Proteasome Inhibitor-Based Regimens in the Frontline Management of Waldenström Macroglobulinemia

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KEYWORDS

• Bortezomib • Carfilzomib • Ixazomib • First-line therapy • Neuropathy

KEY POINTS

- Proteasome inhibitors (PIs) remain an active treatment option for the frontline management of Waldenström Macroglobulinemia (WM).
- Bortezomib is effective either as a single agent or in combination with other regimens with high response rates observed in most studies, but neurotoxicity remains a major concern.
- Second-generation PIs, such as carfilzomib and ixazomib, provide active and neuropathy-sparing options, although with a different toxicity profile than bortezomib.
- The choice of each PI in the treatment of WM should be individualized owing to the heterogeneity of the disease's presentation and based on each patient's unique characteristics.

INTRODUCTION

Since the Swedish physician Jan G. Waldenström described for the first time what is now Waldenström Macroglobulinemia (WM) in 1944,[1] the approach to therapy for the disease has made substantial progress. WM is a rare B-cell non-Hodgkin lymphoma characterized by the infiltration of the bone marrow by clonal lymphoplasmacytic cells leading to monoclonal immunoglobulin M (IgM) production.[2,3] WM accounts for only 1% to 2% of all hematologic malignancies with a 2-to-1 male predominance[4] but has a heterogeneous clinical presentation with clinical features of symptomatic disease that include cytopenias, most commonly anemia, hepatomegaly, splenomegaly, lymphadenopathy, fatigue and other B symptoms, IgM-related disorders, such as hyperviscosity-related symptoms, peripheral neuropathies, cryoglobulinemia, cold

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agglutinin-related symptoms, and light chain amyloidosis.[1,5] Most patients with WM (>90%) carry a somatic mutation in the *MYD88* gene (*MYD88*^{L265P}). In comparison, mutations in the *CXCR4* gene are observed in 30% to 40% of patients and are related to increased levels of IgM and risk of hyperviscosity as well as shorter disease remissions in patients treated with Bruton Tyrosine Kinase inhibitors (BTKis).[6]

WM is considered an incurable disease and, for symptomatic patients with WM treatment, one needs to consider a variety of disease-related complications and therapy-related toxicities, especially for older patients. Today, immunotherapy combinations targeting anti-CD20 (mainly rituximab) with chemotherapy (such as the DRC and BR combinations) remain widely used in everyday clinical practice. However, the introduction of BTKis has offered another very effective treatment option.[7–10] Proteasome inhibitors (PIs), first approved in myeloma, have also shown activity in WM, been used in combination regimens for the treatment of symptomatic newly diagnosed or relapsed/refractory WM, and have also become an essential part of chemotherapy-free regimens. PIs have been explored in several single-arm phase 2 studies and recently in a randomized phase 2 study. This review aims to present the current data on the efficacy of PIs, their toxicity profile, and their role in managing previously untreated patients with WM in the context of currently available options.

PROTEASOME INHIBITORS

Mechanisms of Action

The ubiquitin-proteasome pathway has a key role in the degradation of various proteins, including ubiquitinated proteins. This process is vital for the function and homeostasis of the cells, and its deregulation may affect cancer cells. From that point of view, the proteasome plays an important role in cellular homeostasis and is a target against cancer cells.[11] The 26S proteasome is present in the cytoplasm and nucleus and includes two 19S regulatory complexes and a 20S core composed of 4 rings (2 α and 2 β rings).[12] Each β ring consists of 7 subunits, including 3 sites: a caspase-like site, a trypsin-like site, and a chymotrypsin-like site, which has the most proteolytic ability. The 19S complex identifies the protein that will be degraded and deubiquitinated. PIs are categorized into 5 groups: peptide aldehydes, peptide vinyl sulfones, peptide boronates, peptide epoxyketones, and β-lactones.[13] Different PIs have different affinities for the proteasome catalytic subunits and may be reversible or irreversible inhibitors. For instance, bortezomib is a boronic acid dipeptide that inhibits 26S proteasome reversibly, whereas carfilzomib is a tetrapeptide epoxyketone, an analogue of epoxomicin, and inhibits 20S proteasome irreversibly.[14–16] PIs inhibit the degradation of ubiquitinated proteins by the proteasome, leading to the accumulation of the ubiquitinated proteins and an increase in the stress of the endoplasmic reticulum (ER). The unfolded proteins trigger a signaling pathway, the unfolded protein response (UPR), a stress response. UPR assists cells in handling the increased number of unfolded proteins. An excessive stress UPR can lead to apoptosis.[13,17–19]

Bortezomib in Waldenström Macroglobulinemia

Bortezomib is a dipeptide boronic derivative acid that reversibly inhibits the 26S proteasome. As a result of its inhibitory activity in the proteasome, it induces ER stress-promoting apoptosis.[19,20] Bortezomib is effective and has been approved for treating multiple myeloma (MM) and mantle cell lymphoma. However, the main adverse effect of bortezomib is neurotoxicity, which is not a class effect. The neurotoxicity is mostly reversible, at least to a significant degree, and seems less frequent and severe with

dose modifications (weekly instead of twice a week) and subcutaneous (SC; compared with intravenous [IV]) administration.

