Treatment of relapsed or refractory Waldenström's macroglobulinemia with bortezomib

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Background and Objectives. Bortezomib is a selective proteasome inhibitor which has shown significant activity in a variety of hematologic malignancies including multiple myeloma, mantle cell lymphoma and marginal zone lymphoma. Thus, this agent is worth studying in patients with Waldenström's macroglobulinemia (WM).

Design and Methods. Patients with refractory or relapsed WM were treated with bortezomib administered intravenously at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 in a 21-day cycle for a total of four cycles.

Results. Ten previously treated patients with WM were treated with bortezomib. Most patients had been exposed to all active agents for WM and eight patients had received three or more regimens. Six of these patients achieved a partial response which occurred at a median of 1 month. The median time to progression in the responding patients is expected to exceed 11 months. Bortezomib was relatively well tolerated. The more common toxicities were mild or moderate thrombocytopenia, fever and fatigue while peripheral neuropathy occurred in three patients and one patient developed severe paralytic ileus.

Interpretation and Conclusions. Our preliminary data indicate that bortezomib is an active agent in patients with heavily pretreated relapsed/refractory WM. Four cycles of this agent may be adequate to assess sensitivity in this disease. Further studies are needed to confirm our results and to evaluate combinations of bortezomib with other active agents.

Key words: bortezomib, Waldenström's macroglobulinemia, proteasome inhibitor.

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Waldenström's macroglobulinemia (WM) is a lymphoplasmacytoid lymphoma characterized by the production of serum monoclonal IgM. The disease usually affects older people and symptoms may be caused by anemia, lymphadenopathy, splenomegaly, increased serum viscosity, or a combination of the foregoing. Plasmapheresis, which reduces the amount of circulating IgM, and systemic therapy, which inhibits tumor growth, have been the standard therapy for symptomatic macroglobulinemia. The three main choices for systemic primary treatment are alkylating agents (chlorambucil), nucleoside analogs (fludarabine and cladribine) and the monoclonal antibody rituximab. Objective responses occur in 30% to 80% of previously untreated patients, with a subsequent median survival of 5 to 8 years.[1] Despite long-term disease control in some patients, all patients eventually develop resistance to treatment, and thus, investigation of new agents is warranted.

Bortezomib (formerly PS-341) is a small molecule that is a potent and selective inhibitor of the 26s proteasome, which is the primary component of the protein degradation pathway of the cell.[2,3] Bortezomib has shown activity in 35% of patients with heavily pretreated multiple myeloma, a plasma cell dyscrasia which shares similarities with WM.[4,5] Furthermore, in a phase I study of bortezomib in patients with refractory hematologic malignancies, partial responses were noted in patients with lymphoma, including one patient with WM.[6] Bortezomib at clinically relevant doses induced growth arrest and apoptosis of both the WM-WSU cell line model and tumor cells freshly isolated from patients with WM. Furthermore, bortezomib induced suppression of nuclear factor-kappa B activity in WM-WSU cells, decreased expression of kinases implicated in growth and survival, and conferred increased chemosensitivity to the tumor cells.[7] Based on these data we administered bortezomib, as a single agent, to patients with previously treated WM.

Design and Methods

Ten consecutive patients with WM were treated with bortezomib after they had given written, informed consent to this treatment protocol. Bortezomib was provided to patients with previously treated WM, free of charge, on a compassionate-use basis. The diagnosis of WM was established in all patients by the presence of monoclonal IgM in the serum and infiltration of the bone marrow by lymphoplasmacytoid lymphoma.[1]

Bortezomib was administered intravenously at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 in a 21-day cycle for a total of four cycles. The drug was injected over 3 to 5 seconds into a side arm of an intravenous infusion of normal saline running at 100 mL/h. At the end of the drug infusion, 10 mL of normal saline were infused to flush the line. Doses were repeated if the absolute neutrophil count was ≥1,000/μL and the platelet count was ≥50,000/μL. Dexamethasone was not given with bortezomib at any time during the planned therapy, not even as an antiemetic. Adverse events were assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Treatment was withheld in patients with grade 3 or more non-hematologic toxicity or grade 4 hematologic toxicity until the side effects diminished to grade 1 or less. After resolution of the toxic effect, treatment was resumed at a lower dose level. Stepwise reductions were to 1.0 mg/m^2 and 0.7 mg/m^2. All patients underwent baseline evaluation that included detailed physical examination, blood counts, hepatic and renal function tests, bone marrow biopsy, serum protein electrophoresis, and quantification of serum immunoglobulins and serum β2-microglobulin. Chest X-rays and computed tomography of the abdomen and pelvis were also performed. During the four cycles of bortezomib, patients were followed up with blood counts before each administration of bortezomib and with biweekly renal and liver function tests and serum electrophoretic studies. Thereafter these tests were repeated every two months. Repeat imaging procedures were performed, in patients with abnormal findings at baseline, after completion of the four cycles of bortezomib. Bone marrow biopsy was repeated only if a patient achieved a complete response. Response and progression were defined as previously described by Weber *et al.*[8] Complete response was defined as complete disappearance of serum monoclonal protein by immunofixation, resolution of lymphadenopathy and organomegaly and no signs or symptoms that were directly attributable to WM. Absence of malignant cells in the bone marrow was also required. Partial response was defined as a ≥50% reduction of serum monoclonal protein concentration on electrophoresis and a ≥50% reduction of lymphadenopathy and organomegaly. Progressive disease was defined as a greater than 25% increase in serum monoclonal protein levels from the lowest attained response value. Progressive disease was also documented if there was worsening of anemia, thrombocytopenia, lymphadenopathy or organomegaly directly attributable to WM or appearance of disease-related complications.[8]

