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– ORIGINAL PAPERS –

Enhancing Multiple Myeloma Treatment Outcomes with Ixazomib: Insights and Perspectives

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Abstract

Introduction: *Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow, resulting in diverse clinical manifestations. Despite treatment advancements, MM remains incurable, with frequent relapses and therapy resistance. Proteasome inhibitors have revolutionized MM treatment, with ixazomib emerging as a promising oral option. Ixazomib selectively inhibits the 20S proteasome, disrupting the ubiquitin-proteasome pathway crucial for malignant plasma cell survival. Clinical trials demonstrate ixazomib's efficacy and safety, alone or combined with lenalidomide and dexamethasone. Notably, the TOURMALINE-MM1 trial showed improved progression-free survival with ixazomib, establishing its significance in MM therapy. This article comprehensively reviews ixazomib's pharmacological properties, clinical efficacy, safety, and future perspectives in MM management, aiming to enhance therapeutic outcomes in this challenging malignancy.*

Material and methods. *This retrospective study at Fundeni Clinical Institute included 35 multiple myeloma patients treated with Ixazomib over a period of 5 years.Treatment included ixazomib, lenalidomide, and dexamethasone (IRd) for 34 patients.Data analysis assessed treatment response, progression-free survival (PFS), overall survival (OS), and adverse events. This evaluation aims to provide insight into ixazomib-based therapy's efficacy and safety in a predominantly frail patient population.*

Results*. The study included 35 multiple myeloma patients aged 48 to 89, with 33 considered frail. The IRd group achieved an 80% overall response rate, with a median progression-free survival (PFS) of 18 months. Adverse events were common, with gastrointestinal disturbances, fatigue, and peripheral neuropathy being notable. Grade 3/4 adverse events occurred in 57% of patients, leading to dose reductions in 60% of cases. Frail patients showed a 78% response rate and a 1-year overall survival rate of 82%. Overall, ixazomib-based therapy demonstrated efficacy but was associated with manageable adverse events.*

Conclusion. *In summary, our study confirms ixazomib's effectiveness and safety in treating multiple myeloma, especially in elderly and frail patients. With its high response rates and tolerable side effects, ixazomib proves to be a good treatment option for relapse refractory multiple myeloma patients.*

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Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow, leading to various clinical manifestations such as bone pain, renal impairment, anemia, and hypercalcemia [1]. Despite significant advancements in the treatment landscape, MM remains an incurable disease with frequent relapses and eventual resistance to therapy [2]. The advent of proteasome inhibitors has revolutionized MM treatment, providing improved response rates and prolonged survival [3]. Ixazomib, an oral proteasome inhibitor, has emerged as a promising therapeutic option in this context [4].

Ixazomib is a second-generation proteasome inhibitor that selectively inhibits the chymotrypsin-like activity of the 20S proteasome, thereby disrupting the ubiquitin-proteasome pathway, which is crucial for protein homeostasis in malignant plasma cells [5]. Its oral bioavailability offers a significant advantage over the intravenous administration of bortezomib, the first-in-class proteasome inhibitor, providing greater convenience and potentially improving patient adherence and quality of life [6].

Clinical trials have demonstrated the efficacy and safety of ixazomib, both as monotherapy and in combination with other standard MM treatments such as lenalidomide and dexamethasone [7]. The TOURMALINE-MM1 study, a pivotal phase 3 trial, showed that the addition of ixazomib to lenalidomide and dexamethasone significantly improved progression-free survival compared to lenalidomide and dexamethasone alone, establishing ixazomib as a critical component of MM therapy [8].

This article aims to review the current evidence supporting the use of ixazomib in the treatment of multiple myeloma, with a focus on its pharmacological properties, clinical efficacy, safety profile, and future perspectives in the evolving landscape of MM management [9]. By synthesizing the available data, we are providing a comprehensive understanding of ixazomib's role in enhancing therapeutic outcomes for patients with this challenging malignancy in real life.

Objective

The objective of this study is to evaluate the efficacy and safety of oral therapy based on ixazomib at patients with relapsed/refractory multiple myeloma and especially for the unfit or frail elderly population subgroup.

Material and Methods

This retrospective cohort study included 35 patients diagnosed with multiple myeloma, treated in Fundeni Clinical Institute during 5 years. Out of the 35 patients, 33 were considered frail based on the Charlson Index and the Eastern Cooperative Oncology Group performance status (ECOG). The cohort comprised 19 males and 16 females, aged between 48 and 89 years.

