Multicenter Clinical Trial of Bortezomib in Relapsed/Refractory Waldenstrom's Macroglobulinemia: Results of WMCTG Trial 03-248

Steven P. Treon,[1] Zachary R. Hunter,[1] Jeffrey Matous,[3] Robin M. Joyce,[2] Brian Mannion,[4] Ranjana Advani,[5] David Cook,[6] Joseph Songer,[7] John Hill,[8] Bruce R. Kaden,[9] David Sharon,[10] Ronald Steiss,[11] Xavier Leleu,[1] Andrew R. Branagan,[1] and Ashraf Badros[12]

Abstract

Purpose: Waldenstrom's macroglobulinemia (WM) is a B-cell disorder. Despite advances in the therapy, WM remains incurable. As such, novel therapeutic agents are needed for the treatment of WM.

Experimental Design: In this multicenter study, 27 patients with WM received up to eight cycles of bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11. All but one patient had relapsed/or refractory disease.

Results: Following therapy, median serum IgM levels declined from 4,660 to 2,092 mg/dL ($P < 0.0001$). The overall response rate was 85%, with 10 and 13 patients achieving minor and major responses, respectively. Responses were prompt and occurred at median of 1.4 months. The median time to progression for all responding patients was 7.9 (range, 3-21.4+) months. The most common grade III/IV toxicities occurring in $\geq$5% of patients were sensory neuropathies (22.2%), leukopenia (18.5%), neutropenia (14.8%), dizziness (11.1%), and thrombocytopenia (7.4%). Sensory neuropathies resolved or improved in nearly all patients following cessation of therapy.

Conclusions: The results of these studies show that bortezomib is an active agent in relapsed and refractory WM.

Waldenstrom's macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy (1). This condition is considered to be lymphoplasmacytic lymphoma as defined by the REAL and WHO classification systems (2, 3). Up to 20% of patients with WM may have a familial predisposition for disease (4). Despite advances in the therapy, WM remains incurable. As such, novel therapeutic agents are needed for the treatment of WM.

As part of the Third International Workshop on WM, a consensus panel charged with providing treatment recommendations for WM updated its recommendations on both frontline and salvage therapy in view of ongoing clinical trial results (5). Importantly, the panel emphasized that individual patient considerations should be weighed in making therapeutic choices, including the presence of cytopenias, need for rapid disease control, age, and candidacy for autologous transplant therapy, and that for patients who may be eligible for autologous transplant exposure to alkylator agents and nucleoside analogues should be limited in view of reports suggesting depletion of stem cells by these agents (5). As such, we and others have prioritized development of novel, stem cell sparing therapeutics for WM.

One agent of great interest for the treatment of WM is bortezomib, a stem cell sparing agent (6–8), which is active in multiple myeloma (9, 10), a closely related disorder to WM. In preclinical studies, we showed previously that bortezomib induced apoptosis of primary WM lymphoplasmacytic cells, as well as the WM-WSU WM cell line at pharmacologically achievable levels (11). As such, we investigated the clinical activity of bortezomib in a multicenter trial among patients with relapsed and refractory WM.

Authors' Affiliations: [1]Bing Center for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute and Harvard Medical School; [2]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; [3]Rocky Mountain Cancer Center, Denver, Colorado; [4]St. Elizabeth's Medical Center, Crestview Hills, Kentucky; [5]Stanford University Medical Center, Palo Alto, California; [6]Bay Regional Medical Center, Bay City, Michigan; [7]Ball Cancer Center, Muncie, Indiana; [8]Hendersonville Hematology and Oncology, Hendersonville, North Carolina; [9]Northwest Medical Specialists, Niles, Illinois; [10]Monmouth Hematology and Oncology Associates, Long Branch, New Jersey; [11]Atlanta Cancer Care, Rosewell, Georgia; and [12]Greenbaum Cancer Center, University of Maryland, Baltimore, Maryland

Received 10/17/06; revised 1/5/07; accepted 3/9/07.

