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REVIEW ARTICLE

Bortezomib in multiple myeloma management

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ABSTRACT

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of plasma cells, leading to complications such as bone lesions, renal dysfunction, and immune suppression. Over the past three decades, its incidence has risen significantly, attributed to factors such as aging populations and improved diagnostic methods. Treatment strategies have evolved considerably, transitioning from alkylating agents and high-dose chemotherapy to targeted therapies, including proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs). Bortezomib, a first-in-class PI, has revolutionized MM management by inhibiting proteasome activity, thereby inducing apoptosis in malignant plasma cells. This review evaluates the efficacy, safety, and clinical applications of bortezomib, both as monotherapy and in combination with dexamethasone, IMiDs, and conventional chemotherapies. Key clinical trials, such as VISTA and SUMMIT, demonstrate its superiority over traditional regimens, improving response rates and survival outcomes. However, its use is associated with adverse effects, including peripheral neuropathy, hematologic toxicities, and gastrointestinal disturbances, necessitating dose modifications and supportive care. Emerging combinations with monoclonal antibodies and novel agents further enhance therapeutic potential, though optimal sequencing remains under investigation. Systematic literature search was performed using PubMed and Cochrane to identify relevant studies on the applications of bortezomib. The search was inclusive of all publications up to May 2025, without restriction by publication year, to ensure a thorough review of research on bortezomib. Studies focusing on multiple myeloma (MM) and the efficacy of bortezomib were prioritized. A broad set of keywords was employed reflecting the diverse applications of bortezomib in MM treatment. The search strategy was designed to capture a wide range of relevant studies. By synthesizing evidence from 77 studies, this review highlights bortezomib's pivotal role in MM treatment while addressing challenges in toxicity management. Future research should focus on refining combination strategies and minimizing side effects to maximize long-term patient outcomes.

Keywords: Multiple myeloma, proteasome inhibitors, immunomodulatory drugs, hematologic toxicities, gastrointestinal disturbances.

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Abbreviations
ASCT = autologous stem cell transplantation;
BTZ = Bortezomib;
CiPN = chemotherapy-induced peripheral neuropathy;
CR = complete response;
DKd = Daratumumab-Carfilzomib-Dexamethasone;
DPd = Daratumumab-Pomalidomide-Dexamethasone;
DRd = Daratumumab-Lenalidomide-Dexamethasone;
DRG = dorsal root ganglia;
DVd = Daratumumab-Bortezomib-Dexamethasone;
EPd = Elotuzumab-Pomalidomide-Dexamethasone;
IMiD = immunomodulatory drug;
IRd = Ixazomib-Lenalidomide-Dexamethasone;
Isa-Kd = Isatuximab-carfilzomib-Dexamethasone;
Isa-Pd = Isatuximab-Pomalidomide-Dexamethasone;
KCd = Carfilzomib- Cyclophosphamide-Dexamethasone;
KPd = Carfilzomib-Pomalidomide-Dexamethasone;
KRd = Carfilzomib-Lenalidomide-Dexamethasone;
MCL = Mantle Cell Lymphoma;
MM = Multiple myeloma;
NCCN = National Comprehensive Cancer Network;
NCI-CTC = Cancer Institute's Common Terminology Criteria;
NDMM = newly diagnosed multiple myeloma;
OS = overall survival;
PFS = progression-free survival;
PN = Peripheral neuropathy;
RMM = refractory multiple myeloma;
SNPs = single nucleotide polymorphisms;
TD = thalidomide-dexamethasone;
TNS = Total Neuropathy Score;
VCd = Bortezomib- Cyclophosphamide-Dexamethasone;
VRd = Bortezomib-Lenalidomide-Dexamethasone;
VTd = Bortezomib-Thalidomide-Dexamethasone

INTRODUCTION

Multiple myeloma (MM) is a type of cancer originating from plasma cells, a form of B-lymphocytes, and is marked by symptoms such as anemia, elevated calcium levels, kidney issues, bone damage, and weakened immune defense. This malignancy results from the unchecked growth of abnormal plasma cells within the bone marrow.[1] Multiple myeloma ranks as the second most frequently diagnosed blood cancer, making up around 10% of hematologic malignancies in the United States.[3] Although its occurrence is comparatively lower in Korea, the incidence has grown notably over the past thirty years.[2] Data from the 2012 Korean National Cancer Statistics show that the age-adjusted incidence rate of MM had increased nearly tenfold compared to two decades prior. This trend has been linked to factors such as population aging, environmental influences, and enhanced detection due to broader health insurance coverage, improved healthcare provider education, and greater public awareness.[3]

Over the years, treatment strategies for multiple myeloma (MM) have seen remarkable progress. In the 1980s, therapy primarily relied on alkylating agents combined with steroids and anthracyclines [4], followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). The emergence of targeted therapies significantly changed the treatment landscape. Proteasome inhibitors, including bortezomib, carfilzomib, and ixazomib, along with immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide, have greatly improved outcomes,[5] especially in patients with relapsed or resistant disease. Incorporating these agents into first-line treatment regimens has resulted in better response rates and

extended survival.[6] Furthermore, ongoing clinical research is evaluating new drug combinations to enhance treatment efficacy. The integration of monoclonal antibodies and histone deacetylase inhibitors in recent years has further strengthened therapeutic options, providing more durable and profound responses in MM management.[7]

