

A Review on Impact of Diet and Lifestyle Modifications on Treatment Outcomes in Multiple Myeloma

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Abstract:

This study examines the safety, tolerability, and efficacy of anticancer drugs in the treatment of multiple myeloma, a malignancy of plasma cells characterized by overproduction of monoclonal proteins that damage bones and organs. The disease remains largely incurable despite advances in treatment, necessitating ongoing evaluation of therapeutic approaches. This review focuses on the role of key medications like bortezomib, lenalidomide, and daratumumab, highlighting their mechanisms, clinical efficacy, and associated adverse effects. Bortezomib, a proteasome inhibitor, has shown significant efficacy in both newly diagnosed and relapsed/refractory cases, particularly in combination regimens. However, it is associated with adverse effects such as peripheral neuropathy and hematologic and gastrointestinal toxicities, which require careful management. Strategies such as optimized dosing and subcutaneous administration have improved its safety profile. Future directions include enhancing therapeutic outcomes through personalized medicine, combination regimens, and mitigating resistance. This research underscores the critical need for tailored treatment strategies to improve patient survival and quality of life in multiple myeloma.

Keywords:

BiPN – Bortezomib-induced Peripheral Neuropathy, RRMM –Relapsed and Refractory Multiple Myeloma, NDMM –Newly Diagnosed Multiple Myeloma, PN –Peripheral Neuropathy.

INTRODUCTION

Bone marrow contains plasma cells that are involved in the immune system; multiple myeloma is a malignancy of these cells. It is distinguished by the aberrant growth of these plasma cells, which results in an overabundance of monoclonal proteins that may harm bones and organs. Usually, the disease advances from previous stages like smoldering myeloma and monoclonal gammopathy of unknown significance (MGUS), which might not need therapy right away. Multiple myeloma is still mostly incurable, despite improvements in treatment, which highlights the need of early detection and efficient management techniques.

Optimizing treatment plans and enhancing patient outcomes require a thorough understanding of the safety, tolerability, and effectiveness of medications used to treat multiple myeloma. While tolerability has an impact on patient compliance and quality of life, safety makes sure that patients are not exposed to dangerous side effects that can outweigh the advantages. How well a medication slows the progression of the disease and increases survival rates is determined by its efficacy. For improved illness management, thorough evaluation aids in directing clinical judgments and customizing therapy regimens.[1]

Several important medications are utilized in the treatment of multiple myeloma in order to manage the condition and enhance patient outcomes. Protease inhibitors like bortezomib are frequently used to stop myeloma cells' proteins from breaking down, which helps stop tumor growth.[2] Lenalidomide is an immunomodulatory medication that slows the growth of tumors by enhancing immune function and inhibiting angiogenesis.. A monoclonal antibody called daratumumab, which targets CD38, works well for both relapsed and refractory myeloma another proteasome inhibitor called carfilzomib is used, especially in individuals with PMC who have experienced a recurrence. Additionally, because of its immunomodulatory properties, Thalidomide—despite being an older agent—remains a useful component of combination regimens. To optimize effectiveness and control the course of the disease, these treatments are frequently combined.[3,4]

DRUG USED FOR MANAGEMENT OF MULTIPLE MYELOMA:

Table 1.

S.N.	DRUG	TYPE	MECHANISM	USE
1.	Bortezomib	Proteasome inhibitor	Blocks proteasomes, leading to accumulation of proteins in cancer cells and inducing cell death.	First-line treatment for multiple myeloma.
2.	Lenalidomide	Immunomodulatory drug	Enhances the immune system's ability to fight cancer cells and inhibits their growth	Commonly used for initial treatment and maintenance therapy
3.	Daratumumab	Monoclonal antibody.	Targets CD38 protein on the surface of myeloma cells, leading to their destruction.	Effective for relapsed or refractory multiple myeloma

4.	Thalidomide	Immunomodulatory drug	Inhibits angiogenesis (blood vessel formation) and boosts immune response.	One of the earlier drugs used in multiple myeloma.
5.	Cyclophosphamide	Alkylating agent.	Cross-links DNA, leading to cell death.	Often part of combination regimens for multiple myeloma.

