Bortezomib as a Treatment Option in Patients With Waldenström Macroglobulinemia

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Abstract

Waldenström macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized by lymphoplasmacytic bone marrow infiltration and immunoglobulin M (IgM) monoclonal gammopathy. It remains incurable, with a median survival of 5-10 years in symptomatic WM. Current first-line treatment options include alkylating agents, nucleoside analogues, and rituximab-based therapies. However, primary or secondary resistance invariably develops. Thus, new treatment options are needed. Preclinical studies have shown that the proteasome inhibitor bortezomib targets signaling pathways of relevance in WM. Bortezomib, alone and in combination with rituximab, has demonstrated notable activity in clinical studies in patients with WM, predominantly in phase II trials in the relapsed or refractory setting. In newly diagnosed patients, bortezomib plus rituximab and dexamethasone is highly active (complete response/near-complete response = 22%). Bortezomib-based therapies result in rapid responses, potentially making them suitable treatment options for patients with hyperviscosity-related symptoms who require a rapid reduction in IgM level. In addition, bortezomib appears unique in reducing rituximab-associated IgM flares. Bortezomib is generally well tolerated in WM. However, neurotoxicity is common and might be the cause of dose reduction or treatment discontinuation. Bortezomib has no adverse effect on stem cell harvesting and engraftment, making it a feasible treatment option in transplantation-eligible patients. These encouraging data have led to the inclusion of bortezomib as a salvage treatment option in the recently updated Fourth International Workshop on Waldenström's Macroglobulinemia treatment recommendations.

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Introduction

Waldenström macroglobulinemia (WM) is an incurable, relapsing, rare B-cell lymphoproliferative disorder. It is characterized by lymphoplasmacytic bone marrow infiltration and elevated immunoglobulin M (IgM) levels[1-3] and is associated with cytokine and chemokine upregulation, which facilitate survival of the malignant clone.[4] The most common clinical presentations include cytopenias (notably anemia), increased vascular resistance, and serum hyperviscosity.[5,6] The median overall survival is estimated to be 5-10 years, with disease-specific survival of 11.2 years reported in one study[2,3,5,7-10]; however, because of the relapsing nature of the disease, most patients die of disease progression.[4]

Waldenström macroglobulinemia accounts for 1%-2% of all hematologic malignancies, with an overall incidence of approximately 3 per million persons per year.[2,11,12] The median age at diagnosis varies between 63 years and 75 years, and 55%-70% of patients are men.[2,7,10,11,13] The incidence of WM is higher among the white versus black population, with the latter representing only 5% of all patients.[11,12] Genetic factors might have a role in familial clustering of WM, with 19% of the patients in one study having a first-degree relative with a B-cell neoplasm.[14,15]

The predominant risk factor for the development of WM is preexisting monoclonal gammopathy of unknown significance (MGUS), which confers a 46-fold increased risk of disease in comparison with the general population.[16] Increasing IgM level is linked to a progressive increase in risk of transformation from asymptomatic IgM-MGUS to symptomatic WM.[17] However, although elevated serum IgM causes hyperviscosity and other complications, it does not accurately reflect tumor burden or prognosis alone.[4]

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Poor prognosis has also been associated with advanced age, high β_2-microglobulin level, cytopenias, low albumin level, and organomegaly.[9,10,18,19] Indeed, the International Prognostic Scoring System for WM allows patients to be stratified as low, medium, or high risk based on age, hemoglobin concentration, platelet count, β_2-microglobulin, and M-protein.[20] Inactivation of the *TRAF3* and *TNFAIP3* tumor suppressor genes, which are both negative regulators of the nuclear factor (NF)–κB pathway, has been reported, suggesting a therapeutic role for inhibitors of NF-κB.[21]

The proteasome inhibitor bortezomib acts through inhibition of the NF-κB and additional signaling pathways[22-24] and has demonstrated notable activity in frontline[25,26] and relapsed or refractory[25] multiple myeloma (MM), and in relapsed or refractory[27] mantle cell lymphoma (MCL). Thus, bortezomib might also represent a therapeutic option for patients with WM.

