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Comparative Efficacy of Proteasome Inhibitors in Front-line Treatment of Multiple Myeloma

Dinikins Charles*

Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, USA

Introduction

Multiple myeloma is a plasma cell malignancy that continues to pose therapeutic challenges despite significant advances in treatment. Over the past two decades, the introduction of proteasome inhibitors has transformed the treatment landscape of this disease, particularly in the frontline setting. These agents work by interfering with the function of the proteasome, a protein complex responsible for degrading unneeded or damaged proteins. By disrupting this process, proteasome inhibitors cause an accumulation of toxic proteins within malignant plasma cells, leading to cell stress and apoptosis. This mechanism of action has proven particularly effective in multiple myeloma, a disease known for its reliance on increased protein production and turnover [1].

Description

The first proteasome inhibitor introduced into clinical practice was bortezomib, which quickly became the backbone of multiple myeloma therapy due to its ability to induce deep and durable responses. Its success led to the development of next-generation proteasome inhibitors, including carfilzomib and ixazomib, which differ in chemical structure, mode of administration, toxicity profiles, and in some cases, potency. With multiple options now available, it is important to evaluate and compare the efficacy of these agents in the frontline setting, where the initial therapeutic response can strongly influence long-term outcomes such as progression-free survival and overall survival [2]. Bortezomib was the first proteasome inhibitor to demonstrate superior efficacy compared to traditional therapies in both transplant-eligible and transplant-ineligible patients. When combined with dexamethasone and an immunomodulatory drug or an alkylating agent, bortezomib has consistently yielded high response rates and significant improvements in disease control. Its use in induction regimens before stem cell transplantation has been shown to increase the depth of response and delay disease progression. In patients who are not eligible for transplantation, bortezomib-containing regimens have also improved survival outcomes, establishing it as a foundational component of multiple myeloma treatment [3].

Carfilzomib, a second-generation proteasome inhibitor, was developed with the aim of improving efficacy and reducing certain toxicities associated with bortezomib, particularly peripheral neuropathy. Carfilzomib is an irreversible inhibitor that exhibits higher proteasome binding affinity compared to bortezomib [4]. Clinical trials investigating carfilzomib in the frontline setting, particularly in combination with immunomodulatory agents and corticosteroids, have reported high response rates and prolonged progression-free survival.

Some studies suggest that carfilzomib-based regimens may lead to deeper and more durable responses than bortezomib-based regimens, especially in patients with high-risk cytogenetic features. However, these benefits must be weighed against its potential for cardiovascular adverse effects, which may limit its use in certain populations [5].

Conclusion

In conclusion, proteasome inhibitors represent a cornerstone of frontline therapy for multiple myeloma, offering potent antitumor activity and the ability to achieve deep and durable responses. Bortezomib, as the first-in- class agent, remains a widely used and effective option, with a well- established role in both transplant-eligible and transplant-ineligible populations. Carfilzomib offers potential advantages in terms of response depth and resistance profiles, but its cardiovascular toxicity requires careful patient selection and monitoring. Ixazomib, with its oral formulation and favorable safety profile, represents a promising option, particularly for maintenance therapy and for patients requiring a less intensive regimen. Ultimately, the comparative efficacy of these agents must be considered in the context of patient-specific factors, treatment goals, and healthcare resource availability. Ongoing clinical trials and real-world studies will continue to refine our understanding of the optimal use of proteasome inhibitors in the frontline setting, with the goal of extending survival and improving quality of life for patients with multiple myeloma.

Acknowledgement

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Conflict of Interest

None.

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***Address for Correspondence:** Dinikins Charles, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, USA; E-mail: charles.asdf@gmail.com*

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