Bortezomib has been tested in clinical trials as a single agent or in combination with other regimens in the first-line therapy in patients with WM. The results of the published studies are summarized in **Table 1**.

As a single agent for treatment-naïve patients, bortezomib has been tested as part of 2 clinical trials that included mostly patients with relapsed or refractory WM, and generally in small numbers of patients. Chen and colleagues[21] ran a phase 2 multicenter study and observed that the response rates were similar between treatment-naïve and pretreated patients, 3 out of 12 (25%) and 4 out of 15 (27%), respectively. Neurotoxicity, especially sensory neuropathy, was a frequent adverse event, but overall, the drug was well tolerated. Similar toxicity was described in the majority of enrolled patients, one of whom was previously untreated, in the multicenter study of Treon and colleagues.[22]

Bortezomib has been extensively investigated with other agents, including several studies for treating newly diagnosed symptomatic WM. Ghobrial and colleagues,[23] in a phase 2 study, enrolled 26 untreated patients with WM who received bortezomib and rituximab (VR). Bortezomib was given weekly every 28 days for 6 cycles without maintenance therapy. The overall response rate (ORR) was 88% (in 23/26 patients), whereas major responses (major response rate [MRR]) were observed in 17 (65%) patients. The median time to progression (mTTP) at the time of the study was not reached, and the estimated 1-year event-free survival (EFS) rate was 79%. The long-term results of this study revealed that in a total of 63 patients, including previously untreated (26/63) and pretreated (37/63) ones, the mTTP and median duration of response (DOR) were 1.6 (1.1–5) and 1.4 (0.6–5) years, respectively.[24] The most frequent grade 3 and 4 adverse events were neutropenia, anemia, and thrombocytopenia, but no grade 3 neuropathy was reported. Sensory neuropathy grade 1 to 2 was observed in 14 patients (54%).[23] The updated study confirmed the previous results, suggesting serious adverse events owing to hematological complications in 10 of 63 enrolled patients, previously treated and untreated. Other most common no serious adverse events included fatigue and anemia.[24]

In another study, Zhang and colleagues[25] evaluated bortezomib with dexamethasone in untreated Chinese patients with WM. Considering bortezomib's neurotoxicity, they administered it at a lower dose (1 mg/m^2). The ORR reached 80%, and at a median follow-up time of 36 months, all patients were alive, and 6 (60%) did not have disease progression. The most frequent toxicity was low-grade (G1–2) neuropathy that did not lead to the discontinuation of bortezomib.

The most investigated combination is the chemotherapy-free regimen of bortezomib with rituximab and dexamethasone (BDR). Treon and colleagues[26] tested BDR in 23 previously untreated symptomatic patients with WM. Bortezomib was administered IV at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11, every 21 days for 4 cycles, followed by a maintenance phase. The ORR was 96%, and 19 patients (83%) achieved MRR. Two patients experienced an "IgM flare" and underwent plasmapheresis. Moreover, the median time to response (mTTR) was 1.4 months. The most common toxicities included peripheral neuropathy grade 2 to 3, anemia, infections without neutropenia, and thrombocytopenia. Notably, herpes zoster reactivation was observed in 4 of the first 7 patients, none receiving antiviral prophylaxis. Herpes zoster prophylaxis is now routinely recommended when bortezomib is used, and especially when corticosteroids are added, with or without rituximab, because of the increased risk of the virus reactivation.[26] The long-term outcomes of this study confirmed the high response rates (96% ORR and 91% MRR), and at a median

Table 1
Clinical studies of bortezomib in previously untreated patients with Waldenström macroglobulinemia