Grant support: Research Fund for Waldenstrom's at the Dana-Farber Cancer Institute, Bing Fund for Waldenstrom's macroglobulinemia, and a NIH Career Development Award K23CA087977-03 (S.P. Treon).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: S.P. Treon was the principal investigator for this study; Z.R. Hunter and A.R. Branagan served as clinical research coordinators for this study and accrued and analyzed data; R. Advani, D. Cook, J. Songer, J. Hill, B.R. Kaden, D. Sharon, R. Steiss, and A. Badros were coinvestigators and treated patients on this study. X. Leleu was responsible for translational studies.

Requests for reprints: Steven P. Treon, Bing Center for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute, M547, 44 Binney Street, Boston, MA 02115. Phone: 617-632-2681; Fax: 617-632-4862; E-mail: steven_treon@dfci.harvard.edu.

doi:10.1158/1078-0432.CCR-06-2511

Table 1. Summary of pretherapy clinical and laboratory features for 27 WM patients enrolled on study

Median age	62 (44-79)
Gender	18 Male/9 female
Median prior therapies	2 (0-3)
No prior therapy	1 (3.7%)
Median bone marrow involvement	30 (1-95%)
Extramedullary disease	13 (48%)
Median IgM	4,660 (1,067-9,330 mg/dL)
IgM ≥3,000 mg/dL	19 (70.4%)
Median hematocrit	34.6 (25.6-45.3%)
Hematocrit <30%	3 (11.1%)
Median platelet count	225,000 (6-666,000/mm^3)
Platelet count <100,000/mm^3	4 (14.8%)

Patients and Methods

Study design and treatment. Patients with a clinicopathologic diagnosis of WM using consensus panel criteria (1) who failed at least one first line of therapy as defined by consensus panel 3 of the Second International Workshop on WM (i.e., an alkylator, drug alone, or with steroids, nucleoside analogue, or rituximab), with a baseline platelet count of $\geq 50{,}000 \times 10^9$/L, an absolute neutrophil count of $\geq 0.75 \times 10^9$/L, calculated or measured creatinine clearance of ≥30 mL/min, and who did not have ≥ grade 2 peripheral neuropathy were eligible for this clinical trial. All patients provided informed written consent and the protocol was approved by the institutional review boards at all of the participating enrollment centers. Intended therapy consisted of up to eight cycles of bortezomib, with each cycle consisting of four infusions given at 1.3 mg/m^2 on days 1, 4, 8, and 11. Twenty-seven patients were enrolled in this multicenter study, which used a Simon two-stage design. Sample size calculation was based on the assumption that the expected response rate would be at least 35%. Therefore, to have a 95% confidence interval of approximately ±20%, a sample size of 27 was required. Differences in the response rate between patient groups were evaluated for significance using a two-tailed Fisher's exact test (VassarStats). A P value ≤0.05 was deemed to be significant.

Response determination. A baseline evaluation was obtained within 14 days before initiation of therapy. Patients underwent restaging studies following cycles 2, 4, 6, and 8 of bortezomib therapy and thereafter every 3 months for 2 years or until progression of disease. As part of their response evaluation, all patients underwent history and physical exam, laboratory studies consisting of a complete blood count and differential, serum IgM levels, and a bone marrow biopsy and aspiration if clinically indicated. Response determinations were made using consensus panel criteria adopted from the Third International Workshop on WM (12), and response rates were defined on an intent-to-treat basis. A complete response was defined as having resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. Patients achieving a major response and a minor response were defined as achieving a ≥50% and ≥25% reduction in serum IgM levels, respectively. Patients with stable disease were defined as having ≤25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM. Progressive disease was defined as occurring when a >25% increase in serum IgM level occurred from the lowest attained response value or progression of clinically significant disease-related symptom(s). Time to disease progression was calculated from the start of bortezomib therapy using the Kaplan-Meier method.

Analysis of peripheral blood effector cells. Peripheral blood effector cell studies were done as previously reported (12). Comparison of pre-bortezomib and post-bortezomib variables were done using a two-tailed students t test on Microsoft Excel software for parametric variables by Fisher's exact probability test (VassarStats) and for nonparametric evaluations. A P value ≤0.05 was deemed to be significant.

