* = 13; 43.3%), and cyclophosphamide (*n* = 11; 37%) containing therapies. Twenty-eight (93%) patients received rituximab alone or in combination therapy. Median pre-therapy BM disease involvement was 60% (range, 5%-100%), and serum IgM level was 3980 (range, 536-7770 mg/dL). Twenty-two (73%) patients had an IgM level of > 3000 mg/dL. Median pre-therapy hematocrit and platelet count were 31.0% (range, 24.9%-42.3%), and 194,000 (range 33,000-657,000/mm³), respectively. Twelve (40%) and 3 (10%) of the patients had a hematocrit $\leq 30\%$ and a platelet count of $\leq 100,000/\text{mm}^3$, respectively. Seven patients (23.3%) had adenopathy and/or splenomegaly.

Treatment

Treatment consisted of bendamustine (90 mg/m² I.V. on days 1, 2) with rituximab (375 mg/m² I.V. given on either day 1 or 2) every 4 weeks for 24 patients. In 6 patients, severe rituximab intolerance prevented re-administration of rituximab. In these patients, bendamustine was administered alone (*n* = 4) or with ofatumumab (1000 mg I.V.) given on day 1 (*n* = 2) following a test dose of 300 mg I.V. on day -7 prior to cycle 1 only. Plasmapheresis was performed prior to treatment in patients exhibiting symptomatic hyperviscosity, or with an IgM level ≥ 5000 mg/dL and were to receive monoclonal antibodies in order to prevent a symptomatic IgM flare.¹¹ G-CSF and erythropoietin support were offered in accordance with ASCO guidelines.

Intended therapy consisted of 6 cycles of treatment. The median number of cycles for bendamustine was 5 (range, 2-6). Only 14/30 patients (46.7%) completed all 6 cycles of bendamustine.

Reasons for treatment truncation included: excessive or prolonged myelosuppression (*n* = 4); no response (*n* = 3); infection (*n* = 2); patient/physician decision (*n* = 3); and hypersensitivity to bendamustine (*n* = 2). For 2 patients who ultimately required cessation of therapy, prior bendamustine dose modification had been made. Three patients initiated on bendamustine plus rituximab required cessation for rituximab intolerance.

Responses

Median serum IgM levels for all 30 patients declined from 3980 to 698 mg/dL at best response (*P* < .00001). Pre-therapy, 22/30 (73.3%) patients demonstrated an IgM level ≥ 3000 mg/dL; following treatment, only 3 of 30 (10%) had an IgM level ≥ 3000 mg/dL (*P* < .00001). Categorical responses were as follows: VGPR (*n* = 5); PR (*n* = 20); for an overall and major response rate of 83.3%. One patient with autoimmune hemolytic anemia who was transfusion dependent prior to therapy with Benda-R continues with stable disease at 6.8 months, and became transfusion independent. Four patients were non-responders. The overall and major response rate for patients who received bendamustine with rituximab was 79%, including all 5 VGPR patients. All 4 patients who received bendamustine alone, as well as the 2 patients who received bendamustine with ofatumumab achieved a PR. Among patients with a baseline IgM ≥ 6000 mg/dL, 3/6 (50%) responded, versus 22/24 (92%) patients with a baseline IgM < 6000 mg/dL (*P* = .04). Responses were observed among relapsing (13/14; 93%); refractory (12/16; 75%); previous nucleoside analogue treated (13/14; 93%); previous bortezomib treated (12/13; 92%) and previous cyclophosphamide treated (10/11; 91%) patients. Resolution (*n* = 4) or improvement (*n* = 3) of adenopathy/and or splenomegaly occurred in the 7 patients with pre-therapy extramedullary disease.

Time to Progression

The median follow-up for all patients is 7.5 months (range, 3-14 months), with an estimated median time to progression of 13.2 months (Figure 1). Among 26 patients with stable disease or better, 3 have demonstrated progressive WM disease. One other patient transformed to diffuse large B-cell lymphoma following 4 cycles of Benda-R which was deemed a progressive event. This patient subsequently succumbed to transformed lymphoma. All other patients remain alive.