This review focuses on assessing the effectiveness, safety profile, and clinical relevance of bortezomib in managing multiple myeloma. It examines how bortezomib works at the molecular level, particularly its role in inhibiting proteasome activity, which leads to the accumulation of misfolded proteins and triggers apoptosis in cancerous plasma cells. The discussion also highlights its integration into combination regimens with immunomodulatory drugs, corticosteroids such as dexamethasone, and other emerging agents to enhance therapeutic responses. Additionally, the review addresses potential side effects associated with bortezomib, including peripheral neuropathy and gastrointestinal issues, and underscores the importance of dose modifications to minimize toxicity. Attention is also given to determining the most effective sequence of treatment to achieve better clinical outcomes and prolong remission in patients with multiple myeloma.

METHODS

A comprehensive and systematic literature search was performed using PubMed and Cochrane databases to identify relevant studies on the applications of bortezomib. The search was inclusive of all publications up to May 2025, without restriction by publication year, to ensure a thorough review of research on bortezomib. Studies focusing on multiple myeloma (MM) and the efficacy of bortezomib were prioritized. A broad set of keywords was employed, including "Bortezomib," "Multiple Myeloma," "Dexamethasone," "Thalidomide," "Lenalidomide," "Pomalidomide," "Cancer," "Chemotherapy," "Targeted Agents," and "Proteasome Inhibitor," reflecting the diverse applications of bortezomib in MM treatment. The search strategy was designed to capture a wide range of relevant studies.[8,9] Ultimately, 77 studies were identified and meticulously analyzed to refine the search results (as shown in Figure 1).

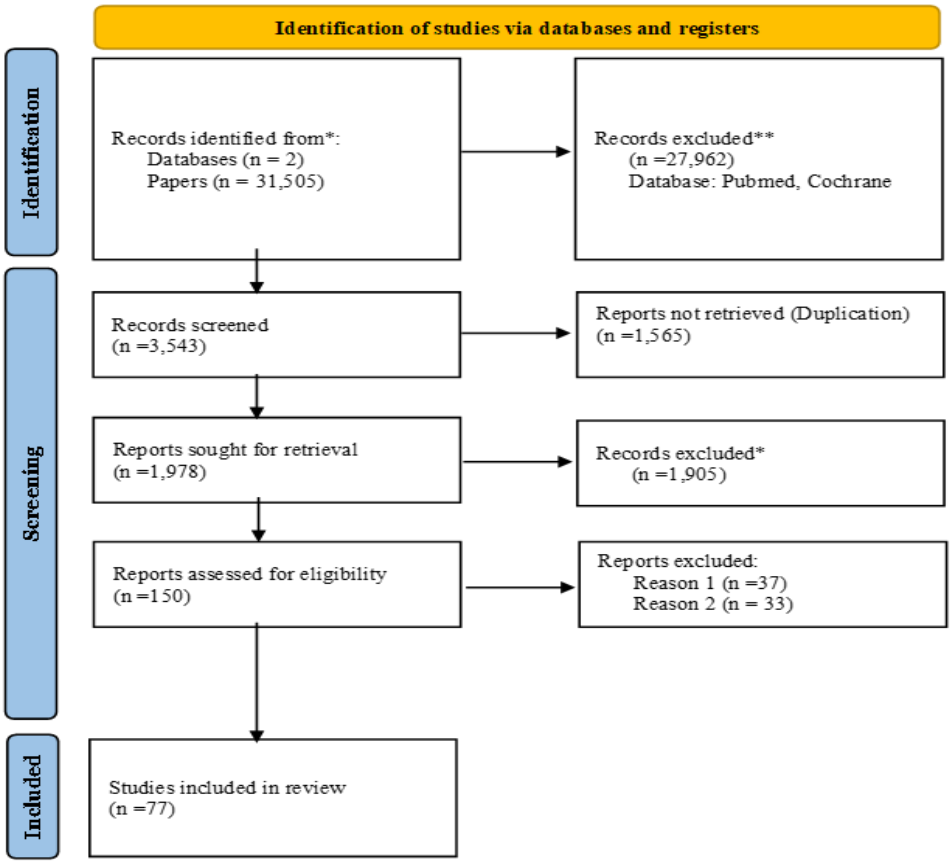

Figure 1. PRISMA flow diagram of the studies selection process

The selected articles were reviewed to identify key findings related to the mechanism of action of bortezomib, combination regimens with immunomodulatory drugs, corticosteroids like dexamethasone, and other emerging agents, potential side effects and the sequence of treatment to achieve better clinical outcomes.