Results

Patients and disease characteristics. The clinical features of the 27 WM patients enrolled in this study are summarized in Table 1. Two (7.4%) patients were included on study through deviations. One patient, not wanting any form of cytotoxic or rituximab therapy, was enrolled having no prior therapy. Another patient suffering from acute immune thrombocytopenia related to disease was enrolled on trial with a platelet count below the eligibility cutoff. Of the 26 previously treated patients, 12 (44.4%) and 15 (55.6%) of patients showed relapsed disease or disease refractory to their prior therapy, respectively. Twelve (44.4%) of the patients were documented to have grade 1 neuropathy at baseline. The median number of cycles of therapy delivered was 6 (range, 3-8), with 9 (33.3%) patients completing all eight cycles of therapy. Reasons for not completing intended therapy included progressive disease (n = 4), sensory neuropathy (n = 5), other nonhematologic

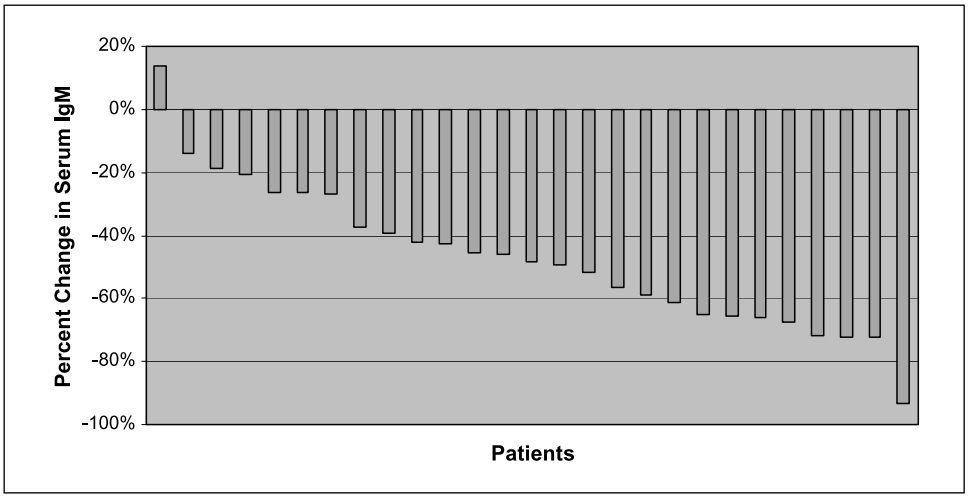

Fig. 1. Percentage change of serum IgM levels for 27 WM patients at best response following treatment with bortezomib.

toxicity (n = 6), and investigator decision for lack of intended clinical benefit (n = 3).

Clinical responses to therapy. The individual changes in serum IgM levels at best response for all patients are shown in Fig. 1. Median serum IgM levels for all 27 patients declined from 4,660 mg/dL (range, 1,067-9,330 mg/dL) to 2,092 mg/dL (range, 96-5,650 mg/dL) at best response ($P = 3.6 \times 10^{-9}$). Pretherapy, 19 of 27 (70.4%) patients showed an IgM level ≥3,000 mg/dL; at best response, only 9 of 27 (33.3%) had an IgM level ≥3,000 mg/dL. Importantly, 3 of 3 patients with hyperviscosity-related complaints showed resolution Overall, 23 of the 27 (85%) patients enrolled on this study showed at least a minor response as their best response. Of these patients, 13 (48.1%) achieved a major response, and 10 (37.0%) achieved a minor response. No complete remissions were observed. The median time to best response for all responding patients was 4.1 (range, 1.0-15.0) months. Among all responders, the median time for a 25% reduction in serum IgM was 1.4 (range, 0.9-3.9) months. Among major responders, the median time for a 50% reduction in serum IgM was 2.4 (range, 0.9-6.1) months. An intriguing finding was an abrupt IgM spike (>10% increase in serum IgM) observed for 13 patients immediately following cessation of all bortezomib therapy (Fig. 2). For three of four patients who continued to be followed up after showing a spike and not summarily taken off study for progressive disease, the IgM decreased below the previously established nadir with further follow-up (Fig. 2). In contrast to our previous studies with the monoclonal rituximab in WM patients, pretherapy IgM levels did not serve as an independent determinant of response nor did pretherapy bone marrow involvement (data not shown).