Current Treatment Options for Waldenström Macroglobulinemia

In accordance with current guidelines, treatment is initiated only when WM patients become symptomatic.[2,3,11,28] Criteria for starting treatment are hemoglobin < 100 g/L, platelets < 100×10^9/L, clinically significant adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of large-cell transformation.[1,2,28] Patients with asymptomatic WM should be followed without treatment until ≥ 1 of the above criteria are met.[29,30]

Most WM therapies were originally derived from those for other lymphoproliferative diseases presenting with elevated immunoglobulin levels, such as MM or chronic lymphocytic leukemia.[4] However, because of the low incidence of WM, clinical trials in this disease have small sample sizes, and no large comparative studies have been performed. Subsequently, there is no US Food and Drug Administration– or European Medicines Agency–approved regimen for frontline or relapsed or refractory WM.[1] Current treatment regimens include alkylating agents, nucleoside analogues, and rituximab.[1,31]

Recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia have recently been published.[28] Treatment options for WM in the front-line setting include single-agent chlorambucil, cladribine, fludarabine, or rituximab and combination treatment comprising doublets of cladribine or fludarabine plus cyclophosphamide or rituximab, or triplets of cladribine, fludarabine or pentostatin plus cyclophosphamide and rituximab.[28] Other recommended therapies include rituximab plus thalidomide (RT), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), and cyclophosphamide, dexamethasone, and rituximab (CDR).[28] Treatment options in the relapsed or refractory setting are similar to those in the frontline setting, with the omission of the CDR regimen and the inclusion of single-agent alemtuzumab or thalidomide, or these agents in combination with dexamethasone.[28] High-dose therapy plus autologous stem-cell transplantation (HDT-ASCT) is also considered a treatment option in various settings.[28]

Unfortunately, response rates for these various regimens are low, with approximately 50% of patients achieving a partial response (PR; ≥ 50% M-protein reduction) and few achieving a complete response (CR; 100% M-protein reduction).[5,32] For example, CR rates in the frontline setting using alkylating agents, nucleoside analogues, and monoclonal antibodies, alone or in combination, are ≤ 10%.[1] Major response rates (≥ PR) in WM are 31%-85% in frontline and 20%-54% in relapsed or refractory settings with single agents and 74%-94% in both settings using combination therapies.[2,7,8,18,33-49]

The choice of treatment for WM depends on several factors, including candidacy for ASCT, the presence of cytopenias, and the need for rapid disease control. Recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia relate to each of these factors.[28] The prolonged use of alkylating agents and nucleoside analogues is unsuitable in patients undergoing ASCT because these therapies can adversely affect bone marrow function,[6] thereby impairing stem-cell mobilization and potentially preventing the harvesting of sufficient stem cells for patients to undergo ASCT. However, cyclophosphamide is an alkylating agent that has no adverse effect on stem cell collection. Rituximab plus thalidomide, R-CHOP, and CDR regimens are therefore appropriate in ASCT candidates.[28] Other alkylating agents can induce myelodysplasia and acute nonlymphocytic leukemia, and nucleoside analogues might induce bone marrow suppression and immunosuppression.[50] The use of these agents is further limited in patients with cytopenias, particularly thrombocytopenia; such patients might benefit from therapies with low myelotoxicity; RT and CDR regimens are suggested as options in these patients, even in non-ASCT patients.[28] A rapid response to therapy is important in WM, particularly for patients presenting with hyperviscosity symptoms. R-CHOP and CDR are recommended for these patients.[28]

Standard therapies typically have slow response rates; for example, with chlorambucil, several months are required to determine the chemosensitivity of the disease, and rituximab has a median time to response of 3.3 months.[5,38,51] Rituximab is also associated with transient increases in IgM titers, known as 'IgM flares.' Flares can lead to hyperviscosity-associated events, including epistaxis, headaches and, in one case, a subdural hemorrhage.[52] In one study, flares occurred in 54% of the patients and were associated with lower response rates (28% vs. 80% for patients with and without flares, respectively).[53]

Because of the limitations of standard therapies in certain patient groups and the relapsing nature of WM, additional treatment options are required for this disease.[4,28] Consequently, novel agents and new approaches continue to be investigated. These include treatment options effective in MM, such as lenalidomide and allogeneic/mini-allogeneic SCT as well as novel agents targeting pathways of relevance in WM, such as Akt and mammalian target of rapamycin inhibitors.[1,2,11,54-57] Bortezomib, effective in MM and MCL, also targets signaling pathways of relevance in WM.[25-27,58,59] Therefore, bortezomib appears a highly suitable treatment option for WM and, as reviewed in the next section, has demonstrated notable activity as a single and combination agent in clinical studies.