Study	Type of Study	Regimen	Dose and Schedule of PI	No of Untreated pts	Mutation	Results	Adverse Events of PI
Chen et al,[21] 2007	Multicenter phase 2 study trial	Bortezomib	1.3 mg/m^2 IV on d 1, 4, 8, 11 on a 21-d cycle for a median 6 cycles	12/27 (44%)	NA	Response rates: 3/12 (25%)	Anemia, neuropathy, Fatigue, nausea, neutropenia, thrombocytopenia[a]
Treon et al,[22] 2007	Multicenter phase 2 study	Bortezomib	1.3 mg/m^2 on d 1, 4, 8, and 11 Median no of cycles: 6	1/27	NA	For all pts: 27 (85.2%) ORR,[a] 13 (48.1%) MRR[a]	Sensory neuropathy, leukopenia, neutropenia, fatigue[a]
Ghobrial et al,[23] 2010	Phase 2 trial	VR	V: 1.6 mg/m^2 IV on d 1, 8, 15, every 28 d for 6 cycles R: 375 mg/m^2 per week in cycles 1 and 4	26 symptomatic	NA	23 (88%) ORR, 17 (65%) MRR, 1 (4%) CR, 1 (4%) nCR, 15 (58%) PR, 6 (23%) MR, 3 (12%) SD m f/u: 14 mo mDOR: NR, mPFS: NR, estimated 1-y PFS: 75%, mTTP: NR, estimated 1-y EFS: 79%, mOS: NR, estimated 1-y OS: 96% mTTNT: NR	G1 (n = 6, 23%), G2 (n = 10, 38%), G3 (n = 7, 27%), G4 (n = 3, 12%) G3–4: reversible neutropenia (n = 3, 12%), anemia (n = 2, 8%), thrombocytopenia (n = 2, 8%) G1–2: fatigue (n = 16, 62%), sensory neuropathy (n = 14, 54%), nausea (n = 12, 46%), hyperglycemia (n = 11, 42%), allergy reaction (n = 7, 27%), herpes reactivation (n = 1, 4%)

Zhang et al,[25] 2017	Retrospective study	lBD	B IV 1.0 mg/m^2, D (40 mg) on d 1, 4, 8, and 11 of a 21-d cycle for at least 4 consecutive cycles Median number of cycles: 8	10	NA	80% ORR, 1 (10%) CR, 1 (10%) VGPR, 6 (60%) PR mTTR 1.8 mo after m f/u period of 36 mo, 100% OS & 6 had no disease progression mTTP 39 mo	G3 neutropenia (n = 1), G3 anemia (n = 2), G1–2 thrombocytopenia (G2 n = 1, G1 n = 5), G1–2 neuropathy (n = 6, 60%), G2 infection (n = 2) G1–2 edema (n = 4, 40%) G1–2 gastrointestinal disorders
Treon et al,[26] 2009	Phase 2 study	BDR	B: 1.3 mg/m^2 IV, D 40 mg po on d 1, 4, 8, 11, every 21 d, R 375 mg/m^2 on d 11 4 cycles induction & 4 cycles maintenance treatment	23	NA	22 (96%) ORR, 19 (83%) MRR, 3 (13%) CR, 2 (9%) nCR, 3 (13%) VGPR, 11 (48%) PR, 3 (13%) MR mTTP: NR estimated mTTP >30 mo mTTR:1.4 mo m f/u of 22.8 mo, PFS 78.3%, OS 100%	G4 neutropenia (n = 1, 4%), G2 infections without neutropenia (n = 10, 43%), G2–3 peripheral neuropathy (n = 16, 69%), herpes zoster reactivation (n = 5, 22%), G2–3 thrombocytopenia (n = 10, 44%), G2 anemia (n = 18, 78%)

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Table 1
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Study	Type of Study	Regimen	Dose and Schedule of PI	No of Untreated pts	Mutation	Results	Adverse Events of PI
Dimopoulos et al,[28] 2013	Prospective phase 2 multicenter trial	BDR	B 1.3 mg/m^2 IV on d 1, 4, 8, & 11 followed by weekly B 1.6 mg/m^2 IV on d 1, 8, 15, & 22 every 35 d for 4 cycles, followed by D 40 mg & R IV 375 mg/m^2 on d 1, 8, 15, & 22 in cycle 2 & 5	59	NA	85% ORR, 68% MRR, 2 (3%) CR, 4 (7%) VGPR, 38 (65%) PR, 10 (17%) MR, 3 (5%) SD, 6 (10%) PD Median time to first response (>MR): 3 mo, median time to best response: 5 mo, 4 (8%) best response 6 mo after completion of therapy m f/u: 42 mo, estimated mPFS:42 mo, 3 y OS: 81%	>G3: neutropenia (15%), sensory neuropathy (7%), infections (7%), respiratory symptoms (10%) 46% fatigue, gastrointestinal disorders
Khwaja et al,[30] 2022	Retrospective multicenter study	BDR, VCD ± R	B (15/27)[a] pts: 1.3 mg/m^2, (12/27)[a] pts: 1.6 mg/m^2 weekly for 3–4 doses per cycle for up to 10 cycles & monthly thereafter Median of 6 cycles	11 BDR 1 VCD ± R	7/8 (88%) *MYD88*^{L265P} 2/3 (67%) *CXCR4*	92% ORR, 83% MRR, 8% CR, 33% VGPR, 42% PR, 8% MR, 8% SD 2 y OS: 100%, 2 y PFS: 88%	G1–2 neuropathy (n = 3, 25%) G1–2 gastrointestinal disorders (n = 1, 8%)
Castillo et al,[31] 2018	Retrospective comparative study (CDR-BDR-Benda-R)	BDR	BDR: B 1.6 mg/m^2 IV or SC, D 20 mg IV or po on days 1, 4, 8 d 11, or 1, 8, 15, & 22, every 3 & 4 wk, R 375 mg/m^2 IV on d 11 or 22, for 4 cycles Maintenance: R	87 BDR	23 (88%) *MYD88*^{L265P} 11 (42%) *CXCR4*	BDR: 9 (11%) CR, 20 (24%) VGPR, 40 (48%) PR, 6 (7%) MR, 8 (10%) NR Received maintenance: 55 (65%) The median times to best response: 20 mo mPFS 5.8 y, m f/u time: 4 y, m OS: NR	Neuropathy