Bortezomib mechanism of action

Bortezomib is a pioneering therapeutic agent known for its reversible and selective inhibition of the proteasome, particularly affecting the ubiquitin-proteasome system responsible for intracellular protein degradation. Initially granted FDA approval in 2003 for treating relapsed or refractory multiple myeloma (MM), its clinical use was later extended to include newly diagnosed MM cases.[1,2] By 2006, bortezomib was also approved for patients with relapsed or refractory mantle cell lymphoma (MCL), with further approval in 2014 for untreated MCL cases. Over time, it has been extensively studied for its potential both as a standalone treatment and in combination with other drugs, especially for hematologic cancers such as MM. Nevertheless, data regarding its impact on solid tumors remains limited.[5]

Mechanistically, bortezomib impairs the proteasome, which is a critical component in protein homeostasis and cellular regulation by binding reversibly to the chymotrypsin-like site of the 26S proteasome (Figure 2). This inhibition disrupts the breakdown of pro-apoptotic proteins, leading to their accumulation within cells. The resulting buildup activates caspase-mediated apoptotic pathways, ultimately promoting cell death, especially in malignant cells that typically evade apoptosis to sustain unchecked growth. [6]

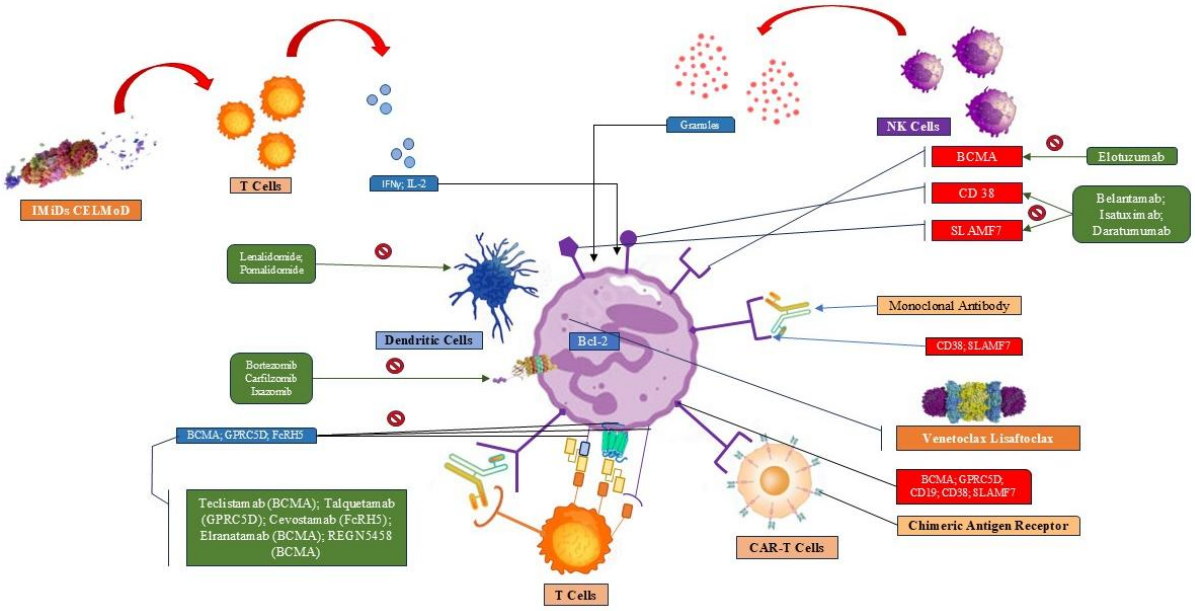

Figure 2: Recent advancements in multiple myeloma (MM) therapy have transformed treatment by focusing on targeted molecular mechanisms and immune modulation. Proteasome inhibitors such as bortezomib and carfilzomib disrupt protein degradation, causing toxic buildup in MM cells and promoting cell death. Immunomodulatory drugs such as lenalidomide and pomalidomide enhance immune responses by stimulating T and NK cells and suppressing inflammatory signals. Monoclonal antibodies, including daratumumab and elotuzumab, bind to MM-specific markers such as CD38 and SLAMF7, triggering immune-mediated cytotoxicity. Innovative therapies such as CAR T-cell treatments reengineer a patient's T cells to recognize myeloma-specific antigens such as BCMA, offering personalized and potent anti-tumor effects. Targeted therapies now focus on intracellular signaling pathways, including PI3K/AKT/mTOR and Bcl-2, as well as proteins such as XPO1 and HDACs, to induce apoptosis and inhibit proliferation. Emerging strategies also include bispecific antibodies such as teclistamab and elranatamab, which simultaneously bind MM cells and immune cells to direct a focused immune attack. Other novel targets include GPRC5D and FcRH5, offering new therapeutic avenues. These approaches reflect a move toward precision medicine, aiming to improve outcomes through more specific, less toxic, and individualized treatments.