Bortezomib as a Treatment Option in Waldenström Macroglobulinemia

Preclinical Studies

Preclinical studies have elucidated the mechanism of action of bortezomib in a number of tumor types. Bortezomib blocks the

ubiquitin-proteasome degradation pathway through reversible inhibition of the 26S proteasome, thereby affecting multiple signaling pathways, including NF-κB, via inhibition of transcription. This process induces cell-cycle inhibition, endoplasmic reticulum stress through disruption of the unfolded protein response, and apoptotic induction, resulting in antitumor, antiangiogenic, and antiproliferative activities.[22-24]

Preclinical studies have demonstrated the activity of bortezomib in WM. Bortezomib promoted apoptosis in the WM-WSU cell line and in primary tumor cells isolated from patients with WM, including patients whose disease was refractory to fludarabine- or rituximab-based therapies, via suppression of NF-κB and upregulation of AP-1. This resulted in downregulation of antiapoptotic proteins and in caspase-8 and -9 activation.[60] The induction of endoplasmic reticulum stress by bortezomib might also be important because this process has been identified as a therapeutic target in WM.[61,62]

Bortezomib has demonstrated synergistic/additive preclinical activity in combination with numerous agents in WM cells. Synergistic activity was observed with the combination of bortezomib, rituximab, and dexamethasone in WM cells. Bortezomib in combination with perifosine, an Akt inhibitor, showed enhanced cytotoxicity in WM cells by targeting NF-κB signaling pathways and reducing PI3K/Akt and extracellular signal–regulated kinase (ERK) signaling,[63] while in combination with another proteasome inhibitor, NPI-0052, synergistic cytotoxicity was demonstrated in WM cells through NF-κB inhibition and caspase-3, -8, and -9, and PARP cleavage. This synergistic activity occurred through differential effects on Akt activity and chymotrypsin, caspase, and trypsin-like proteasomal activities.[64] Resveratrol, an antioxidant constituent of plant, has demonstrated antiproliferative activity and apoptotic induction through synergistic cytotoxicity in combination with bortezomib in WM cell lines, WM primary tumor cells, IgM-secreting cells, and peripheral blood mononuclear cells.[65] Further synergistic activity has been established with simvastatin, which decreases IgM secretion in WM and increases bortezomib cytotoxicity. Interestingly, as with perifosine, this cytotoxic activity in combination with bortezomib was linked to a reduction in Akt and ERK signaling, suggesting that bortezomib might also negatively affect these pathways.[66] Finally, plerixafor (AMD3100), a CXCR4-receptor inhibitor, caused reduced adhesion of WM cells to stromal cells, leading to increased bortezomib cytotoxicity.[67] Based on its activity in MM and the preclinical studies described, bortezomib has been investigated in clinical studies in patients with WM.

Clinical Studies

Efficacy

The preclinical activity of bortezomib in WM cells has been confirmed in clinical studies of bortezomib in patients with WM. Bortezomib has been investigated alone or in combination in 12 phase I and II clinical trials in both the frontline and relapsed or refractory settings. Seven of these studies contained ≥ 5 patients with WM (Tables 1A and 1B).

As a single agent, bortezomib has shown substantial activity in multiple phase II studies of patients with WM alone or as part of broader patient populations, with the majority of studies including patients with relapsed or refractory WM.[68-73] In the phase II multicenter study by Treon et al (Waldenström's Macroglobulinemia Clinical Trials Group [WMCTG] study), where 26 of 27 patients had relapsed disease or were refractory to previous therapy, the overall response rate was 85%, with 13 (48%) major responses (≥ PR) and 10 (37%) minor responses (MRs; ≥ 25% and < 50% M-protein reduction). Importantly, all 3 patients with hyperviscosity-related complaints demonstrated symptom resolution.[73] In a second phase II study in 27 relapsed/refractory patients treated with single-agent bortezomib, Chen et al (National Cancer Institute of Canada [NCIC] trial) observed ≥ MR by serum IgM reduction alone in 21 patients (78%), with 12 patients (44%) achieving a PR.[68] In a preliminary single-center study involving 10 relapsed or refractory patients, Dimopoulos et al reported major responses by serum IgM reduction in 6 patients (60%), of whom 3 had a ≥ 75% serum IgM reduction, with a further 2 patients (20%) achieving an MR. One patient, who had WM complicated by serum hyperviscosity and type 1 cryoglobulinemia, with severe acrocyanosis, demonstrated a reduction in IgM from 9 to 5 g/dL, after a single course of bortezomib. Importantly, 1 of 3 patients with disease refractory to alkylators and rituximab achieved a PR.[69]