Bone marrow and extramedullary responses to therapy. Posttherapy bone marrow biopsies were not required for response determination but were available for 10 patients who showed a median decrease in bone marrow involvement from 50% (range, 20-95%) to 20% (range, 5-80%; P = 0.018). Overall, the median change in bone marrow involvement (-50%) for these 10 patients paralleled the median change in serum IgM levels (-44%). However, in 3 of 10 patients, we observed discordance between serum IgM levels, bone marrow involvement, and/or adenopathy. This was most apparent in one patient, in whom serum IgM decreased from 2,310 to 637 mg/dL (-72.42%), whereas bone marrow involvement rose from 25% to 50%. For two other patients, a disproportionately greater decrease in serum IgM levels was observed compared with bone marrow disease involvement, whereas their adenopathy, which was marginal, remained unchanged. Improvements in extramedullary disease were also observed following bortezomib therapy. Four of 13 (31%) patients with adenopathy showed improvement in their adenopathy, whereas splenomegaly remained unchanged for one patient with splenomegaly despite decreased adenopathy following treatment. Among three patients with extramedullary masses, reductions in masses were observed in two patients following bortezomib. Biopsies of these masses were done and showed lymphoplasmacytic lymphoma for the two responsive patients and extensive amyloidosis in the unresponsive patient's mass.

Time to progression. The median time to progression for all patients was 6.6 (range, 2.9-21.4+) months. With a median follow-up of 18.2 (range, 12-25.5+) months, 17 of the 23 responding patients have progressed. The median time to progression for all responding patients was 7.9 (range, 3-21.4+) months and was slightly longer but not significantly different for major responders compared with minor responders at 8.9 and 6.6 months, respectively (P value is not significant).

Changes in hematologic variables in WM patients treated with bortezomib. Pretherapy, 3 (11.1%) and 2 (7.4%) of the 27 patients showed a hematocrit of ≤30% and platelet count of ≤100,000/mm^3, respectively. One patient with a platelet count of 6,000/mm^3 attributable to disease-related autoimmune thrombocytopenia was permitted on study following approval of a protocol deviation. Following therapy, at best response, none and 1 of the 27 (3.7%) patients showed a hematocrit of ≤30% and platelet count of ≤100,000/mm^3, respectively. A significant increase in the median hematocrit was noted for all patients from 34.6% (range, 25.6-45.3%) to 38.1% (range, 31.5-46.9%) following bortezomib therapy ($P = 4.7 \times 10^{-5}$). Pretherapy and posttherapy median platelet and neutrophil counts remained unaffected by bortezomib therapy (P value is not significant). No patients received granulocyte colony-stimulating factor in support of their neutrophil count on this study. One patient entered on study with disease-related