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Bortezomib in combination therapy Dexamethasone

Initial phase II studies, such as the SUMMIT and CREST trials, assessed the use of bortezomib in patients with relapsed or refractory multiple myeloma (RRMM).[10] These investigations highlighted enhanced effectiveness when bortezomib was administered alongside dexamethasone, aligning with earlier laboratory findings that suggested a synergistic interaction between proteasome inhibitors and corticosteroids. As a result, this combination has gradually replaced the use of bortezomib alone. The National Comprehensive Cancer Network (NCCN) in the United States currently lists the bortezomib-dexamethasone regimen as a category 1 recommendation for RRMM treatment, based on strong clinical evidence, even in the absence of phase III trial confirmation. Dimopoulos and colleagues [11] performed a retrospective matched-pair analysis comparing this combination to bortezomib alone as a second-line therapy. The study reported a significantly better response rate (75% vs. 41%) and a longer median time to disease progression (13.6 months vs. 7 months) with the combination treatment. Although triple-drug regimens are increasingly preferred due to their improved efficacy, the two-drug bortezomib-dexamethasone option remains important, especially for patients unable to undergo more aggressive treatment strategies.

Immunomodulatory drugs

Triplet therapies have become a cornerstone in the management of both newly diagnosed and relapsed/refractory multiple myeloma. These regimens typically consist of a proteasome inhibitor, an immunomodulatory agent such as thalidomide, lenalidomide, or pomalidomide, along with the corticosteroid dexamethasone. [12] The rationale behind this approach lies in the synergistic action of the three components, each targeting different aspects of myeloma cell survival and proliferation. This strategy enhances treatment efficacy while allowing adaptability based on patient-specific factors, disease stage, and prior responses, thus supporting personalized treatment plans.[13]

A pivotal phase III study in Italy (BO-2005 trial) demonstrated that the combination of bortezomib, thalidomide, and dexamethasone (VTD) significantly outperformed the thalidomide-dexamethasone (TD) regimen,[14] particularly in patients undergoing double autologous stem cell transplantation. The trial showed improved very good partial response (VGPR) rates—62% post-induction and 89% post-transplant—and extended progression-free survival (PFS). These outcomes were reinforced by similar success with a carfilzomib-thalidomide-dexamethasone regimen in a European Myeloma Network phase II study.[15] Simultaneously, lenalidomide-based triplets (RVD: lenalidomide, bortezomib, dexamethasone) have shown exceptional results. One phase II study recorded a 100% response rate, with 67% achieving at least a VGPR. The SWOG S0777 and IFM2009 trials confirmed that RVD improves survival outcomes over the lenalidomide-dexamethasone (Rd) doublet, especially when paired with autologous stem cell transplants, highlighting its role as a preferred frontline therapy.[16]

Conventional chemotherapy (alkylating agents/doxorubicin)

The therapeutic benefits of proteasome inhibitors in treating multiple myeloma are significantly enhanced when used alongside conventional chemotherapeutic agents such as alkylating agents and anthracyclines, which were previously the cornerstone of treatment.[17] Historically, the combination of melphalan and prednisone (MP) served as the primary frontline therapy for patients who were not suitable candidates for transplantation. Clinical evaluations have since explored the incorporation of the three approved proteasome inhibitors into the MP regimen. In particular, the effectiveness of the bortezomib-melphalan-prednisone (VMP) combination has been validated by multiple phase III clinical trials.[18,19] One of the most influential among these was the VISTA trial,[20] which directly compared VMP against MP alone. The results supported the approval of bortezomib for use in initial therapy, as its addition led to markedly higher response rates, including a greater number of complete responses, and

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yielded improved long-term patient outcomes. Extended follow-up data from the trial revealed that the VMP group had a median overall survival of 56.4 months, compared to 43.1 months for the MP group. These outcomes highlight the value of introducing potent therapies early in the treatment process rather than delaying their use until after relapse.

Novel targeted agents

The therapeutic management of multiple myeloma frequently relies on a combination of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), particularly bortezomib. These drug classes serve as the foundation for commonly used doublet and triplet treatment protocols. In current clinical research, they are often combined with novel or investigational targeted agents for both newly diagnosed multiple myeloma (NDMM) and relapsed/refractory multiple myeloma (RRMM).[20]

The phase III CASTOR study investigated the addition of daratumumab to the standard regimen of bortezomib and dexamethasone (Vd, a standard of care and a platform for several triplet regimens) in patients with RRMM, who had typically undergone two previous treatments. The daratumumab-based combination significantly enhanced therapeutic outcomes, with at least a very good partial response (VGPR) observed in 59% of participants, compared to just 29% in the control group receiving Vd alone (Table 1). Progression-free survival (PFS) was also significantly extended in the daratumumab arm, with the median not reached versus 7.2 months in the control group.[21]

Similarly, the PANORAMA1 phase III trial assessed the integration of panobinostat, a histone deacetylase inhibitor, with Vd in RRMM treatment. Results showed notable improvements, including a higher rate of complete or near-complete responses (28% compared to 16%) and an increase in median PFS to 11.99 months versus 8.08 months. Importantly, in patients who had previously been treated with both a PI and an IMiD, the median PFS extended to 12.5 months, as opposed to 4.78 months with Vd alone. Consequently, panobinostat has been approved for use with Vd in RRMM patients previously treated with both drug classes.[22]

While these advancements are promising, the number of large-scale phase III trials focused on new PI-based combinations remains relatively small. However, this gap is being addressed through ongoing research. For example, the Cassiopeia trial (NCT02541383) is evaluating daratumumab in conjunction with VTD (bortezomib, thalidomide, dexamethasone) for transplant-eligible NDMM patients (Table 1), both during induction and consolidation phases. Meanwhile, the Alcyone trial (NCT02195479) is testing daratumumab with VMP (bortezomib, melphalan, prednisone) in patients who are not eligible for transplant.[23]

In addition to currently approved drugs, novel agents are also being examined within the Vd treatment framework. The BOSTON trial (NCT03110562) is exploring selinexor, a selective inhibitor of nuclear export, when combined with Vd in RRMM. [24] Likewise, the Bcl-2 inhibitor venetoclax is under phase III investigation (NCT02755597) in combination with Vd. Early-stage studies are also underway to assess new histone deacetylase inhibitors such as vorinostat and ricolinostat in similar regimens.