Abeykoon et al,[7] 2021	Comparative study (Benda-R)-(DRC)-(BDR)	BDR	BDR, 6 cycles (cycle 1: 21 d, cycles 2–5: 35 d per cycle) B 1.3 mg/m^2 IV or (SC) on d 1, 4, 8, and 11 of cycle 1, & at 1.6 mg/m^2 in subsequent cycles, D 40 mg on d 1, 8, 15, 22 of the 2 cycle and beyond, R 375 mg/m^2 IV on d 1, 8, 15, 22 on 2 & 5 cycle	45 BDR	14/24 (58%) *MYD88*^{L265P}	84% ORR, 68% MRR mTTNT 2.6 y, event-free survival: 1.6 y, time to best response: 6.7 mo, estimated mPFS: 1.8 y m f/u for 5.2 y, DOR 3.6 y, 4-y OS 87%	>G3 neuropathy (10.5%), neutropenia (2.5%), fatigue (2.5%) <G3 anemia (2.5%)
Auer et al,[32] 2016	Prospective randomized multicenter, noncomparative phase 2 (BCR-FCR)	BCR	BCR: B 1.6 mg/m^2 SC days 1, 8, 15, C 250 mg/m^2 po d 1, 8, 15, R 375 mg/m^2 IV d 1, 8, 15, 22, cycles 2 and 5 only	42 BCR	NA	97.6% ORR 78.6% MRR CR = 1, VGPR = 8, PR = 24, MR = 7, SD = 1 3 progressed, 1 death	No >G3 neuropathy >G3: anemia (n = 5, 11.9%), neutropenia (n = 11, 26.2%), thrombocytopenia (n = 7, 16.7%), infection (n = 2, 4.8%)
Leblebjian et al,[33] 2015	Retrospective study	CyBorD ± R	Bortezomib: 9/15[a] pts: 1.3 mg/m^2 on a twice-weekly, 6/15[a] pts weekly on d 1, 8, & 15	4/15 (27%)	NA	1 CR, 1 PR, 2 MR 100% ORR mTTP 18.6 mo	Neuropathy
Buske,[34] 2020	Prospective randomized multicenter European phase 2 study (B-DRC-DRC)	B-DRC	DRC (D 20 mg po d 1, R 375 mg/m^2 IV d 1 cycle 1 & 1400 mg SC d 1 cycle 2–6, C 100 mg/m^2 × 2 po d 1–5) & B SC 1,6 mg/m^{2}d 1, 8, 15) for 6 cycles (28 d interval)	101	26/72 *MYD88*^{MT} & *CXCR4*^{WT} 8/72 *MYD88*^{MT}/*CXCR4*^{MT} 5/72 *MYD88*^{WT}/*CXCR4*^{WT}	91.2% ORR, 79.1% MRR, 18.7% CR/VGPR mPFS NR, estimated 2-y PFS 80.6%, mOS NR, 5 deaths	G ≥ 3 cytopenia, infection G3 (n = 2) & G1–2 (n = 16) peripheral sensory neuropathy

Abbreviations: B, bortezomib; B-DRC, bortezomib-dexamethasone-rituximab-cyclophosphamide; CyBorD, cyclophosphamide-bortezomib-dexamethasone; D, dexamethasone; G, grade; lBD, low-dose bortezomib-dexamethasone; m f/u, median follow-up; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; MT, mutation; mTTNT, median time to next therapy; NA, not available; nCR, near-complete response; NR, not reached; po, per os; pts, patients; R, rituximab; Benda-R, bendamustine-rituximab; SD, stable disease; WT, wild type.