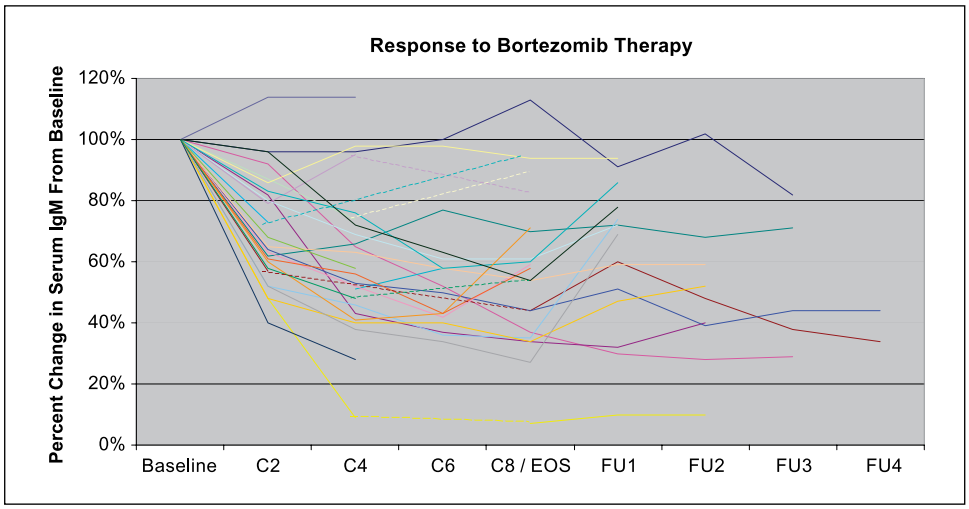

Fig. 2. Serial changes in serum IgM levels for 27 WM patients following bortezomib therapy. Response was assessed every two cycles (C2-C8). Patients received an end of study assessment either at cycle 8 or at conclusion of therapy.

Table 2. Toxicities experienced by the 27 patients on study deemed to be possibly, probably, or definitely related to bortezomib therapy

Toxicity	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Anorexia	0/27 (0)	1/27 (3.7)	0/27 (0)
Bone pain	1/27 (3.7)	0/27 (0)	0/27 (0)
Constipation	5/27 (18.52)	0/27 (0)	0/27 (0)
Cough	1/27 (3.7)	0/27 (0)	0/27 (0)
Diarrhea	2/27 (7.41)	1/27 (3.7)	0/27 (0)
Dizziness	0/27 (0)	3/27 (11.11)	0/27 (0)
Dysgeusia	1/27 (3.7)	0/27 (0)	0/27 (0)
Dyspnea	1/27 (3.7)	0/27 (0)	0/27 (0)
Edema	1/27 (3.7)	0/27 (0)	0/27 (0)
Fatigue	9/27 (33.33)	1/27 (3.7)	0/27 (0)
Headache	1/27 (3.7)	0/27 (0)	0/27 (0)
Hypotension	1/27 (3.7)	1/27 (3.7)	0/27 (0)
Infection	3/27 (11.11)	1/27 (3.7)	0/27 (0)
Insomnia	1/27 (3.7)	0/27 (0)	0/27 (0)
Leukopenia	6/27 (22.22)	5/27 (18.52)	0/27 (0)
Liver function abnormalities	2/27 (7.41)	0/27 (0)	0/27 (0)
Mood alteration/ depression	1/27 (3.7)	0/27 (0)	0/27 (0)
Mucositis	1/27 (3.7)	0/27 (0)	0/27 (0)
Myalgia	1/27 (3.7)	0/27 (0)	0/27 (0)
Nausea	4/27 (14.81)	1/27 (3.7)	0/27 (0)
Neutropenia	3/27 (11.11)	3/27 (11.11)	1/27 (3.7)
Pleural effusion	0/27 (0)	1/27 (3.7)	0/27 (0)
Rash	4/27 (14.81)	0/27 (0)	0/27 (0)
Sensory neuropathy	5/27 (22.22)	6/27 (22.2)	0/27 (0)
Thrombocytopenia	4/27 (14.81)	2/27 (7.41)	0/27 (0)
Weakness	2/27 (7.41)	0/27 (0)	0/27 (0)
Xerophthalmia	1/27 (3.7)	0/27 (0)	0/27 (0)

autoimmune thrombocytopenia had a significant reduction in platelet support.

Toxicities. Most toxicities attributable to bortezomib rated as ≤ grade 2 (Table 2). The most common grade III/IV toxicities occurring in ≥5% of patients were as follows: sensory neuropathies (22.2%), leukopenia (18.5%), neutropenia (14.8%), dizziness (11.1%), and thrombocytopenia (7.4%). Other grade III/IV toxicities included development of pleural effusion (3.7%), diarrhea (3.7%), infection (3.7%), anorexia (3.7%), fatigue (3.7%), nausea (3.7%), and hypotension (3.7%; Table 2). Among the six patients experiencing a ≥ grade 3 sensory neuropathy, five patients had either complete resolution (n = 2) or improvement of the neuropathy to ≤ grade 2 (n = 3) at a median time to improvement of 6 months following onset of the neuropathy. One patient with a grade 3 sensory neuropathy succumbed to progressive disease 14 months following termination of therapy for neuropathy without improvement.