Moreover, a phase II clinical study led by Jakubowiak et al. (NCT01478048) examined the effectiveness and safety of combining elotuzumab with Vd (EVd) in RRMM patients. This trial reported a longer median PFS of 9.7 months for the EVd group versus 6.9 months for those on Vd alone, along with a modest improvement in overall response rate (66% compared to 63%), without a notable increase in adverse effects. [25] A previous study by Richardson et al. obtained similar results with the drug lenalidomide in combination with Vd.[26]

Sequencing of proteasome inhibitor therapy

With the approval of three proteasome inhibitors for the treatment of multiple myeloma, optimizing the sequence in which these agents are administered has become a critical consideration in patient management. While the most effective order of administration is still under investigation, existing research indicates that prior treatment with one proteasome inhibitor may lessen the efficacy of subsequent agents within the same drug class. This trend mirrors earlier findings involving retreatment with bortezomib, where reduced therapeutic response was observed.[27]

Results from major clinical trials have shown that previous treatment with bortezomib can influence the effectiveness of subsequent therapies in relapsed or refractory multiple myeloma. The phase 3 ENDEAVOR trial

demonstrated that patients previously exposed to bortezomib had shorter median progression-free survival (PFS) when receiving either carfilzomib with dexamethasone (Kd) or bortezomib with dexamethasone (Vd). [28] Nonetheless, Kd showed superior clinical benefits over Vd, regardless of prior bortezomib use (Table 1). In the ASPIRE trial, the combination of carfilzomib, lenalidomide, and dexamethasone (KRd) was compared with lenalidomide and dexamethasone (Rd) (Table 1). In patients without earlier bortezomib exposure, KRd extended median PFS to 30.3 months, compared to 18.2 months for Rd. Among those with previous bortezomib treatment, KRd still offered better outcomes, though with a reduced median PFS of 24.4 months versus 16.6 months for Rd.[29] These data underline the importance of treatment history in determining future therapeutic success and support the need for research into optimal sequencing of proteasome inhibitors as myeloma care shifts toward continuous, personalized treatment models.[30]

Safety and adverse effects

Proteasome inhibitors, particularly bortezomib, have proven highly effective in managing multiple myeloma; however, their use is often associated with notable side effects. [31] Clinical studies such as SUMMIT and CREST have highlighted common adverse reactions, including fatigue, nausea, diarrhea, thrombocytopenia, loss of appetite, peripheral neuropathy, vomiting, fever, anemia, limb swelling, and shortness of breath. These effects are generally mild to moderate in severity and rarely require stopping treatment.[32] However, in the case of severe toxicities such as grade 3 or higher for non-hematological issues and grade 4 for hematological complications, the treatment should be temporarily halted until symptoms improve, after which a reduced dose may be reintroduced. While gastrointestinal issues and fatigue are frequent, nerve damage and low platelet counts are the most critical factors limiting dosage.[33] Insights from the VISTA trial also led to a modification in the dosing schedule, shifting from twice-weekly to once-weekly administration. This adjustment helped minimize toxic effects and improved patient compliance with therapy. Overall, careful management of adverse effects is essential to maintaining the effectiveness of bortezomib while ensuring patient safety.[34]

Table 1. Major treatment regimens in multiple myeloma [62-76]