[a] For both untreated/previously treated pts.

follow-up time of 8.5 years, the mTTP was 5.5 years,[27] with a 5-year progression-free survival (PFS) of 57% and 5-year overall survival (OS) of 95%. With the longer follow-up, peripheral neuropathy resolved in 8 out of 16 patients (50%) or improved to G1 in 5 patients.[27]

In a larger phase 2 prospective study, 59 untreated patients received BDR.[28] Unlike the Treon study,[26] maintenance therapy was not given; there was an induction with bortezomib before the addition of rituximab to avoid an IgM flare, and the drug was used weekly at a dose of 1.6 mg/m^2, as an IV infusion. The ORR was 85%, and a major response was attained in 68% of patients. Sensory neuropathy developed in almost half of the patients (46%), with 4 (7%) having neuropathy grade 3 or higher. Other common adverse events included fatigue and gastrointestinal disorders. After administering rituximab in the second cycle, a $\geq$25% elevation of IgM was recorded in 11% of the enrolled patients, with the median absolute increase being 1614 mg/dL; however, none of the patients needed to undergo plasmapheresis. This was attributed to the initial induction with bortezomib, which reduced IgM levels by a median of 18%, allowing a safer introduction of rituximab in cycle 2. The final results of this study, after a median follow-up of 86 months, showed a median PFS of 43 months, but the DOR in patients who achieved at least PR was 64.5 months and the OS rate at 7 years was 66%.[29] The sensory neuropathy resolved or decreased to grade 1 in all patients. Moreover, disease transformation to diffuse large B-cell lymphoma was recorded in 3 patients, but none developed secondary myelodysplasia. In a retrospective study,[30] 11 patients received BDR, and one patient received bortezomib, cyclophosphamide, and dexamethasone (VCD) as frontline therapy. ORR and MRR were 92% and 83%, respectively. After 2 years, all patients (100%) were alive, and the 2-year PFS was 88%. Regarding side effects, neuropathy grade 1 to 2 was observed in 3 patients (25%), and one patient (8%) had gastrointestinal disorders grade 1 to 2. Furthermore, secondary myelodysplastic syndrome was not observed.

There are limited studies that prospectively compare regimens with versus without bortezomib and somewhat more data from retrospective studies. A retrospective study by Castillo and colleagues[31] compared the outcomes in patients who received primary therapy with cyclophosphamide, dexamethasone, and rituximab (DRC), BDR, and bendamustine and rituximab (Benda-R). Among 87 patients treated with BDR, 11% achieved complete response (CR), 24% achieved very good partial response (VGPR), and 48% achieved partial response (PR). The median PFS was 5.8 years, and at a median follow-up interval of 4 years, the estimated 5-year OS rate was 96%. Even though 58 patients received bortezomib twice a week and 29 patients received bortezomib once per week, there was no difference in the response rates and PFS between them. Neuropathy was the most common toxicity, which improved in frequency by modification of the dose or the route of administration of bortezomib. Compared with the other treatment combinations (BR and DRC), there was no difference in the response rates. However, the patients on BDR and Benda-R attained the best response faster. Patients that received Benda-R had numerically longer median PFS than those treated with BDR and DRC (5.8, 5.5, and 4.8 years, respectively). However, between BDR and DRC, the difference was not statistically significant (log-rank $P = .69$).[31] Abeykoon and colleagues[7] compared data from treatment-naïve patients that received Benda-R, BDR, or DRC. In the BDR group, *MYD88* mutations were linked to better ORR (75% in *MYD88*^{L256P} vs 67% in *MYD88*^{WT}). The data revealed that the Benda-R regimen compared with BDR and DRC was superior in terms of MRR (96%, 68%, 53%, respectively), time to best response, and PFS (median, 5.2, 1.8, 4.3 years, respectively). The EFS was not reached in the Benda-R group, whereas the BDR and DRC groups were 1.6 and 4.3 years. Time to next

therapy (TTNT) and DOR were not reached in patients with Benda-R; in the BDR group, these parameters were 2.6 and 3.6 years, respectively, and in the DRC group were 4.4 and 3.9 years, respectively. Moreover, bortezomib was discontinued in 2 patients owing to neurotoxicity.

In another study, Auer and colleagues[32] found that treatment-naïve patients who were administered SC bortezomib in combination with cyclophosphamide and rituximab (BCR) achieved high response rates (98% ORR and 79% MRR). This prospective, randomized study revealed that the efficacy of BCR seemed similar to the combination of fludarabine, cyclophosphamide, and rituximab (FCR) with 82.4% of patients reaching ORR and 76.5% of patients reaching MRR. The BCR regimen was not associated with grade 3 neuropathy.[32] Notably, myelodysplastic syndrome occurred in 2 patients treated with FCR, leading to their deaths. A retrospective study by Leblebjian and colleagues[33] evaluated bortezomib in combination with cyclophosphamide and dexamethasone (n = 15). In 7 patients, rituximab was added. Among 4 previously untreated patients with WM, one achieved CR, one achieved PR, and 2 achieved minor responses (MRs), with ORR reaching 100%. The mTTP was 18.6 months, and the most common toxicity was neuropathy.[33]