Patients with WM might benefit from a therapy that can induce response rapidly and decrease IgM levels in order to alleviate hyperviscosity and other disease-related symptoms. Responses to bortezomib were rapid, with median times to first and best responses of 1.4 months and 4.1 months, respectively, in the WMCTG trial. The authors noted that the median time to response appeared favorable with bortezomib, in comparison with alkylating agents and rituximab, indicating a possible therapeutic option in patients with hyperviscosity-associated symptoms requiring a rapid reduction in IgM levels.[73] In the NCIC trial, median time to first response by IgM reduction was 6 weeks (2 cycles). Nodal responses were slower and occurred in most patients with nodal disease, with a median time to PR of 12 weeks (4 cycles) in 5 patients. The authors note that the lower response rate might reflect the reported lag in nodal tumor disease reduction and suggest that extended therapy might be of benefit to maximize tumor impact in these patients.[68] In addition, Dimopoulos et al reported a median time to response of 1 month and suggested that bortezomib might induce responses in WM more rapidly than any other agent.[69] Such rapid responses have been associated with rare reports of tumor lysis syndrome in patients with MM; however, this has not been described with bortezomib in patients with WM.[74-76]

Reductions in IgM levels were reported in some of the single-agent bortezomib studies. For example, median plasma IgM level decreased from 4,660 mg/dL to 2,092 mg/dL at best response in the WMCTG trial.[73] The median change in bone marrow involvement (–50%) generally paralleled the median change in serum IgM levels following treatment (–44%) in the 10 patients for whom data were available.

Time-to-event outcomes in the WMCTG trial included a median time to progression (TTP) of 6.6 months in all patients and 7.9 months in responding patients. Median TTP in patients with major responses (8.9 months) appeared longer than in patients with minor responses (6.6 months), although this difference was not statistically significant.[73] The NCIC trial noted a median

Table 1A Clinical Studies of Bortezomib in Untreated or Relapsed/Refractory Waldenström Macroglobulinemia

Study	Design	Regimen	Total Enrolled	Response	Outcomes	Toxicities
			Monotherapy			
Treon et al[73]	Single-agent bortezomib; WMCTG 03-248 trial; phase II multicenter study; patients with relapsed/ refractory WM	≥ 8 3-week cycles of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11	27 (1 untreated)	CR + PR + MR,[a] 85%; PR, 48%; MR, 37%; median time to first response, 1.4 months; median time to best response, 4.1 months	Median TTP, 6.6 months; median TTP (responders), 7.9 months; median follow-up, 18.2 months	Drug-related grade 3/4 toxicities: sensory neuropathy, 22%/0; leukopenia, 19%/0; neutropenia, 11%/4%; dizziness, 11%/0; and thrombocytopenia, 7%/0
Chen et al[68]	Single-agent bortezomib; National Cancer Institute of Canada; phase II multicenter study; patients with untreated or relapsed WM	3-week cycles of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 (until PD; no maximum number of cycles)	27 (12 untreated, 15 relapsed)	M-protein criteria: CR + PR + MR, 78%; PR, 44%; median time to first response, 6 weeks (2 cycles); composite criteria[b]: PR, 26%; 25% in untreated patients, 27% in relapsed patients; median time to response, 12 weeks (4 cycles)	Median PFS, 16.3 months; median DOR (PR), 10 months; median duration of SD, 14.3 months	Drug-related grade 3/4 toxicities: thrombocytopenia, 26%/4%; neutropenia, 19%/0; fatigue, sensory neuropathy, and myalgia, 11%/0; anemia, 7%/4%; neuropathic pain, diarrhea, and dyspnea, 7%/0
Dimopoulos et al[69]	Single-agent bortezomib; preliminary single-center study; patients with relapsed/ refractory WM	4 3-week cycles of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11	10 (7 relapsed; 3 refractory)	PR,[c] 60%; median time to response, 1 month	Expected median TTP, > 11 months	Grade 3 toxicities: ileus, 30%; fatigue, neuropathy, and thrombocytopenia, 20%; and neutropenia, 10%
Strauss et al[72]	Single-agent bortezomib; phase II multicenter study; patients with relapsed/refractory lymphoma	8 3-week cycles of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11	51 (WM: 5)	2 PR[c]	NA	NA