Regimen	Drug	Dose	Route	Schedule	Cycle
NTA	Bortezomib	1.3 mg/m²	SC	Days 1, 8, 15, 22	Every 4 weeks
	Thalidomide	100–200 mg	Oral	Days 1–21	–
	Dexamethasone	20–40 mg	Oral	With/after bortezomib	–
VCd / CyBord	Cyclophosphamide	300 mg/m²	Oral	Days 1, 8, 15, 22	Every 4 weeks
	Bortezomib	1.3 mg/m²	SC	Days 1, 8, 15, 22	–
	Dexamethasone	40 mg	Oral	Days 1, 8, 15, 22	–
VRd	Bortezomib	1.3 mg/m²	SC	Days 1, 8, 15	Every 4 weeks
	Lenalidomide	25 mg	Oral	Days 1–14	–
	Dexamethasone	20–40 mg	Oral	Days 1, 8, 15, 22 or with bortezomib	–
KCd	Carfilzomib	20–27 mg/m²	IV	Days 1, 2, then 1, 2, 8, 9, 15, 16	Every 4 weeks
	Cyclophosphamide	300 mg/m²	Oral	Days 1, 8, 15	–
	Dexamethasone	40 mg	Oral	Days 1, 8, 15, 22	–
KRd	Carfilzomib	20–27 mg/m²	IV	Days 1, 2, 8, 9, 15, 16	Every 4 weeks
	Lenalidomide	25 mg	Oral	Days 1–21	–
	Dexamethasone	40 mg	Oral	Days 1, 8, 15, 22	–
KPd	Carfilzomib	20–27 mg/m²	IV	Days 1, 2, 8, 9, 15, 16	Every 4 weeks
	Pomalidomide	4 mg	Oral	Days 1–21	–
	Dexamethasone	40 mg	Oral	Days 1, 8, 15, 22	–
DRd	Daratumumab	16 mg/kg	IV	Weekly ×8, biweekly ×4, then monthly	Every 4 weeks
	Lenalidomide	25 mg	Oral	Days 1–21	–
	Dexamethasone	40 mg	IV	Days 1, 8, 15, 22	–
DVd	Daratumumab	16 mg/kg	IV	Same as DRd	Every 4 weeks
	Bortezomib	1.3 mg/m²	SC	Days 1, 8, 15, 22	–
	Dexamethasone	40 mg	IV/Oral	IV on Dara days, oral otherwise	–
DPd	Daratumumab	16 mg/kg	IV	Weekly ×8, biweekly ×4, then monthly	Every 4 weeks
	Pomalidomide	4 mg	Oral	Days 1–21	–
	Dexamethasone	40 mg	IV	Days 1, 8, 15, 22	–
DKa	Daratumumab	1500 mg	SC	Weekly ×4, biweekly ×4, then monthly	Every 4 weeks
	Carfilzomib	20–56–70 mg/m²	IV	Days 1, 8, 15	–
	Dexamethasone	40 mg	IV/Oral	Days 1, 8, 15, 22	–
IRd	Ixazomib	4 mg	Oral	Days 1, 8, 15	Every 4 weeks
	Lenalidomide	25 mg	Oral	Days 1–21	–
	Dexamethasone	40 mg	Oral	Days 1, 8, 15, 22	–
EPd	Elotuzumab	10–20 mg/kg	IV	Weekly ×8, then monthly	Every 4 weeks
	Pomalidomide	4 mg	Oral	Days 1–21	–
	Dexamethasone	As per protocol	IV/Oral	As per protocol	–
Isa-Pd	Isatuximab	10 mg/kg	IV	Weekly ×4, then biweekly	Every 4 weeks
	Pomalidomide	4 mg	Oral	Days 1–21	–
	Dexamethasone	As per protocol	IV/Oral	As per protocol	–
Isa-Kd	Isatuximab	10 mg/kg	IV	Weekly ×4, then biweekly	Every 4 weeks
	Carfilzomib	20–56–70 mg/m²	IV	Days 1, 8, 15	–
	Dexamethasone	40 mg	IV/Oral	Days 1, 8, 15, 22	–

Peripheral neuropathy

Peripheral neuropathy (PN) is a frequent and often debilitating consequence experienced by individuals with multiple myeloma (MM), whether as a direct manifestation of the disease or more commonly as a side effect of treatment. [35] It significantly diminishes patients' quality of life and functional independence. This disorder may occur due to the pathological effects of monoclonal proteins or spinal involvement but is more typically induced by neurotoxic agents used during therapy. Medications such as bortezomib, thalidomide, vinca alkaloids, and cisplatin are well-known contributors (Figure 2).[36]

Approximately 20% of MM patients present with PN at the time of diagnosis, while nearly three-quarters are likely to develop it during the course of treatment.[37] Clinical manifestations include altered sensory perception, ranging from heightened or reduced sensitivity, tingling sensations, burning pain, to motor symptoms such as muscle weakness.[38] These symptoms usually begin in the hands and feet and may progress proximally.[39]

For evaluating PN, the National Cancer Institute's Common Terminology Criteria (NCI-CTC) is commonly used. However, pairing it with patient-reported outcomes—such as the FACT/GOG-Ntx,[25] total neuropathy score (TNS), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20-item scale (EORTC CIPN20), and chemotherapy-induced peripheral neuropathy outcome measures (CI-PERINOMS), offers a more comprehensive assessment. Nonetheless, these tools were not tailored specifically for MM populations, indicating a need for more accurate, disease-specific instruments for patient evaluation.[40]

Bortezomib, a key agent in MM therapy, works by reversibly inhibiting the 26S proteasome, thereby interrupting protein degradation (Figure 2). Preclinical research suggests that the accumulation of undegraded proteins within dorsal root ganglion (DRG) cells may underlie its neurotoxic effects.[41] Though the precise mechanisms remain elusive, inflammatory pathways are suspected to play a role. In support of this, genetic studies such as those from the HOVON consortium, have identified inflammation-related genetic variants associated with increased susceptibility to bortezomib-induced PN.[42] Interestingly, pre-existing conditions like diabetes or previous neurotoxic exposures (e.g., to thalidomide or vincristine) have not been consistently linked to increased risk (Figure 2). Regular neurological evaluations during therapy are therefore encouraged to facilitate early detection and management.[43]