Results

Ten patients with WM were treated with bortezomib (Table 1). Three patients were progressing despite treatment (2 had a refractory relapse, 1 had primary refractory disease) and seven patients were relapsing from an unmaintained response. Most patients had been exposed to all active agents for WM and eight patients had received three or more regimens. The median time from primary treatment to bortezomib administration was 60 months (range: 22 to 100 months). A total of 33 cycles of bortezomib were administered. Toxicities are listed in Table 2. Overall, treatment with bortezomib was relatively well tolerated. The most common hematologic toxicity was mild or moderate thrombocytopenia (40%). This side effect was readily reversible and was not associated with bleeding. The most common non-hematologic toxicities were fatigue, fever and diarrhea. Fever was noted in 50% of patients and occurred several hours after the administration of bortezomib. Diarrhea was mild and occurred in 50% of patients. Three patients developed peripheral neuropathy which was severe in two of them. None of these patients had a clinically evident IgM-related neuropathy; however one patient had residual neuropathy from prior exposure to thalidomide. Six of ten patients with WM received all four planned cycles. One patient received three cycles and, despite lack of significant side effects, he discontinued treatment. Another patient developed upper gastrointestinal bleeding due to aspirin consumption after the second course of bortezomib and declined further treatment. An 84-year old woman developed severe paralytic ileus after the second course of bortezomib. This complication resolved but the patient refused further treatment. Finally, one patient received one course of bortezomib without complications but declined further treatment for social reasons. Six patients received the full dose of bortezomib while in four patients the dose was reduced to 1 mg/m^2 (2 patients) and to 0.7 mg/m^2 (2 patients).

Six of ten patients achieved a partial response after treatment with bortezomib, including three patients who had a more than 75% reduction of serum monoclonal protein. In two patients a 25% reduction of serum monoclonal protein was observed and in one patient there was no change of the monoclonal protein (Table 3). One patient, an immigrant from Albania,

Table 1. Patients' characteristics and disease features.

Patients (n.)	10
Male/female	8/2
Median age (years)	78
range	48-84
Median serum M-protein (g/dL)	2.7
range	0.7-9.0
Serum β2-microglobulin >3.5 mg%	4
Prior treatments (n.)	
alkylating agents	9
anthracyclines	3
nucleoside analogs	7
rituximab	10
thalidomide	8
Number of prior regimens (n.)	
1	1
2	1
3	4
4	1
5	3

Table 2. Toxicity grading.

Toxicity	*1*	*2*	*3*	*4*
Anemia	2	2	0	0
Neutropenia	0	0	1	0
Thrombocytopenia	0	2	2	0
Fever	0	5	0	0
Nausea/vomiting	1	2	0	0
Diarrhea	4	1	0	0
Fatigue	2	3	2	0
Hypotension	0	2	0	0
Neuropathy	0	1	2	0
Ileus	0	0	3	0

with advanced and refractory WM complicated by symptomatic hyperviscosity and type I cryoglobulinemia with severe acrocyanosis, received one course of bortezomib which resulted in a significant symptomatic improvement and reduction of monoclonal protein from 9 g/dL to 5 g/dL. The patient tolerated this treatment without side effects but decided to return to his home country and thus did not have any further therapy. He was rated as a non-responder. One patient who was primary refractory to alkylating agents and rituximab did not respond to bortezomib. Another patient who was progressing despite treatment with cyclophosphamide, doxorubicin and prednisone achieved a partial response after treatment with bortezomib. Overall one of three patients with refractory WM achieved a partial response after treatment with bortezomib. Five of six patients who received the planned four cycles of bortezomib responded to treatment. Figure 1 shows the changes of the monoclonal protein after treatment with bortezomib. Response to bortezomib was prompt and a 50% reduction of monoclonal protein occurred in a median of 1 month (range 0.7 to 2 months)(Table 3). Two responding patients developed progressive disease 9 and 11 months after the initiation of bortezomib. Four responders remain without progression for a period of 2 to 12 months, now. The median time to progression for responding patients is expected to exceed 11 months (Table 3).

Table 3. Changes of monoclonal protein after treatment with bortezomib.

