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Original Article

Efficacy and safety of ixazomib-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma patients

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Abstract: Objective: To evaluate the therapeutic efficacy and safety profile of the ixazomib-lenalidomide-dexamethasone (IRd) combination in patients with relapsed/refractory multiple myeloma (RRMM). Methods: Between May 2022 and January 2025, 120 RRMM patients were assigned to a control group (n=52) receiving lenalidomide-dexamethasone (Rd) or an observation group (n=68) treated with IRd. Comparative analyses were conducted to assess therapeutic effectiveness, safety (fatigue, infections, gastrointestinal disturbances, peripheral neuropathy, thrombocytopenia, and leukopenia), bone turnover markers (alkaline phosphatase [ALP], osteocalcin [BGP], C-terminal telopeptide of type I collagen [CTX-I]), inflammatory markers (C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α]), and other serum biomarkers (erythrocyte sedimentation rate [ESR], M protein, β_2-microglobulin [β_2-MG]). Predictive factors for treatment response were identified through univariate and multivariate regression modeling. Results: The observation group demonstrated superior overall effectiveness compared to the control group ($P<0.05$), without significant differences in adverse event incidence ($P>0.05$). Post-treatment evaluations showed significantly greater reductions in CTX-I, CRP, IL-6, TNF-α, ESR, M-protein, and β_2-MG levels in the IRd cohort, alongside increased ALP and BGP levels (all $P<0.05$). Univariate analysis identified Revised International Staging System (R-ISS) classification, IL-6, ESR, M-protein levels, and treatment protocol as significant predictors of therapeutic response (all $P<0.05$). Multivariate modeling confirmed M-protein concentration as an independent prognostic factor ($P<0.05$). Conclusions: The IRd regimen demonstrates enhanced clinical efficacy in RRMM management, maintaining a safety profile comparable to the conventional Rd regimen. Furthermore, it effectively improves bone metabolism, reduces serum inflammation, and modulates serum biochemical parameters. Elevated M-protein expression correlates with poorer treatment outcome in RRMM.

Keywords: Ixazomib, lenalidomide, dexamethasone, relapsed/refractory multiple myeloma, therapeutic outcomes and safety

Introduction

Multiple myeloma (MM) is a clinically heterogeneous hematologic malignancy that presents significant therapeutic challenges and high fatality [1, 2]. In 2022, MM affected approximately 35,000 individuals in the U.S. and caused 13,000 deaths [3]. The disease is characterized by clonal expansion of intramedullary plasma cells, which secrete excessive monoclonal immunoglobulins. These contribute to hypercalcemia, renal insufficiency, anemia, osteolytic lesions, and an increased susceptibility to infections [4]. The effectiveness and safety of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), the mainstays of MM treatment, have been established; however, disease relapse remains a significant challenge for many patients [5]. Relapsed/refractory multiple myeloma (RRMM), often associated with poor outcome, is of particular concern [6]. Thus, novel therapeutic approaches are urgently needed to improve clinical outcomes for these patients.

The Ixazomib-Lenalidomide-Dexamethasone (IRd) regimen, approved by both the European Union and the U.S., is a promising new targeted

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triplet therapy for RRMM that combines a PI, an IMiD, and a corticosteroid [7]. Ixazomib, a second-generation PI, is designed for oral administration and offers superior antitumor efficacy through proteasome inhibition, owing to its favorable pharmacokinetic and pharmacodynamic properties [8, 9]. Lenalidomide, a next-generation IMiD, exerts its antineoplastic effects through immune modulation and angiogenesis inhibition [10]. Dexamethasone, a corticosteroid, provides anti-inflammatory and immunosuppressive effects, reducing inflammation in the tumor microenvironment [11]. Although the Lenalidomide-Dexamethasone (Rd) regimen has been a standard of care for RRMM, improving its efficacy and safety remains essential [12, 13].

This study compares IRd and Rd in RRMM, aiming to evaluate the possiblel clinical superiority of IRd in treating RRMM. By analyzing treatment efficacy and safety data, it aims to provide evidence supporting the clinical advantages of IRd. This research is innovative in two key aspects: (1) It compares the clinical benefits of IRd versus Rd, aiming to optimize RRMM management while providing a better treatment option. (2) It offers robust evidence to guide RRMM treatment strategies by systematically examining clinical efficacy, safety, bone metabolic status, serum inflammation, and biochemical indices.

Materials and methods

Patient enrollment

A total of 120 RRMM patients treated at Fujian Medical University Union Hospital were enrolled retrospectively. Participants were recruited between May 2022 and January 2025 and received either the standard Rd regimen (n=52, control group) or the Ixazomib-Lenalidomide-Dexamethasone (IRd) regimen (n=68, observation group). Ethical approval for the study was granted by the Fujian Medical University Union Hospital review board.