Data from pivotal Phase III clinical trials further underscore the significance of this issue. The APEX trial reported PN in 37% of patients (with 9% experiencing grade 3 or higher), while the VISTA trial observed a 47% incidence (13% grade >3). The development of grade I PN with pain or grade II bortezomib-induced neuropathy (BiPN) often prompts clinicians to intervene. Strategies such as dose reduction and the shift to subcutaneous administration have proven effective in minimizing neurotoxic effects without reducing treatment efficacy. Notably, BiPN does not seem to adversely affect therapeutic response or overall survival.[44]

Effective management of PN involves adherence to established dose-modification guidelines such as those outlined in the APEX study as well as supportive measures like physical rehabilitation and exercise to maintain muscle function.[45] Although many pharmacologic interventions for symptom control are extrapolated from data on chemotherapy-induced peripheral neuropathy (CiPN), specific research focused on MM-related PN is limited. Agents such as gabapentin, pregabalin, and duloxetine, along with nutraceuticals including acetyl-L-carnitine and alpha-lipoic acid, have shown promise. Additionally, topical treatments such as combinations of baclofen, amitriptyline, ketamine, or menthol-based creams that may provide localized relief.[46] However, the current treatment landscape remains largely empirical due to the lack of controlled trials specific to MM populations.[47]

Hematological adverse events

Hematologic toxicities have been frequently observed during early phase III clinical trials of bortezomib. For instance, the APEX phase III trial reported a higher incidence of thrombocytopenia in patients receiving bortezomib compared to those treated with dexamethasone (35% vs. 11%; grade 3/4: 26%/4% vs. 5%/1%). Neutropenia also appeared more commonly with bortezomib (19% vs. 2%; grade 3/4: 12%/2% vs. 1%), whereas anemia was less prevalent, with grade ≥3 events occurring in only 9% of cases as noted in the SUMMIT and CREST phase II studies.[48] Thrombocytopenia is often linked to initial platelet counts, which may reflect the extent of

bone marrow infiltration by plasma cells or prior exposure to myelosuppressive treatment. Grade 4 thrombocytopenia tends to be confined to individuals with baseline platelet counts below 70,000/mm³ and is generally transient, resolving between treatment cycles.[49] Bortezomib might interfere with platelet formation by affecting NF-κB-mediated maturation of megakaryocytes. Therefore, regular monitoring of complete blood counts is essential, especially before initiating the first two treatment cycles, and thereafter based on clinical judgment.[49] If platelet levels drop under 30,000/mm³, a temporary halt in treatment is advised, while a 25% dose reduction should be considered only when hematologic adverse effects lead to missed doses in at least half of a cycle. Despite the increased frequency of thrombocytopenia, serious bleeding or therapy discontinuation due to bleeding complications remains relatively rare.[50]

Gastrointestinal adverse events

Gastrointestinal (GI) complications are common in patients receiving bortezomib therapy, with symptoms such as nausea, vomiting, diarrhea, and constipation frequently reported. Findings from the phase III VISTA trial, which evaluated a treatment regimen combining bortezomib, melphalan, and prednisone (VMP) in newly diagnosed multiple myeloma (NDMM) patients, demonstrated a higher occurrence of GI side effects in the VMP group compared to those treated with melphalan and prednisone (MP) alone. (51) Incidences included nausea in 48% of VMP patients versus 28% in the MP group, diarrhea in 46% versus 17%, constipation in 37% versus 16%, and vomiting in 33% compared to 16%. These gastrointestinal effects typically arise during the first one or two treatment cycles and are generally mild to moderate in severity.

Management of these adverse effects involves the use of antiemetics for nausea and vomiting, antidiarrheal medications such as loperamide or diphenoxylate-atropine for diarrhea, and agents such as stool softeners or laxatives to alleviate constipation. In less severe cases of diarrhea, dietary modifications may be effective, while probiotics or somatostatin analogs may be needed for more persistent or severe cases. In situations where diarrhea is linked to bile acid malabsorption, colesevelam can be beneficial. Patients should also be encouraged to stay well-hydrated and avoid caffeinated beverages.[52]

Importantly, GI toxicity tends to be more pronounced with newer oral proteasome inhibitors such as ixazomib and oprozomib, which often limits their dosing potential. While the exact pathophysiological mechanisms behind bortezomib-induced GI symptoms are still being explored, autonomic neuropathy is believed to contribute to these effects.[53]

Cardiovascular toxicity

Bortezomib and carfilzomib, two proteasome inhibitors used in the treatment of multiple myeloma, have been linked to a range of cardiovascular side effects. Both drugs include warnings regarding potential cardiac toxicity in their official U.S. prescribing information. (54) A retrospective analysis of data from 3,954 patients enrolled in phase 2 and 3 clinical trials of bortezomib assessed its cardiovascular safety profile. Findings showed relatively low occurrences of arrhythmias (ranging from 1.3–5.9% for grade >2 and 0.6–4.1% for grade >3), ischemic heart conditions (1.2–2.9% across all grades and 0.4–2.7% for grade >3), and cardiac-related deaths (0–1.4%). Notably, these rates did not significantly differ between regimens including bortezomib and those without it. However, some investigations, such as pooled analyses of transplant-related studies, did observe higher rates of low-grade edema (grade 1/2) in patients receiving bortezomib. Comparative trial data using logistic regression analysis further supported that bortezomib-based regimens do not elevate cardiac risk relative to non-bortezomib therapies.[55]