[a]Third International Workshop on Waldenström's Macroglobulinemia consensus response criteria.[96]
[b]Composite response criteria (ie, reduction in IgM protein and bidimensional disease as per Cheson criteria).[97]
[c]Second International Workshop on Waldenström's Macroglobulinemia consensus uniform response criteria.[98]
Abbreviations: CR = complete response; DOR = duration of response; MR = minor response; NA = data not given; nCR = near-complete response, PD = progressive disease; PR = partial response; SD = stable disease; TTP = time to progression; WM = Waldenström macroglobulinemia; WMCTG = Waldenström's Macroglobulinemia Clinical Trials Group

progression-free survival (PFS) of 16.3 months and a median duration of response (DOR) of 10 months for patients achieving a PR.[68] In the Dimopoulos et al study, 2 of the responders developed progressive disease after 9 and 11 months, while, importantly, 4 patients remained progression-free for 2 months to 12 months. The median TTP was expected to exceed 11 months.[69] In addition, bortezomib as a single agent has demonstrated activity in other phase I and II trials in patients with relapsed or refractory hematologic malignancies, including WM.[70-72]

Bortezomib has also been investigated in combination with rituximab in patients with relapsed/refractory WM. Ghobrial et al observed a response rate (≥ MR) of 83%, including 6% CR/nCR and 48% PR, in 35 of 37 response-evaluable patients with WM. After a median follow-up of 1 year, the median TTP and DOR were not reached. After 2 years of follow-up, 8 of 35 patients (23%) had shown disease relapse. Rituximab IgM flares were noted only in (20%) patients, compared with 60% with rituximab monotherapy and 40%-75% with other rituximab-based combinations, suggesting that bortezomib might help to decrease rituximab-mediated IgM flare.[52,77-80] In a further study of 45 patients with B-cell lymphomas, including 10 with recurrent WM, Agathocleous et al noted that 8 (80%) of the patients with WM achieved a PR, with a median reduction in M-protein of 77.5% among responding patients. Three patients with WM requiring transfusion before therapy had normal hemoglobin levels restored.[81]

In the front-line setting, Treon et al investigated bortezomib in combination with dexamethasone and rituximab (BDR) in 23 patients with previously untreated WM. The overall response rate (≥ MR) was 96%. An impressive major response (≥ PR) rate of 83% was reported, and 5 patients (22%) achieved CR/nCR. Responses were rapid, with a median time to ≥ 25% IgM decrease of 1.1 months. In all patients, serum IgM level decreased significantly (4,830-682 mg/dL; $P = .0009$), and median hematocrit levels increased significantly (28.9%-38.2%; $P = .0002$). After a median follow-up of 22.8 months, 18 of 23 patients remained progression free.[82] Rituximab-associated IgM flares occurred in 9% of patients with the BDR. Bortezomib might therefore increase the number of patients for whom rituximab therapy is suitable.

Table 1B Clinical Studies of Bortezomib in Untreated or Relapsed/Refractory Waldenström Macroglobulinemia