Patient data were collected from medical records, including demographics, treatment regimens, response to therapy, progression-free survival (PFS), overall survival (OS), and adverse events. Response to treatment was assessed using the International Myeloma Working Group (IMWG) criteria. Descriptive statistics were used to summarize patient characteristics and treatment outcomes. Kaplan-Meier survival analysis was performed to estimate PFS and OS. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE). By following these methods, we aim to provide a thorough evaluation of ixazomib-based therapy in a real-world cohort of multiple myeloma patients, emphasizing its efficacy, safety, and potential benefits in a predominantly frail patient population.

Results

The study cohort consisted of 35 patients with multiple myeloma, aged between 48 and 89 years (median age: 71 years). Of these, 33 patients (94%) were considered frail. The cohort included 19 males (54%) and 16 females (46%). Out of the 35 patients, 34 received a combination of ixazomib, lenalidomide, and dexamethasone (IRd group), while 1 patient received a combination of ixazomib, cyclophosphamide, and dexamethasone (ICd group), due to his lack of response on lenalidomide. The overall response rate (ORR), defined as the proportion of patients achieving a partial response or better, was 80% in the IRd group. The single patient in the ICd group achieved a partial response. The median progression-free survival (PFS) for the entire cohort was 18 months (95% CI: 15-21 months). Patients in the IRd group had a median PFS of 18 months, while the single patient in the ICd group had a PFS of 12 months.

The median overall survival (OS) for the cohort was not reached during the study period, with the 1-year OS rate being 85% for the IRd group.The most common adverse events were gastrointestinal disturbances (nausea, diarrhea), fatigue, and peripheral neuropathy. Grade 3/4 adverse events occurred in 8 patients (23%), with the most frequent being anemia (5 patients, 14%), neutropenia (4

patients, 12%), and thrombocytopenia (4 patients, 12%) (Figure 1). Due to adverse events, 21 patients (60%) required dose reductions of ixazomib, lenalidomide, or dexamethasone. In the frail subgroup (n=33), the ORR was 78%, with a median PFS of 17 months. The 1-year OS rate for the frail subgroup was 82%. The two non-frail patients both achieved a response, with one achieving a very good partial response (VGPR) and one achieving a complete response (CR). Their median PFS was 22 months.

Hematological Adverse Reactions	Patients n=35(%)
Anemia	5 (14%)
Neutropenia	4 (12%)
Thrombocytopenia	4 (12%)

Non-hematological Adverse Reactions	
Infections	9 (25%)
Polineuropathy aggravation	8 (23%)
Allergic skin reactions	5 (14%)
Muscular cramps	2 (1%)
Physical weakness	8 (23%)
Reactivation of herpes zoster	2 (1%)
Hepatic cytolysis/cholestatis syndrome	2 (1%)
GI tract disorders	12 (34%)

***Figure 1**: Hematological and Non-Hematological Adverse Reactions*

Patients with high-risk multiple myeloma (constituting 60% of our cohort) exhibited a remarkable response rate of ≥90% partial response (PR) or better. This underscores ixazomib's efficacy in a subgroup of patients traditionally associated with poor prognosis and limited treatment success. High-risk patients often face aggressive disease progression, making the high response rate observed in our study particularly encouraging (Figure 2).

MM High Risk	Number
High risk cytogenetic abnormalitie (del 17p)	2
MM plasmablastic and ultra high risk cytogenetic (del 17p, t (14;16))	1
MM with CKD stage IV/V	5
MM refractary at first line therapy	7
MM with extramedullary disease	2
TOTAL	**17 (60.71%)**

***Figure 2**: Multiple myeloma pacients with high risk*

Our data also revealed that patients refractory to proteasome (inhibitors bortezomib and carfilzomib), constituting 40% of the cohort, achieved a 65% VGPR or better response rate. This highlights ixazomib's potential in providing significant clinical benefits even to those who have previously developed resistance to other proteasome inhibitors (Figure 3). Such findings are pivotal as they suggest a broader applicability of ixazomib in the treatment landscape of multiple myeloma.