Pt No.	*Baseline IgM (g/dL)*	*Nadir IgM (g/dL)*	*Weeks to 50% reduction*	*TTP (months)*
1	1.3	1.0	N/A	N/A
2	0.85	0.4	8	12+
3	8.3	1.7	3	11
4	2.8	1.3	4.5	12+
5	3.9	0.4	2.5	9
6	2.2	1.2	N/A	N/A
7	1.7	1.0	N/A	N/A
8	4.6	1.4	4.5	11+
9	9	5	N/A	N/A
10	0.7	0.2	3	2+

N/A: not applicable, TTP: time to progression for responding patients.

Discussion

In vitro and *in vivo* data suggest that the proteasome is an important target in the treatment of hematologic malignancies. Proteasome inhibition results in the disruption of a variety of pathways and checkpoints leading to cellular apoptosis.[3] Mitsiades *et al.* recently reported that bortezomib may act against WM through a variety of mechanisms including induction of apoptosis, suppression of NF-κB activity and enhancement of sensitivity to other agents. By using gene expression profiling they detected co-ordinated patterns of transcriptional changes induced by bortezomib.[7] The well-documented efficacy of bortezomib in multiple myeloma led to its approval by the USA and European Union regulatory agencies for the treatment of multiple myeloma in patients in whom at least two prior therapies have failed. Furthermore recent data suggest that bortezomib has significant activity in patients with non-Hodgkin's lymphomas, especially those with mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma.[9,10]

Our preliminary results indicate that the proteasome inhibitor bortezomib is active in patients with previously treated WM. Despite the fact that most of our patients had been exposed to alkylating agents, nucleoside analogs, rituximab and thalidomide, the administration of bortezomib resulted in partial responses in six of ten patients. We decided to administer a limited

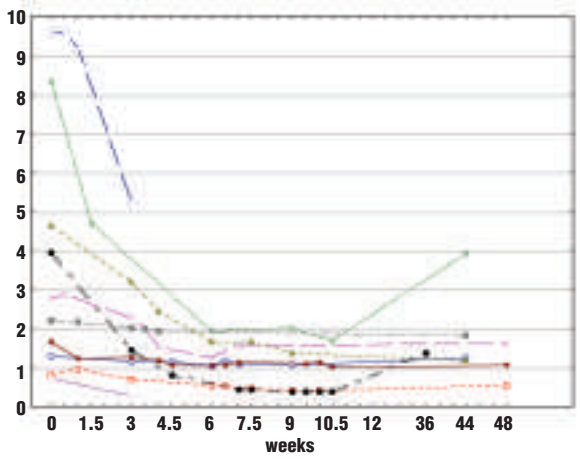

Figure 1. Kinetics of serum monoclonal protein after the first day of bortezomib infusion.

number of four cycles of bortezomib because most of our patients had been previously exposed to thalidomide, another neurotoxic agent. Furthermore, these is clear evidence from multiple myeloma trials that the response to bortezomib is rapid, usually occurring within one or two cycles of therapy. Indeed, this sensitivity to bortezomib was confirmed in the context of WM since five of the six responses occurred after two cycles of bortezomib and the median time to response was 1 month. Despite our limited experience with bortezomib in WM, there is evidence that this may be the fastest agent in inducing responses in this disease. Indeed, the median time to achieve a response to chlorambucil ranges between 6 and 12 months; the time for nucleoside analogs is 2 to 6 months and that for rituximab 3 to 4 months.[1] Despite the limited courses of bortezomib the median time to progression for responding patients is projected to exceed 11 months. We found only one other study of bortezomib in WM, which was presented in abstract form. Chen *et al.* administered bortezomib as a single-agent to 16 patients with either untreated or pretreated WM who had received ≤3 prior regimens. Six of 13 evaluable patients (46%) achieved a partial response.[11] The final results of this ongoing study are awaited with interest.

Treatment with bortezomib was relatively well tolerated. Non-threatening and readily reversible thrombocytopenia, short-lived fever and manageable fatigue were the more common side effects. One patient developed severe paralytic ileus. Despite a limited course of treatment, peripheral neuropathy occurred in only three patients although it was severe in two of them.

We conclude that there is preliminary evidence suggesting that bortezomib is an active agent in heavily pretreated patients with WM. Further studies are needed to confirm these results, to assess a more extended administration of bortezomib and to evaluate the duration of response. Moreover, it would be worth evaluating bortezomib in previously untreated patients as well as combinations of bortezomib with other active agents, especially rituximab.

MAD contributed to the conception and design of the study and analysis/interpretation of the data, drafting the article and approved the final article to be published; AA contributed to the design of the study and analysis/interpretation of the data, critically revised the article and, finally approved the article to be published; MCK contributed to the design and analysis/interpretation of data, critically revised the article and approved the final article to be published; EC and AB contributed to the design of the study and analysis/interpretation of data, critically revised the article and approved the final article to be published; GP contributed to the conception and design of the study, analysis/interpretation of data, critically revised the article and approved the final article to be published. The also declare that they have no potential conflicts of interest.

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