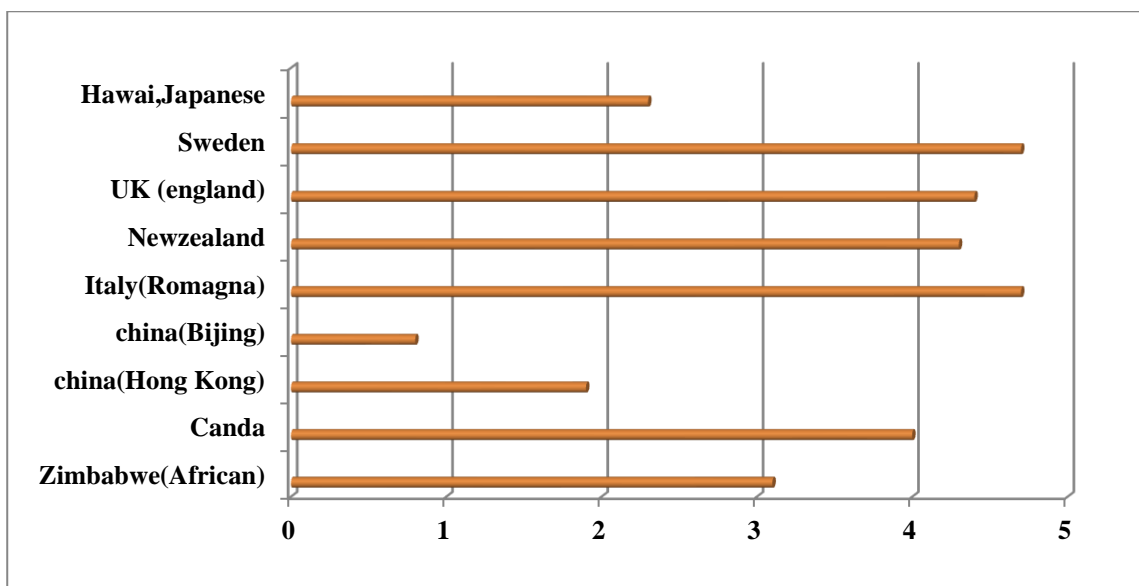
DISEASE: MULTIPLE MYELOMA

EPIDEMIOLOGY:

In 2002, multiple myeloma was responsible for approximately 0.8% of all cancer diagnoses and 0.9% of cancer-related deaths globally.[5] The reported incidence of multiple myeloma during 1993–1997 varies by country and ethnicity, as seen in Figures 1a and 1b. Incidence rates were higher among males than females, and highest among African Americans.[6] Incidence rates for white Americans, Canadians and in most European countries were generally similar. Rate rates in Asian countries and in Chinese populaces dwelling in Los Angeles District and Hawaii tended to be lower than rates in European and/or Caucasian populaces, with the special case of Israel.

Around 2% of cancer fatalities in the United States occur from multiple myeloma, making it the ninth most prevalent cause of cancer mortality for women and the fourteenth most common cause for men. Multiple myeloma is ranked 16th for females and 14th for males in the United States in terms of incidence.[7]

MULTIPLE MYELOMA IN MALES



Age – adjusted (world standard population) incidence rate per 100,000

FIGURE 1 – International and ethnic variability of reported multiple myeloma incidence [males] from 1993 to1997.Adapted from Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, Cancer Incidence in Five Continents, 2002, Vol. 8, Lyon: IARC.

American Cancer Society estimated that there would be 15,980 new cases of multiple myeloma diagnosed in the US in 2005 and 11,300 deaths, accounting for 15% of all LHC cases and 27% of all LHC deaths. The estimated US age-adjusted incidence rate is 5.6 per 100,000 person-years (py) overall, with higher rates in males than females (7.1 per 100,000 py) vs. (4.5 per 100,000 py),and a 2-fold excess in incidence rates in African Americans as compared to Caucasians (11.1 per 100,000 py)vs. (5.3 per 100,000 py). Overall US age-adjusted mortality rates are 3.8 per 100,000 py, and rates range from a high of 8.8 per 100,000 py for black males to 2.9 per 100,000 py for white females. [7, 15]

ETIOLOGY:

Although the precise origin of multiple myeloma is unknown, a mix of immune-related, environmental, and genetic variables are thought to be responsible. The following provides a thorough overview of the main causes of multiple myeloma:

1. GENETIC FACTOR-

i) Chromosomal abnormalities: Multiple myeloma is largely caused by genetic mutations and chromosomal abnormalities. Typical chromosomal alterations include:

- Chromosome 14 translocations involving the IgH region cause oncogenes such as MMSET, MAF, and CCND1 (Cyclin D1) to overexpress.
- The deletion of chromosome 13 is frequently linked to a bad prognosis.
- In hyperdiploid multiple myeloma, trisomies with odd-numbered chromosomes (such as 3, 5, 7, 9) are commonly observed.