Study	Design	Regimen	Total Enrolled	Response	Outcomes	Toxicities
Combination Therapy						
Treon et al[82]	Bortezomib plus dexamethasone and rituximab; WMCTG 05-180; phase II, multicenter study; patients with previously untreated WM	Four 3-week cycles of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11; dexamethasone 40 mg on days 1, 4, 8, 11; rituximab 375 mg/m^2 on day 11; 3-month pause, then 4 more cycles each 3 months apart	23	CR + PR + MR: 96%; CR + PR: 83%; CR/nCR: 22%; median time to ≥ 25% decrease in IgM, 1.4 months	Median TTP, not reached; 18/23 patients progression free after median follow-up of 22.8 months (range, 3.3-33.2 months)	Grade 3/4 toxicities: neutropenia, 26%/4%; peripheral neuropathy, 30%/0; thrombocytopenia, 9%/0; 81% of patients had resolution of grade ≥ 2 PN to grade ≤ 1 at a median time of 6 months
Ghobrial et al[77]	Bortezomib plus rituximab; phase II, multicenter study; patients with relapsed/refractory WM	Six 4-week cycles of bortezomib 1.6 mg/m^2 on days 1, 8, 15, all cycles; rituximab 375 mg/m^2 on days 1, 8, 15, 22, cycles 1 and 4 only	37 (21 relapsed; 5 refractory; 11 relapsed and refractory)	CR + PR + MR[a]: 83% CR + PR: 54% CR/nCR: 6% SD: 14%	Median DOR, not reached; median TTP, not reached	Grade 3/4 toxicities: neutropenia, 14%; anemia, 11%; thrombocytopenia, 11%; peripheral neuropathy, 5% (no grade 4)
Agathocleous et al[81]	Bortezomib plus rituximab; phase I/II, multicenter study; patients with recurrent FL, MCL, or WM	Eight 3-week cycles of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11; rituximab 375 mg/m^2 on day 1 (twice-weekly schedule) OR Six 5-week cycles of bortezomib 1.6 mg/m^2 on days 1, 8, 15, 22, all cycles; rituximab 375 mg/m^2 on days 1, 8, 15, 22, cycles 1 and 4 only (weekly schedule)	45 (WM, 10)	PR,[b] 80%; no significant difference in efficacy between twice-weekly and weekly schedules	NA	Grade 3/4 toxicities (all 45 patients): neutropenia, 12%/12%; thrombocytopenia, 12%/9%; neurotoxicity, 7%/5%; diarrhea, 2%/2%; no significant difference in toxicity between twice-weekly and weekly schedules

[a]Second International Workshop on Waldenström's Macroglobulinemia consensus uniform response criteria.[98]
[b]Third International Workshop on Waldenström's Macroglobulinemia consensus response criteria.[96]
Abbreviations: CR = complete response; DOR = duration of response; FL = follicular lymphoma; MCL = mantle cell lymphoma; MR = minor response; NA = data not given; nCR = near-complete response; PD = progressive disease; PN = peripheral neuropathy; PR = partial response; SD = stable disease; TTP = time to progression; WM = Waldenström macroglobulinemia; WMCTG = Waldenström's Macroglobulinemia Clinical Trials Group

Safety

Bortezomib is generally well tolerated, with the safety profile in WM reflecting the well-characterized safety profiles seen in MM and MCL.[68,69,73,77,82] However, the incidence of bortezomib-associated sensory neuropathy in patients with WM appeared higher than in patients with relapsed or refractory MM.[68,73,83-85] In the single-agent bortezomib WMCTG study, 6 of 27 patients (22%) developed grade ≥ 3 sensory neuropathy,[73] while the NCIC trial reported 20 patients (74%) with new or deteriorating neuropathy, with 12 (44%), 2 (7%), and 6 (22%) patients having sensory neuropathy, neuropathic pain, and mixed sensory and painful neuropathy, respectively.[68] In the studies investigating bortezomib in combination with rituximab, grade 3 peripheral neuropathy was reported in 5% of patients by Ghobrial et al and grade 3/4 neurotoxicity occurred in 12% of the patients in the Agathocleous et al study.[77,81] In addition, grade 3 peripheral neuropathy was reported in 30% of patients being treated with the BDR regimen.[82] These data might reflect an underlying WM-associated clinical or subclinical neuropathy, both of which have been commonly observed.[11,68,73,86] Indeed, the WMCTG trial reported 12 patients (44%) with grade 1 sensory neuropathy at baseline.[73] Development of bortezomib-associated neuropathy did not appear to be related to neuropathy at baseline in patients with WM.[68,73] The NCIC trial noted that 5 patients developed grade 3 neuropathy, of whom only 1 had pre-existing neuropathy.[68]

Previous studies in newly diagnosed and relapsed/refractory MM have shown bortezomib-associated peripheral neuropathy to be reversible in most patients.[59,87-91] Similar findings have been reported with sensory neuropathy or neuroparesthesias in WM, with the majority of patients experiencing improvement or complete resolution of the toxicity.[68,73,82] In the WMCTG trial, 5 of the 6 patients (83%) with grade ≥ 3 sensory neuropathy achieved complete resolution or improvement in symptoms to grade ≤ 2, in a median time of 6 months after onset. The remaining patient ceased therapy for grade 3 sensory neuropathy, without improvement, and died due to disease progression 14 months after termination of therapy.[73] Furthermore, the NCIC trial reported that 15 of 20 patients (75%) with new or deteriorating neuropathy achieved improvement