Effector cell and humeral immunity studies. Pretherapy and posttherapy peripheral blood effector and uninvolved immunoglobulin studies were available for 11 patients who were treated at the Dana-Farber Cancer Institute. Following a median of six cycles (range, 4-8 cycles) of therapy, the total peripheral blood lymphocyte count declined from 1,380/mm3 to 1,010/mm3 (P = 0.26). Absolute levels of total T cells ($CD3^+$), helper T cells ($CD4^+$), cytotoxic T cells ($CD8^+$), as well as B cells ($CD19^+$) remained unaffected. In contrast, natural killer cell ($CD16^+CD56^+$) levels declined from 189/mm^3 to 113/mm^3 following bortezomib therapy (P = 0.049). Following a median of six cycles of therapy, a modest decrease in serum IgG (491-460 mg/dL) levels was observed, whereas IgA (25-28 mg/dL) levels remained unchanged (P value is not significant).

Discussion

The results of this multicenter study show that bortezomib is active in WM, producing an overall response rate of 85% among patients with relapsed and refractory disease. Included in these responses were both major (48%) and minor (37%) responders. These results are consistent with the preliminary reporting by others for bortezomib activity within smaller series of WM patients, the majority of whom had relapsed or refractory disease. Chen et al. (13) reported major responses among 6 of 13 (46%) patients with either untreated or previously treated WM, whereas Dimopoulos et al. (14) observed major responses in 6 of 10 (60%) previously treated WM patients. Among two WM patients included in a series of relapsed or refractory patients with non-Hodgkin's lymphoma, Goy et al. (15) observed a major response in one patient.

Responses to therapy in this study were prompt, with a median time of 1.4 months to achieving at least a minor response (i.e., 25% reduction in serum IgM) to therapy. The time to response with bortezomib compared favorably with more prolonged periods reported with other therapies including alkylator drugs and rituximab and suggests that bortezomib may be a consideration for those patients in whom a more immediate reduction in serum IgM is required, such as patients with hyperviscosity-related symptoms. The time to progression for all responding patients in this study was 7.9 months and was slightly longer but not significantly different for major responders compared with minor responders at 8.9 and 6.6 months, respectively. Similar response durations have been reported with single-agent bortezomib among patients with relapsed and refractory multiple myeloma (9, 10). Compared with other salvage therapies used in the second or third-line setting of WM, wherein response rates and time to progression have historically hovered ~30% to 40% and 6 to 9 months, respectively, the results observed with bortezomib in this study seem encouraging, particularly in relation to the overall response rate (5, 16, 17).

An interesting observation in this study was the discordance observed between serum IgM and bone marrow responses in some patients. Although unilateral bone marrow sampling may be invoked as a potential variable to explain these irregularities, Strauss et al. (18) have also made similar observations in WM patients receiving bortezomib. Why discordance between serum IgM levels and disease burden occurs in a subset of patients receiving bortezomib remains to be clarified. Equally intriguing is why many patients show a spike in their serum IgM levels immediately following cessation of therapy. One potential reason for these findings may lie in the intracellular processing of IgM through the rough endoplasmic reticulum, which is specialized in lymphoplasmacytic cells to support the production and secretion of large volumes of immunoglobulins. Disruption of endoplasmic reticulum processing of proteins induces the unfolded protein response (19). Bortezomib induces endoplasmic reticulum stress and promptly upregulates components of the unfolded protein response,

including PERK, the endoplasmic reticulum stress-specific elf-2α kinase that inhibits *de novo* protein synthesis, and ATF4, which induces a proapoptotic cascade mediated by CHOP/GADD153 under conditions of severe endoplasmic reticulum stress (20). As shown recently by us, great heterogeneity in expression of proteins of the unfolded protein response exists among patients with WM perhaps explaining why a subset of WM patients may suppress IgM production independent of tumor cell killing (21). For the same rationale, termination of bortezomib therapy may relieve endoplasmic reticulum stress and lead to resumption of IgM production, invoking the spike in serum IgM levels that we observed in many patients at end of therapy. Studies addressing the effect of bortezomib on unfolded protein response components in WM, along with IgM production and induction of apoptosis, are ongoing in our laboratory. However, from a clinical perspective, clinicians need to be aware of possible discordance of serum IgM levels and clinical response to bortezomib, and a bone marrow biopsy (and/or computed tomography scans in the event the patient had baseline adenopathy/splenomegaly) can be considered to clarify response in circumstances where the patient's underlying clinical status remains to be clarified. In as well, a rapid increase in serum IgM levels following termination of bortezomib therapy should not per se be summarily accepted as evidence of disease progression and further clinical follow-up, including additional serum IgM level testing can be considered.