ii) Gene mutations: The development of disease may be accelerated by point mutations in oncogenes and tumor suppressor genes, including NRAS, KRAS, and TP53.

iii) Familial predisposition: A tiny proportion of cases exhibit familial clustering, indicating a possible genetic vulnerability, despite the fact that this is uncommon.[3]

2. ENVIRONMENTAL FACTOR-

- Radiation energy: Multiple myeloma risk has been associated with a history of ionizing radiation exposure, such as in atomic bomb survivors.
- Chemical exposure: Multiple myeloma risk is believed to be increased by some pollutants, especially benzene and other petroleum compounds.
- Herbicides and pesticides: Multiple myeloma has been found to be more common in agricultural workers exposed to particular herbicides.
- Obesity: Chronic inflammation and immune system alterations linked to obesity may raise the risk of multiple myeloma.[10]

3. IMMUNE DISREGULATION-

- Chronic immune stimulation: Long-term immunological stimulation, like that seen in autoimmune disorders or persistent infections, may raise the risk of plasma cell cancer. Monoclonal plasma cells may proliferate as a result of prolonged antigenic stimulation.

- **Monoclonal Gammopathy of Undetermined Significance (MGUS):** A small number of aberrant plasma cells create a monoclonal protein in MGUS, a benign disease that precedes almost all cases of multiple myeloma.
 - **Immune Microenvironment:** Changes in the bone marrow microenvironment, such as interactions between immune cells and the production of cytokines (such IL-6), might encourage the survival and growth of cancerous plasma cells.[3,10]
4. **VIRAL INFECTION-**
- According to certain research, viral infections could be connected to multiple myeloma. For instance, although research has been done on Hepatitis C Virus (HCV) and Human Herpesvirus 8 (HHV-8), their precise function is still unknown.
 - Through persistent inflammation and immunological activation, chronic infections may indirectly cause myeloma.[11]

SAFETY, TOLERABILITY AND EFFICACY ASSESSMENT OF DRUG USED IN MANAGEMENT OF MULTIPLE MYELOMA:

Bortezomib-

A proteasome inhibitor called bortezomib is used to treat mantle cell lymphoma and multiple myeloma. It functions by blocking the 26S proteasome, which causes a buildup of proteins that kill cells, especially cancer cells. Bortezomib can be injected or applied topically. It has a virtually full bioavailability when used intravenously and a comparable level of effectiveness when applied topically, albeit with a slower rate of absorption. With a plasma protein binding rate of about 83%, mostly to albumin and α 1-acid glycoprotein, it has a high volume of distribution, suggesting extensive tissue distribution. The cytochrome P450 enzymes CYP3A4, CYP2C19, and CYP1A2 are the main enzymes responsible for the hepatic metabolism of bortezomib, and its metabolites have little pharmacological activity. Less than 1% of it is eliminated unaltered in the urine, and its elimination is biphasic, with an initial half-life of 10–17 hours and a terminal half-life of 40–193 hours. Although renal impairment usually has no effect on its clearance, hepatic impairment may require dosage changes because of its metabolism in the liver.[11]

1) Safety evaluation-

The various PI have been linked to a number of significant toxicities, either as a class effect of PI or as a particular side effect of a single agent, despite their exceptional effectiveness in treating MM.

Bortezomib's most frequent side effects include fatigue (65%), nausea (64%), diarrhea (51%), thrombocytopenia (43%), anorexia (43%), peripheral neuropathy (37%), vomiting (36%), pyrexia (36%), anemia (32%), peripheral edema (25%), and dyspnea (22%). The severe (grades 3 and 4) adverse effects noted in significant trials. The majority of side effects (grades 1 or 2) were mild to moderate in intensity and did not necessitate stopping or delaying bortezomib treatment. When \geq grade 3 non-hematologic toxicities or grade 4 hematologic toxicities occur, bortezomib should be stopped until the toxicity goes away and a lower dose can be used for retreatment.[13] The main dose-limiting toxicities of bortezomib are peripheral neuropathy (PN) and thrombocytopenia, despite the fact that fatigue and gastrointestinal issues are the most frequent side effects. Treatment discontinuation was a significant issue with the original VISTA regimen, which resulted in biweekly doses being administered once weekly and a drop in the rate of cessation.[14]

Info. Of Adverse effect and dose modification;