The European Consortium for WM[34] conducted a prospective randomized clinical trial comparing DRC with DRC plus bortezomib SC. DRC remains a standard therapeutic regimen for previously untreated patients with WM, and in this study, was given every 4 weeks (instead of every 3 weeks in the original publication). In the experimental arm, bortezomib was given SC at a dose of 1.6 mg/m^2 on days 1, 8, and 15 for 6 cycles in addition to DRC. In cycle 1, rituximab 375 mg/m^2 was administered IV on day 1 and in the subsequent cycles 2 to 6 at a dose of 1400 mg SC on day 1. The study enrolled 202 patients (101 in DRC and 101 in B-DRC arm). The results showed that ORR and MRR were attained in 91% and 79% of patients treated with B-DRC, whereas the response rates in the DRC group were 86.7% and 68.9%, respectively. PFS was not reached in patients with B-DRC regimen, whereas PFS in DRC was 50.1 months, with the estimated PFS at 24 months being comparable at 81% and 73%, respectively. The mutation status of the *MYD88* and *CXCR4* genes impacted neither the response rates nor the PFS. Both regimens were well-tolerated. Among patients who received B-DRC, 43% experienced grade 3 or higher adverse events. Sensory neuropathy grade 3 occurred in 2 patients, whereas sensory neuropathy grade 1 to 2 occurred in 16 patients.

Carfilzomib

Carfilzomib is a second-generation tetrapeptide epoxyketone PI that, unlike bortezomib, irreversibly inhibits the 20S proteasome subunit.[35] It is administered IV and is a neuropathy-sparing option. However, cardiotoxicity has been described in 3% to 4% of patients with MM treated with carfilzomib, and thrombotic microangiopathy has been observed in several studies. Hence, attention should be paid to elderly patients with preexisting cardiovascular disease.[36,37] Carfilzomib has been approved by the Food and Drug Administration (FDA) for MM as a single agent or in combination with dexamethasone or dexamethasone and lenalidomide.

Treon and colleagues[38] investigated carfilzomib in combination with rituximab and dexamethasone (CaRD) in a prospective study (**Table 2**). Carfilzomib was given in 3-week cycles on days 1, 2, 8, and 9 for 8 induction cycles, followed by maintenance treatment on days 1 and 2 every 8 weeks for 8 cycles. Thirty-one patients were enrolled, and 28 patients were previously untreated. ORR and MRR were 89% and 71%, respectively, and were not influenced by *MYD88*^{L256P} or *CXCR4*^{WHIM} mutation status. At a median follow-up time of 15.4 months, no patient had died. The most

Table 2
Clinical studies of carfilzomib in previously untreated patients with Waldenström macroglobulinemia

Study	Type of Study	Regimen	Dose and Schedule of PI	No. of Untreated pts.	Mutation	Results	Adverse Events of PI
Treon et,al.[38] 2014	Prospective, open-label, single stage, phase 2 study	CaRD	Ca IV 20 mg/m^2 (cycle 1) & 36 mg/m^2 (cycles 2–6), D IV 20 mg, on d 1, 2, 8, & 9, R 375 mg/m^2, on d 2 & 9 every 21 d Maintenance therapy: IV Ca 36 mg/m^2, IV D 20 mg, on d 1 & 2, R 375 mg/m^2, on d 2 every 8 wk for 8 cycles	28/31 (90.3%)	29/30 (96.6%)[a] *MYD88*^{L265P} 11/30 (36.7%)[a] *CXCR4*^{WHIM}	25/28 (89.2%) ORR, 20/28 (71.4%) MRR, 1/28 (3.5%) CR, 9/28 (32.1%) VGPR, 9/28 (32.1%) PR, 6/28 (21.4%) MR m f/u of 15.4 mo: no deaths, OS 100%	G1-3 hyperlipasemia, hyperamylasemia neutropenia G3 cardiomyopathy [a] G2 hyperbilirubinemia
Chaudhry et al,[40] 2019	Retrospective, single-center study	CaRD	Ca IV 20 mg/m^2 (cycle 1) & 36 mg/m^2 (cycles 2–6), D IV 20 mg, on d 1, 2, 8, & 9, R 375 mg/m^2, on d 2 & 9 every 21 d Maintenance therapy: IV Ca 36 mg/m^2, IV D 20 mg, on d 1 & 2, R 375 mg/m^2, on d 2 every 8 wk for 8 cycles	6	5/6 (83%) *MYD88* 0 *CXCR4*	67% MRR, 1 (17%) CR, 3 (50%) PR, 2 (33%) MR At an m f/u of 33.5 mo: OS 100% & PFS 66%	No neuropathy & cardiomyopathy