The development of neuropathy constituted the most concerning adverse event encountered in this study. A total of six (22.2%) patients developed a ≥ grade 3 sensory neuropathy, at a median of six cycles of therapy. No motor neuropathy was observed. The occurrence of ≥ grade 3 sensory neuropathy observed in this study seems to be higher than that reported with bortezomib monotherapy in patients with relapsed and refractory non-Hodgkin's lymphoma (5-13%) and multiple myeloma (12-14%; refs. 15, 22–25). Development of a sensory neuropathy depended on the cumulative dose of bortezomib received, with 9 of 11 cases of therapy-related grade ≥2 neuropathy diagnosed after four cycles of therapy. Among the six patients developing a grade ≥3 neuropathy, five had improvement (to ≤ grade 2) or complete resolution at a median of 6 months from onset of the neuropathy. Eleven (44%) patients on this study had a grade 1 neuropathy at baseline, a finding common to patients with WM in whom IgM-related neuropathies are frequently observed (26). Presence, however, of a preexisting neuropathy did not predict for a therapy-related neuropathy, as only 5 of the 11 patients who developed a therapy-related neuropathy had a baseline neuropathy. In an effort to abrogate bortezomib therapy–related neuropathies, alternative schedules of bortezomib administration are being examined in combination studies with rituximab. De Vos et al. (27) are examining bortezomib administered once versus twice a week along with rituximab, whereas, in a trial combining bortezomib with dexamethasone and rituximab, the WM Clinical Trials Group is administering bortezomib on a twice a week schedule for four cycles followed by four additional cycles each administered 12 weeks apart.

Last, an intriguing finding in this study was the observation that bortezomib spared peripheral blood effector cells and uninvolved immunoglobulins (i.e., IgA and IgG) with the notable exception of natural killer cells that showed a 40% decline following a median of six cycles of therapy. It remains unclear whether the decrease in peripheral blood natural killer cells was due to their killing or relocation. Natural killer cells have been implicated as important effector cells in therapeutic outcomes with the CD20-directed monoclonal antibody rituximab (28–32), which as noted above is being evaluated in combination studies with bortezomib. However, as shown in various preclinical models, synergism rather than antagonism has been observed when bortezomib has been combined with rituximab, possibly based on an enhanced direct apoptotic effect (32, 33).

In conclusion, bortezomib is active in patients with relapsed and refractory WM producing high rates of response and durable responses. In a small subset of patients with WM, discordance between bone marrow response and serum IgM levels can be observed. Sensory neuropathies remain the most concerning adverse event associated with bortezomib therapy in WM patients and are associated with cumulative dosing of bortezomib. However, most WM patients experiencing bortezomib-related sensory neuropathies show resolution or improvement following cessation of therapy. Efforts to administer bortezomib on alternative dosing schedules as part of combination treatment strategies are currently being explored by us and others in hopes of enhancing efficacy and minimizing treatment-related morbidities, including sensory neuropathies.