Type of Adverse effect	Dose modification required or not
Grade 1 (weakness, lack of reflexes) without discomfort or impairment.	No
Grade 1 with pain or grade 2 without pain.	Yes(25% reduction)
Grade 2 discomfort or grade 3 (difficulty with daily life tasks).	Give the drug until toxicity arised
Grade 4 (disabling sensory neuropathy or life-threatening motor neuropathy that causes paralysis).	Discontinue the drug

Table 02 ; : Dose Modifications for Patients with Adverse Events of Bortezomib**1.1) Peripheral Neuropathy –**

One of the most significant side effects of myeloma treatment is peripheral neuropathy, which impairs everyday activities and the quality of life for patients. The effects of the monoclonal protein or radiculopathy from direct compression, as well as specific treatments like bortezomib, thalidomide, Vinca alkaloids, and cisplatin, can all contribute to PN.

Phase III studies indicated a prevalence of peripheral sensory neuropathy, with the APEX study reporting a rate of 37% (9% > grade 3) and the VISTA study reporting a rate of 47% (13% ≥ grade 3). A 25% dose reduction is necessary for treatment of Grade I (painful) or Grade II BiPN, according to the Accepted Manuscript. Because of injury to tiny nerve fibers, PN can also be autonomic and manifest as orthostatic hypotension. PN typically develops after five 3-week cycles, tends to plateau with eight cycles in the APEX trial in RRMM, and reaches a plateau after four 6-week cycles in the VISTA trial in NDMM. The frequency of PN increases with pre-existing PN and cumulative dose using the standard dose and schedule (15,16). Without sacrificing its effectiveness, several clinical trials have shown a lower incidence of PN when bortezomib is administered subcutaneously as opposed to intravenously and weekly as opposed to twice weekly. With dose escalation or medication stoppage, 64% of patients with grade 2 or higher episodes experienced resolution in a median of 3.6 months, demonstrating the luckily reversible nature of BiPN. Despite the lack of conclusive evidence, concurrent use of potent CYP3A4 inhibitors may raise the rate of PN. Some prospective and retrospective investigations have shown that prolonged exposure to or reinitiation of bortezomib does not cause cumulative neurotoxicity; however, this could be due to bias in patient selection.(17,18) The rates of PN associated with the next-generation PIs carfilzomib and ixazomib, on the other hand, are significantly lower than those associated with bortezomib. This suggests that the distinct pharmacologies of these medications lead to varying risks for PN.(19)

Trial group	Any grade AE%	Grade ≥3 AE, %.	Grade ≥3 AE, %.				Treatment discontinuation%
			Peripheral neuropathy	Diarrhea	Thrombocyto- penia	Neutropenia	
APEX GROUP							
Bor alonw	100	61	08	07	30	14	37
High-dose Dex	98	44	13	02	06	01	29
VISTA GROUP							
Bor+Mel+Pred	99	91	14	08	38	41	15
Mel+pred	97	80	00	01	31	38	14

Table-3: Summary of adverse events, observed in the key clinical trials with bortezomib: percentage of patients experiencing each event (Table adapted from Brinthen and associates (20) Abbreviations: AE= adverse event; Bor = bortezomib; DEX= dexamethasone; Mel= Melphalan; Pred = Prednisolone .

1.2) Hematological Adverse Events-

Early phase III studies frequently reported hematologic toxicities; in the APEX phase III study, thrombocytopenia (35% vs. 11%; grade 3/4, 26/4 vs. 5%/1%) and neutropenia (19% vs. 2%; grade 3/4, 12/2 vs. 1%) were significantly more common with single agent bortezomib compared to dexamethasone.(15)

The baseline platelet count, which is correlated with the extent of bone marrow plasma cell infiltration, and myelosuppression brought on by prior treatments are both necessary for the development of thrombocytopenia. Grade 4 thrombocytopenia seldom occurs in patients until their baseline count is less than 70,000/mm³. The thrombocytopenia is temporary and goes away in the time between cycles.(21) It is believed that NF-kB is necessary for platelet budding from megakaryocyte progenitors, and bortezomib may momentarily block this route. Depending on the doctor's judgment, blood counts should be taken before the first two cycles of bortezomib and after that. Usually, thrombocytopenia does not require stopping bortezomib; if the platelet count drops to less than 30,000/mm³ platelets, a dosage should be stopped; the dose of bortezomib will only be lowered by 25% if two of the four doses are stopped because of hematological toxicity. However, relatively few major bleeding problems or the necessity to forgo bortezomib have been documented in the literature in place of these higher rates of thrombocytopenia.(15,22)