Abbreviation: Ca, carfilzomib.
[a] For both untreated/previously treated pts.

common adverse effects were asymptomatic hyperlipasemia, often accompanied with elevated amylase, neutropenia, possibly attributed to carfilzomib, and one patient developed cardiomyopathy. Hyperlipasemia and hyperamylasemia led to the reduction of the dose of carfilzomib in affected patients. Only neuropathy grade 1 and 2 was recorded, and no patient required discontinuation of the treatment because of neuropathy, suggesting that carfilzomib is associated with a low risk for neurotoxicity, in contrast to bortezomib.[38] Long-term results[39] from the study confirmed similarly high response rates; the median PFS was achieved at 46 months, and all patients were still alive. There were no additional safety concerns, suggesting that carfilzomib could be an active, well-tolerated, and neuropathy-sparing treatment option. However, cardiac toxicity should always be considered.[39]

In the prospective study of Chaudhry and colleagues,[40] six untreated patients with symptomatic WM received the combination CaRD. Even though 80% were positive for *MYD88*^{L265P} mutation, the researchers claimed that the mutational status did not influence the treatment's response. Of patients, 67% achieved MRR, and all had a clinical benefit as anemia and B symptoms resolved. At a median follow-up of 34 months, all patients were alive, and PFS was 66%. No cardiomyopathy was noted. Hence, the researchers suggested that carfilzomib could be a good first-line treatment choice because it led to high response rates, and it seemed to be well-tolerated.[40]

Ixazomib

Ixazomib is an orally administered boronic acid analogue of bortezomib that reversibly binds to the β5 subunit of the 20S proteasome. It received approval from the the FDA for treating relapsed or refractory MM in combination with lenalidomide and dexamethasone. The clinical results of ixazomib as a first-line therapy in WM are described in **Table 3**.

Castillo and colleagues,[41] in a prospective phase 2 study, administered ixazomib in combination with dexamethasone and rituximab (IDR) in 26 symptomatic, previously untreated WM patients. Ixazomib was given orally at a dose of 4 mg on days 1, 8, and 15 every 4 weeks for 6 cycles as induction therapy, followed by 6 cycles every 8 weeks as maintenance therapy. Rituximab therapy started after 2 cycles of ixazomib and dexamethasone to reduce the risk of an IgM flare. All patients harbored *MYD88*^{L265P} mutation, whereas 15 (58%) patients carried *CXCR4* mutations. The ORR was 96% (including 15% VGPR, 62% PR, and 19% MR); the depth of response was related to PFS duration. No grade 4 adverse effects were reported, and most of the adverse events were grade 1 to 2 infusion reactions attributed to rituximab in 39% of patients and nausea in 35% of patients. The long-term results of this study showed that VGPR and PR rates improved to 19% and 58%, respectively.[42] After a median follow-up of 52 months, median PFS, DOR, and TTNT were 40, 38, and 40 months and were not influenced by the *CXCR4* mutations. Ixazomib was not associated with neuropathy or adverse cardiovascular events in this study, and no grade 4 toxicities or deaths were recorded. Hence, the researchers suggested that the IDR combination is a safe, well-tolerated, and effective option for treatment-naïve patients with WM. Alloo and colleagues[43] presented 2 cases, one patient with MM and another with WM, who developed cutaneous necrotizing vasculitis with ixazomib use, that resolved after a reduction in the dose of ixazomib.

NEW PROTEASOME INHIBITORS

Oprozomib is an oral tripeptide epoxyketone PI, analogous to carfilzomib. It binds irreversibly to the proteasome and activates caspases 3, 8, and 9 and poly(ADP) ribose

Table 3
Clinical studies of ixazomib in previously untreated patients with Waldenström macroglobulinemia

Study	Type of Study	Regimen	Dose and Schedule of PI	No. of Untreated pts.	Mutation	Results	Adverse Events of PI
Castillo et al,[41] 2018	Prospective investigator-initiated phase 2 study	IDR	po I 4 mg + IV or po D 20 mg on d 1, 8, & 15 every 4 wk for induction cycles 1 and 2 + IV R 375 mg/m^2 on d 1, every 4 wk for cycles 3–6 Maintenance therapy: every 8 wk for 6 cycles	26 symptomatic	26 (100%) *MYD88*^{L265P} 15 (58%) *CXCR4*	25 (96%) ORR, 20 (77%) MRR, 0 CR, 4 (15%) VGPR, 62% PR, 19% MR, 7 PD mTTR: 8 wk, mPFS: NR at m f/u of 22 mo	No G4 G3: neuropathy (n = 1, 3%), pneumonia (n = 1, 3%), sepsis (n = 1, 3%) G1 & 2: infusion reactions (n = 10, 38.5%), nausea (n = 9, 34.6%), insomnia (n = 7, 26.9%), rash (n = 7, 26.9%)