In the phase III ENDEAVOR trial, individuals with relapsed or refractory multiple myeloma who received a combination of carfilzomib, bortezomib, and dexamethasone showed a higher occurrence of adverse cardiovascular effects compared to those treated with only bortezomib and dexamethasone. Specifically, increased rates of shortness of breath (28% vs. 13%), elevated blood pressure (25% vs. 9%), and heart failure (8% vs. 3%) were observed in the carfilzomib group.[57] Additionally, a prospective study involving 62 patients treated with carfilzomib indicated a potential link between cardiovascular side effects and endothelial dysfunction.[58] Emerging research suggests that cardiotoxicity might not be limited to a single agent but could be a broader concern across the proteasome inhibitor drug class.[56]

Another important adverse effect associated with bortezomib is hypotension, particularly in patients who have a history of fainting, are on antihypertensive medications, or are dehydrated.

To mitigate this risk, it is crucial to evaluate the patient's hydration status before and during therapy, especially in the presence of gastrointestinal symptoms such as nausea or vomiting. For individuals on blood pressure medications, careful monitoring and potential dosage adjustments are recommended. In certain cases, the use of mineralocorticoids has been beneficial in managing bortezomib-induced hypotension. If a patient develops grade 3 hypotension, treatment with bortezomib should be paused until symptoms resolve, after which therapy can be resumed at a reduced dose, typically 25% lower.[57]

Other notable toxicities

Clinical trial data have revealed specific side effects linked to multiple myeloma treatments. In the APEX Phase III trial, which studied patients with relapsed or refractory multiple myeloma, a significantly higher rate of herpes zoster virus reactivation of 13% was observed among those receiving bortezomib, as compared to just 5% in the dexamethasone group ($p<0.001$). To reduce this risk, the use of antiviral medications such as acyclovir or famciclovir has proven effective. As a result, prophylactic antiviral therapy is now commonly recommended for patients undergoing treatment with bortezomib to prevent viral reactivation.[58]

Dose modifications due to adverse effects

In the management of multiple myeloma, bortezomib is commonly administered at a dose of 1.3 mg/m² through a rapid intravenous injection, typically lasting between 3 to 5 seconds. The standard schedule involves two doses per week for two consecutive weeks, with a minimum 72-hour interval between doses to help healthy cells restore proteasome function.[59] This dosing pattern includes administration on days 1, 4, 8, and 11, completing one treatment cycle, which is then followed by a 10-day break (days 12 to 21) without medication.[60] Adjustments in dosage are advised if patients experience peripheral neuropathy, severe non-hematologic adverse effects (grade 3), or significant hematologic toxicities (grade 4). Clinical findings show that around 9–16% of patients discontinued therapy due to side effects, demonstrating that the treatment is generally well-tolerated for long-term use.[61]

CONCLUSION

Bortezomib, recognized as the first proteasome inhibitor approved for both newly diagnosed and relapsed multiple myeloma, has become a central component of therapeutic strategies for this disease. Current clinical trends increasingly support the use of triplet therapies such as those combining bortezomib with thalidomide or lenalidomide and also highlight the continued efficacy of doublet regimens such as bortezomib with dexamethasone. These modern combinations are gradually replacing older treatment approaches, contributing to notable improvements in both progression-free survival (PFS) and overall survival (OS) rates.

Initially, the adoption of proteasome inhibitor-based regimens raised concerns due to their potential for cumulative toxicity. Surprisingly, when bortezomib is used in combination with another neurotoxic agent like thalidomide, the overall toxicity profile appears to be reduced. This is possibly attributed to thalidomide's anti-inflammatory actions, which may counteract the neurotoxic effects of bortezomib.

Despite its efficacy, bortezomib is not without safety concerns. Patients may experience serious side effects such as severe diarrhea and blood-related complications, including thrombocytopenia and lymphocytopenia. Chronic diarrhea is often resulting from infections, malabsorption syndromes, or autonomic neuropathy and can greatly affect patient well-being. Therefore, close observation of clinical symptoms and laboratory findings is crucial to maintain effective and sustained therapy. For specific details related to the administration of bortezomib therapy, the authors suggest that clinicians refer to the protocols used in the major trials and to the product monograph. Most toxicities are reversible if dose modification guidelines are followed.

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Conflict of Interest

None

Author Contributions

NS, MNI, SC, MCJ: Supervised the data collection process, and checked writing, approved methodology, manuscript editing, and supervised all steps, including final editing; HI, RAM, SA: Researched literature, web-survey design, coordinated and monitored the data collection process with collaborators, wrote the first draft of the manuscript; PR, FA: Paper revision; HHA: Interpreted data, checked writing; MSR: Manuscript editing; RAM, SA, MSR: Final editing, reviewing, and supervising the steps. All authors have read and approved the final manuscript.

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