1.3) Gastrointestinal adverse event-

Gastrointestinal toxicities are commonly reported with bortezomib, including diarrhea, nausea, constipation, and vomiting. In the VISTA phase III trial in NDMM, the rates of nausea (48% vs 28%), diarrhea (46% vs 17%), constipation (37% vs 16%) and vomiting (33 vs 16%) were all significantly elevated with VMP compared to MP.(23)

These may emerge at any moment during therapy, although in clinical trials primarily noticed during the first or second cycle and were generally mild to moderate in intensity. Nausea and vomiting may need the use of anti-emetics. Antidiarrheal medications may usually be used to manage diarrhea. Dietary adjustments may minimize mild diarrhea. Diuretics and stool conditioners can be utilized to treat obstruction. Patients should be encouraged to stay away from coffee and drink as much water as they can. Lopermid, diphenoxylate + atropine, probiotics and also

in Accepted Manuscript case of severe symptoms; long-acting somatostatin can be administered. In addition, cholesevelam can be added the treatment of diarrhea caused by bile acid malabsorption .(24)

By contrast, gastrointestinal toxicities have been found more frequently with the experimental oral proteasome inhibitor oprozomib or ixazomib, by being dose-limiting and resulting in the study of alternate dosage regimens. The pathogenesis of gastrointestinal toxicities with proteasome inhibition still needs to be explored, but it has been proven that some of the gastrointestinal symptoms of bortezomib could be related with autonomic neuropathy.(25,26)

2) Efficacy evaluation-

As previously stated, 16 years of proven findings from several trials show that bortezomib is an effective therapy for MM. Currently, bortezomib remains the cornerstone of the MM treatment regimen and is being studied in a number of highly active new drug combinations. It is also widely utilized in induction, consolidation, and maintenance therapy in the frontline treatment environment. This section summarizes the main clinical bortezomib efficacy data in both the newly diagnosed and relapse/refractory settings, with an emphasis on important phase III trials in each setting. A thorough review of the literature that includes all the studies and combination regimens investigated with all the different agents is outside the purview of this review.

2.1) Single Agent Activity-

Study of Uncontrolled Myeloma Management with proteasome Inhibition Therapy (Trial A) and Clinical Response and Efficacy Study of bortezomib in the Treatment of refractory myeloma (Trial B) in MM.(27,28,29) In the Trial A, the overall response rate (ORR) after receiving up to eight courses was 35% with a median duration of response of 12 months using the Group for Blood and Marrow Transplantation criteria. The second phase II trial with single agent bortezomib in RRMM was the Trial B, where bortezomib dose escalation was studied. ORR (including complete response, near Complete response and partial response) was 30% and 50% respectively. After a median follow-up of approx. 5 years the median overall survival (OS) was 26.8 (1.0 mg/sq.m.) and 60.0 (1.3 mg/sq.m.) months.(29)

Based on these promising results, a phase III trial-the Assessment of Proteasome inhibition for Extending remissions (Apex) trial was conducted. In this trial patients treated with bortezomib had higher response rates, a longer time to progression (the primary end point), and a longer survival than patients in dexamethasone arm.(30,31) The Overall response rate (Complete response and Partial response) of 38% for bortezomib and 18% for dexamethasone ($p < 0.001$), and the Complete response rates were 6% and $< 1\%$, respectively ($p < 0.001$). The 1-year OS was 80% and 66% among patients receiving bortezomib and dexamethasone, respectively ($p = 0.003$). (31)

2.2) Combining bortezomib with other agents-

2.2.1) Dexamethasone

Early phase II trials of bortezomib in RRMM (Trial A & B) have demonstrated the improved efficacy of adding dexamethasone and corroborate the preclinical evidence with corticosteroids and PI(28,29). In the absence of phase III results in RRMM, the United States National Comprehensive Cancer Network (NCCN) guidelines recommend bortezomib-dexamethasone as a category 1 treatment choice (32). This doublet treatment approach has largely replaced single agent bortezomib over time, and it is supported by a wealth of data that shows this doublet is more effective than single agent bortezomib.(33,34) In 2015, Dimopoulos et al. conducted a retrospective matched-pairs analysis of myeloma patients receiving bortezomib-dexamethasone or bortezomib as second-line therapy. The experiment showed a higher response rate of 75% compared to 41%, as well as a longer median time to advancement of 13.6 and 7 months when analyzed retrospectively.(35)

Although triplet regimens are increasingly used in the RRMM cohort due to their proven efficacy, the bortezomib-dexamethasone doublet treatment regimen remains an active therapy option that may provide clinical benefit, especially for those who cannot receive more complex treatment regimens. (28)

2.2.2) Conventional chemotherapy (alkylating agents/doxorubicin)

The fact that proteasome inhibitors have demonstrated synergy and clinical efficacy with traditional chemotherapeutic drugs, such as alkylating agents and anthracyclines, which were the previously accepted standard of care for MM, is a significant factor in their success.