References

1. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's macroglobulinemia. Semin Oncol 2003;30:110–5.
2. Harris NL, Jaffe ES, Stein H. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361–92.
3. Harris, NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17:3835–49.
4. Treon SP, Hunter ZR, Aggarwal A, et al. Characterization of familial Waldenstrom's macroglobulinemia. Ann Oncol 2006;17:488–94.
5. Treon SP, Gertz MA, Dimopoulos M, et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom's macroglobulinemia. Blood 2006;107:3442–6.
6. Jagannath S, Durie BG, Wolf J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol 2005;129:776–83.
7. Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin, and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol 2005;129: 755–62.
8. Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma. Preliminary results of an IFM phase II study. Blood 2004; 104:416a.
9. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352: 2487–98.
10. Richardson PG, Barlogie B, Berenson J, et al. Extended follow-up of a phase II trial in relapsed, refractory multiple myeloma: final time to event results from the SUMMIT trial. Cancer 2006;106: 1316–9.
11. Mitsiades CS, Mitsiades N, McMullan CJ, et al. The proteasome inhibitor bortezomib (PS-341) is active against Waldenstrom's macroglobulinemia. Blood 2003;102:181a.
12. Kimby E, Treon SP, Anagnostopoulos A, et al. Update on recommendations for assessing response from the third international workshop on Waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma 2006;6:380–3.
13. Chen CI, Whitte D, Kouroukis T, et al. Antitumor activity of bortezomib in a phase II study of patients

with previously untreated or treated Waldenstrom's macroglobulinemia. Blood 2004;104:896a.

14. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Treatment of relapsed or refractory Waldenstrom's macroglobulinemia. Haematologica 2005;90: 1655–7.

15. Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005;23:667–75.

16. Gertz MA, Merlini G, Treon SP. Amyloidosis and Waldenstrom's macroglobulinemia. Hematology Am Soc Hematol Educ 2004;257–82.

17. Dimopoulos MA, Kyle RA, Anagnostopoulos A, Treon SP. Diagnosis and management of Waldenstrom's macroglobulinemia. J Clin Oncol 2005;23: 1564–77.

18. Strauss SJ, Maharaj L, Hoare S, et al. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of *in vitro* sensitivity and tumor necrosis factor α response with clinical activity. J Clin Oncol 2006;24:2105–12.

19. Gunn KE, Gifford NM, Mori K, Brewer JW. A role for he unfolded protein response in optimizing antibody secretion. Mol Immunol 2004;41: 919–27.

20. Obeng EA, Carlson LM, Gutman DM, et al. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. Blood 2006;107: 4907–16.

21. Leleu X, Xu L, Santos DD, et al. The unfolded protein response is a determinant of disease activity in Waldenstrom's macroglobulinemia. Blood 2005; 106:292a.

22. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2005;23:676–84.

23. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867–74.

24. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609–17.

25. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 2006;24: 3113–20.

26. Levine T, Pestronk A, Florence J, et al. Peripheral neuropathies in Waldenstrom's macroglobulinemia. J Neurol Neurosurg Psychiatry 2006;77:224–8.

27. De Vos S, Dakhil S, McLaughlin P, et al. Bortezomib plus rituximab in patients with indolent non-Hodgkin's lymphoma (NHL): a phase 2 study. Blood 2005;106:10a.

28. Janakiraman N, McLaughlin P, White CA, et al. Rituximab: correlation between effector cells and clinical activity in NHL. Blood 1998;92:337a.

29. Hurst D, Gluck A, Yuen A, et al. IL-2 plus rituximab results in clinical responses in advanced patients with non-Hodgkin's lymphoma related to the degree of natural killer cell expansion. Proc Am Soc Clin Oncol 2002;21:283a.

30. Cartron G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor Fcγ RIIIA gene. Blood 2002;99:754–8.

31. Treon SP, Hansen M, Branagan AR, et al. Polymorphisms in FcγRIIIA (CD16) receptor expression are associated with clinical responses to rituximab in Waldenstrom's macroglobulinemia. J Clin Oncol 2005;23:474–81.

32. Hernandez-Ilizaliturri FJ, Kotowski A, Czuczman MS. PS341 inhibits cell proliferation, induces apoptosis of and enhances the biological effects of rituximab on non-Hodgkin's lymphoma (NHL) cell lines and lymphoma xenografts. Blood 2003;102:903a.

33. Smolewski P, Duechler M, Linke A, et al. Additive effect of bortezomib in combination with anti-CD20 or anti-CD52 monoclonal antibodies on chronic lymphocytic leukemia cells. Leuk Res 2006;30:1521–9.