Changes in Hematological Parameters

A significant increase in the median hematocrit was noted for all patients from 31.0% (range, 24.9%-42.3%) to 36.6% (range, 25.3%-46.3%) following treatment (*P* < .0002), with 19 of the 30 (63.3%) patients demonstrating a hematocrit rise of > 2%. Conversely, the median platelet count decreased following treatment from 194,000/mm³ (range, 33,000-657,000/mm³) to 174,000/mm³ (range 30,000-380,000/mm³); *P* = .14, though for most patients this decrease was not clinically significant.

Toxicities

Toxicities attributed to bendamustine led to dose reduction and/or truncation of intended therapy in 8/30 (26.6%) patients and included excessive or prolonged myelosuppression (*n* = 4) inclusive

of 3 patients previously treated with a nucleoside analogue; infection (n = 2); and hypersensitivity manifested by fever and rash (n = 2). Intolerance to rituximab due to infusion related reactions resulted in its discontinuance in 3 patients. Both patients with a previous rituximab intolerance who received ofatumumab with bendamustine experienced no infusion related or other adverse events. Other expected toxicities included: grade 1/2 nausea (n = 5); upper respiratory tract infections (n = 4); diarrhea (n = 2); reversible transaminitis (n = 1); and mucositis (n = 1). Unexpectedly, 3 patients developed superficial thrombophlebitis at sites of bendamustine infusions, and one of these patients required anticoagulation for the duration of therapy. One responding patient transformed to diffuse large B-cell lymphoma following 4 cycles of Benda-R, and subsequently succumbed to transformed disease. Prior therapies for this patient included CVP-R, Velcade/Rituximab, and CHOP-R. One patient developed myelodysplasia, without cytogenetic abnormalities following 5 cycles of Benda-R. Prior therapies for this patient included fludarabine/rituximab, and CP-R.

Discussion

To our knowledge, this study represents the first experience of bendamustine therapy in relapsed/refractory WM. We observed an overall and major response rate of 83.3%, which compares favorably to that achieved with other salvage based therapies in WM.¹² Importantly, we observed responses among patients who received bendamustine alone, or in combination with a CD20-containing antibody. Ninety-three percent of patients had previous rituximab therapy. The value therefore of adding a CD20 directed antibody in patients who previously received rituximab, and then go on to receive bendamustine needs to be further clarified, including impact on PFS.

Overall, treatment was well tolerated with dose reduction and/or truncation of therapy for toxicity occurring in 8/30 patients (26.6%). Excessive or prolonged myelosuppression accounted for half of these events, which included 3 patients who previously received nucleoside analogue therapy. In such patients, dose modification of bendamustine, or more limited duration of therapy may be required. One patient transformed while on treatment, and another patient developed myelodysplasia after completion of therapy. Both of these patients were heavily pre-treated. An increased risk of disease transformation and myelodysplasia has been observed in WM patients receiving nucleoside analogues, and may potentially be related to the "nucleoside analogue component" of bendamustine. Longer follow-up will be required to clarify such risks in this patient population. In 2 North American studies, the risk for development of myelodysplasia and/or myeloid leukemias among previously treated NHL patients was 1%-3%.^{3,4} With a median follow-up of almost 3 years, comparable rates of treatment-related myelodysplasia and/or myeloid leukemia were observed in a

combined analysis of 2 randomized studies that compared Benda-R to other anti-lymphoma regimens (CHOP-R, fludarabine/rituximab).¹³ Additionally, the impact on stem cell collection remains to be clarified. No patient on this study went on to have stem cells collected. While one in vitro study reported minimal impact of bendamustine on stem cell assays,¹⁴ the use of bendamustine should be weighed against other options in those patients seriously being considered for autologous stem cell transplantation until more information on stem cell collection and engraftment is available.

In conclusion, bendamustine is highly active in previously treated WM, both as monotherapy, and with CD20-directed monoclonal antibodies. Treatment is well tolerated, though in patients who previously received nucleoside analogue therapy, prolonged myelosuppression may occur and dose modification of bendamustine, or more limited duration of therapy may be considered. Long-term risks of bendamustine treatment including transformation risk, development of myelodysplasia, and stem cell collection need to be better clarified in patients with WM.

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