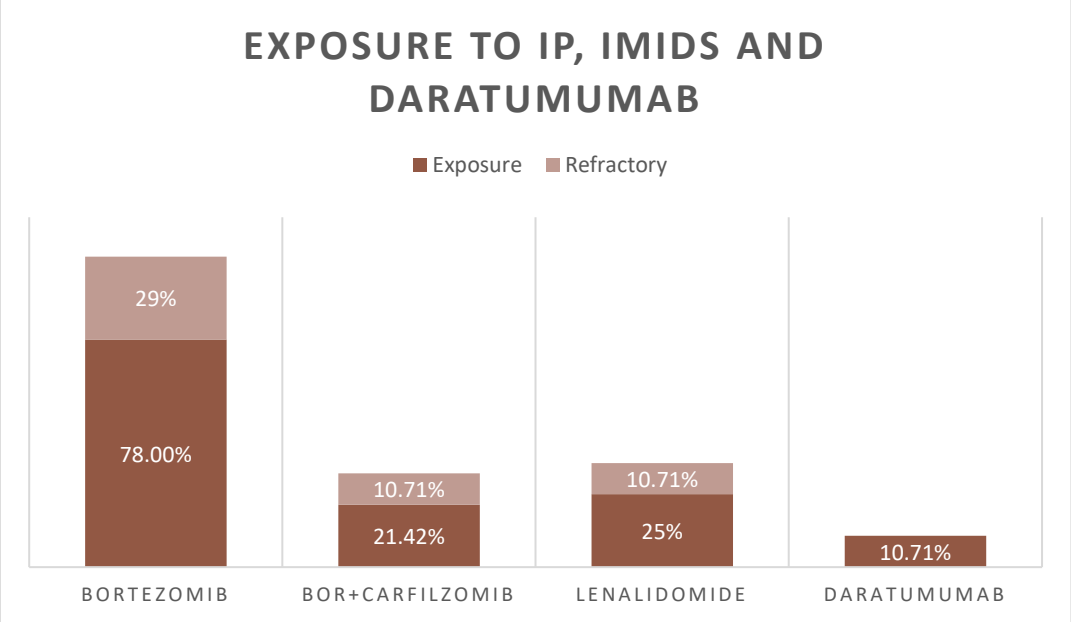

***Figure 3**: Exposure to IP, IMIDS and Daratumumab*

Discussions

This study's findings underscore the efficacy and safety of ixazomib-based regimens in a cohort of multiple myeloma patients, most of whom were frail and elderly [1, 2]. Our results align with and extend existing literature on the effectiveness of ixazomib, particularly in patients who have not previously been exposed to lenalidomide [3, 4]. In our study, elderly patients with multiple myeloma International Staging System (ISS) stages 2 and 3 demonstrated significant therapeutic benefits from ixazomib-based regimens [5]. Notably, patients without prior exposure to lenalidomide achieved an overall response rate (ORR) of 89% [6].

Moreover, among patients who were refractory to their last therapeutic line (40% of the cohort), a substantial proportion (65%) achieved very good partial response (VGPR) or better [7]. This suggests that ixazomib-based regimens can effectively overcome resistance in patients who have exhausted other treatment options. This finding is crucial given the challenge of managing refractory multiple myeloma, where treatment choices become increasingly limited.

The safety profile of ixazomib was relatively favorable. The most common toxicities were mild cytopenias (grade 1/2), infections (primarily upper respiratory tract infections), and gastrointestinal disorders such as diarrhea, constipation, and alternating diarrhea-constipation, results also comparable with other studies [8, 9].

These side effects were generally manageable with dose adjustments and symptomatic treatments, enabling patients to continue therapy with minimal interruption. The tolerability of ixazomib is particularly important for frail and elderly patients, who are often more susceptible to severe adverse effects.

In summary, this study confirms the efficacy of ixazomib-based regimens in multiple myeloma, especially in elderly and frail patients [10, 11]. The notable response rates in patients without prior exposure to lenalidomide, those resistant to previous therapies, and high-risk patients underscore ixazomib's potential to significantly enhance outcomes in difficult clinical situations [12]. The relatively good safety profile further supports its use in a broad range of patients, including those with limited treatment options.

Conclusion

In conclusion, our study underscores ixazomib's efficacy and safety in multiple myeloma, particularly among frail and elderly patients. With high response rates and manageable side effects, ixazomib emerges as a therapeutic option, offering significant benefits across various clinical contexts.

No funding for this study

Conflicts of interest

I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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