For many years, melphalan-prednisone (MP) was the go-to medication for treating patients who were not suitable for transplants. Clinical trials have looked into adding all three of the licensed proteasome inhibitors to MP (38). The bortezomib-MP (VMP) regimen has been shown to be effective in several phase III trials, including the important VISTA study of VMP vs MP, which resulted in the approval of bortezomib as a frontline therapy (36,37).

By adding bortezomib to VISTA, response rates—particularly in CRs—rose significantly, and long-term results improved as well. Crucially, long-term follow-up revealed that these improvements translated into an improvement in OS (median 56.4 vs. 43.1 months), establishing the crucial idea that active therapies should be administered in the frontline rather than "saving" them for the relapse setting after conventional chemotherapy.(23)

2.2.3) Immunomodulatory drug

The most successful triplet regimens for NDMM and RRMM include combinations of dexamethasone, an IMiD (thalidomide, lenalidomide, or pomalidomide), and a proteasome inhibitor. The effectiveness of these regimens demonstrates the amazing synergy between these two modes of action, and the possibility of exploring different combinations in countless contexts within the treatment protocols is provided by the availability of three authorized drugs per class (38).

The Italian BO-2005 study, which compared bortezomib plus thalidomide and dexamethasone (VTD) versus TD alone as induction and consolidation therapy within double transplantation regimens, was the first phase III study to demonstrate the superiority of such triplet regimens compared to actual standards of care in frontline treatment. A 62% rate of \geq VGPR was demonstrated with only three cycles of treatment as induction, rising to 89% after ASCT and consolidation, and there was also an improvement in PFS compared to TD (23). More recently, the

combination of carfilzomib, thalidomide, and dexamethasone has shown equally expressive outcomes in a multicenter phase 2 research conducted by the European Myeloma Network (40).

Future prospects:

Bortezomib, a cornerstone in the treatment of multiple myeloma, continues to demonstrate promise in improving patient outcomes, with ongoing advancements in its safety and efficacy profiles. Studies have shown that modifying treatment schedules, such as transitioning to weekly dosing, can maintain its therapeutic benefits while reducing adverse effects like peripheral neuropathy, a common issue with its use. Additionally, its integration into combination therapies, such as with lenalidomide, dexamethasone, or novel monoclonal antibodies like daratumumab, enhances its efficacy in newly diagnosed and relapsed cases.

Future prospects for bortezomib include refining its use in personalized medicine, particularly through molecular profiling to identify patients most likely to benefit from its inclusion in therapy. Research is also exploring ways to mitigate resistance, which remains a challenge in relapsed or refractory myeloma. Advances in drug formulations, like subcutaneous administration, aim to improve patient convenience and compliance.

Ongoing clinical trials are expected to yield insights into optimizing combination regimens and dosing strategies to maximize progression-free survival while minimizing toxicity. These efforts, coupled with the development of newer proteasome inhibitors, are likely to expand bortezomib's role in the evolving landscape of multiple myeloma therapy.

Conclusion:

In this review give an idea about how Bortezomib has transformed the treatment of multiple myeloma, offering significant improvements in survival and disease control through its targeted proteasome inhibition mechanism. Clinical studies consistently demonstrate its efficacy, particularly in combination with other agents, in both newly diagnosed and relapsed/refractory cases. It improves progression-free survival and overall survival, establishing its role as a cornerstone therapy. However, the drug's safety profile warrants attention, as adverse effects like peripheral neuropathy, gastrointestinal symptoms, and hematologic toxicities are common. Innovations such as subcutaneous administration and optimized dosing schedules have effectively reduced toxicity while maintaining efficacy. With proper monitoring and supportive care, these side effects can be managed, ensuring patient adherence and quality of life. As research advances, integrating bortezomib into combination regimens and identifying biomarkers for personalized treatment will further enhance its therapeutic potential, cementing its role in multiple myeloma management.

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