Abbreviations: I, ixazomib; PD, progressive disease.

polymerase and prevents the chymotrypsin-like activity of the proteasome, migration, and angiogenesis.[44] Moreover, oprozomib seems to have bone-anabolic activity and reduces bone resorption.[45] Oprozomib has not been studied in previously untreated patients with WM, and the experience is limited in the relapsed setting, especially owing to an increased risk of gastrointestinal adverse events, which included 3 events of death associated with gastrointestinal hemorrhage deemed to be related to oprozomib.[46] Oprozomib is no longer being developed for the treatment of plasma cell dyscrasias.

Marizomib is a beta-lactone, irreversible PI.[47] Marizomib has yet shown activity only in preclinical settings. Roccaro and colleagues[48] showed that marizomib induced cytotoxicity in patients' WM cells and did not harm the normal peripheral blood mononuclear cells. The cytotoxicity was triggered by dose-dependent apoptosis through caspase-8 and PARP cleavage without acting on caspases-3 and -9. In addition, marizomib downregulated the antiapoptotic protein Mcl-1 and increased the second mitochondria-derived activator of caspases (Smac/DIABLO) from mitochondria to cytosol. However, clinical data on marizomib in WM are lacking.

SUMMARY

PIs have now been used for almost 20 years in the treatment of myeloma and other plasma cell dyscrasias as well as in the treatment of WM. Their use has been associated with a significant improvement in the survival of patients with MM, and PIs are part of backbone therapies in every disease setting. In WM, PIs are not a backbone therapy, although their use is associated with certain benefits. PI-containing regimens rapidly decrease IgM levels, reduce the risk of IgM flare, and do not expose patients to the risk of significant short- or long-term myelotoxicity, thus providing a "chemotherapy-free" option. On the other hand, administration of bortezomib is associated with a significant risk of neurotoxicity and carfilzomib with a risk of cardiac toxicity, while both drugs require weekly administration (depending on the setting, in a hospital environment) for a fixed, yet long, duration of therapy. Ixazomib is a new option with convenience in terms of administration (given weekly orally), but still with some gastrointestinal toxicity. The pros and cons of these agents should be viewed also in the context of the available treatment options for WM, which include chemoimmunotherapy and BTKis, as well as upcoming BCL2 inhibitors. Bortezomib combinations with rituximab offer a fixed duration, low-cost, chemotherapy-free alternative regimen for selected patients, which is probably noninferior to DRC. With appropriate measures (weekly administration and close follow-up for neuropathy), this regimen can be considered for patients with cytopenias, cardiovascular diseases, WM-related amyloidosis, or other IgM-related complications. The results of the ECWM-1 showed that the added benefit of bortezomib to an effective chemoimmunotherapy regimen, such as DRC, is not substantial. Still, the combination may have a role in managing some patient subgroups without significantly increasing toxicity. Patients with AL amyloidosis, cryoglobulinemia, cold agglutinin disease, and those presenting with high IgM levels who may not be optimal candidates for BTKis or Benda-R owing to concurrent cardiovascular issues and myelotoxicity, respectively, may be candidates for bortezomib-containing therapy. Ixazomib may offer a more convenient but significantly more expensive option than bortezomib. Given its weekly IV administration and cardiac toxicity risk, carfilzomib is not attractive. Given the central role of BTKis and chemoimmunotherapies today, the role of PI-based combinations as primary therapy for WM may be less critical. However, combinations of BTKis with PIs are being explored in prospective clinical trials (NCT04263480). Based on preclinical data,

such combinations could induce deep hematologic responses, which cannot be achieved by BKTis alone, and perhaps offer an opportunity for a fixed duration regimen or at least allow safer discontinuation of BTKis. The impact of genotype (*MYD88* and *CXCR4* mutations) should also be investigated further to elucidate if these mutations play a role in the efficacy of PIs, and current data on this topic are limited.

In conclusion, although the treatment approach for WM is changing, PIs remain a treatment option for select patients with WM. In an individualized therapy approach, PIs can be a part of chemotherapy-containing or chemotherapy-free, fixed-duration regimens for patients not eligible for chemotherapy or at high risk for IgM-related complications.

CLINICS CARE POINTS

- The use of PIs in WM is associated with certain benefits since they rapidly decrease IgM levels, reduce the risk of IgM flare and are considered as a chemotherapy-free treatment option.
- Bortezomib is associated with neurotoxicity, while carfilzomib with cardiac toxicity.
- Ixazomib is given weekly orally and its gastrointestinal toxicity should be taken into consideration.
- The use of PIs should be viewed in the context of the available treatment options and the choice of each regimen should be individualized.

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