Eligibility criteria

Inclusion criteria: (1) Confirmed RRMM diagnosis according to established criteria [14]. (2) Stage II or III disease per the Revised International Staging System (R-ISS) [15]. (3) Expected survival >12 months. (4) Availability of complete clinical records.

Exclusion criteria: (1) Comorbid metabolic disorders (e.g., diabetes, osteoporosis). (2) Coagulopathies or active infections. (3) Severe cardiovascular, cerebrovascular, hepatic, or renal impairment. (4) History of allergic reactions or intolerance to study medications. (5) Recent (<3 months) major stressful events. (6) Concurrent malignancies or prior alternative myeloma therapies. (7) Cognitive impairments or communication difficulties.

Treatment protocols

Patients in the control group received the standard Rd regimen. Lenalidomide was administered orally at 25 mg/day from days 1 to 21 of each 28-day cycle. Dexamethasone was administered intravenously at 40 mg once weekly on days 1, 8, 15, and 22 for each cycle. A total of 3 cycles were completed.

In contrast, patients in the observation group received the IRd regimen, combining ixazomib with the same Rd protocol. Ixazomib was administered orally at 4 mg once weekly on days 1, 8, 15, and 22. Three consecutive cycles were completed.

Both groups selected their regimen independently after consultation with their attending physicians, who provided recommendations based on individual patient conditions and clinical protocols.

Testing indicators

(1) Clinical Effectiveness: Complete response (CR): Resolution of serum and urinary M-protein, plasmacytomas, and bone marrow plasma cell (BMPC) percentage ≤5%.

Partial response (PR): ≥90% decrease in serum M-protein, 24-hour urine M-protein <100 mg, and ≥50% decrease in BMPCs.

Minimal response (MR): ≥50% reduction in serum M-protein.

Progressive disease (PD): Serum M-protein ≥5 g/L, 24-hour urine M-protein ≥200 mg, or ≥10% increase in BMPCs.

Objective response rate (ORR): CR + PR + MR as a percentage of total cases.

Imaging assessment: Whole-body low-dose computed tomography to confirm regression

Table 1. Comparison of participant characteristics

Indicator	n	Control group (n=52)	Observation group (n=68)	χ^2/t	P
Sex				0.083	0.774
Male	71	30 (57.69)	41 (60.29)		
Female	49	22 (42.31)	27 (39.71)		
Age (years)	120	54.12±6.69	53.74±7.33	0.292	0.771
Disease duration (years)	120	2.25±0.99	2.49±1.33	1.090	0.278
Body mass index (kg/m^2)	120	22.94±2.48	23.12±2.52	0.390	0.697
R-ISS classification				1.335	0.248
II	51	19 (36.54)	32 (47.06)		
III	69	33 (63.46)	36 (52.94)		
Prior treatment regimen				0.499	0.779
First-line therapy	61	26 (50.00)	35 (51.47)		
Second-line therapy	38	18 (34.62)	20 (29.41)		
Third-line/other therapies	21	8 (15.38)	13 (19.12)		

Note: R-ISS, Revised International Staging System.

of plasmacytomas. BMPCs were quantified from bone marrow aspirates analyzed by flow cytometry and microscopy.

(2) Safety: Adverse events (fatigue, infections, gastrointestinal disturbances, peripheral neuropathy, thrombocytopenia, leukopenia) were recorded, and their incidence rates were analyzed.

(3) Bone Metabolism: Serum samples (6 mL of fasting venous blood) were obtained from each patient before and after treatment. Osteocalcin (BGP) and C-terminal telopeptide of type I collagen (CTX-I) levels were measured by electrochemiluminescence immunoassays, while alkaline phosphatase (ALP) was measured by ELISA.

(4) Serum Inflammatory Markers: C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) levels were measured by ELISA using serum samples obtained from 3 mL of fasting venous blood.

(5) Additional Serum Biochemical Parameters: Erythrocyte sedimentation rate (ESR) and serum M-protein concentrations were measured using a dynamic hematocrit analyzer and automated biochemistry analyzer, respectively. β_2-microglobulin (β_2-MG) levels were assessed by ELISA.

Statistical analysis

Statistical analyses were performed using SPSS software (version 20.0). Continuous variables were expressed as mean ± standard error of the mean (SEM). Between-group differences were analyzed with independent samples t-tests, and within-group pre- vs. post-treatment changes were assessed with paired t-tests. Categorical variables are presented as counts (percentages), with group differences analyzed using χ^2 tests. Statistical significance was defined as a two-tailed *P*-value <0.05. Using a two-group rate comparison formula (α=0.05, power =0.75), the required minimum sample size per group was ≥48 participants. Both groups met this sample size requirement.

Results

Comparison of baseline characteristics

Measurements such as gender, age, disease duration, body mass index (BMI), R-ISS classification, and prior treatment plans showed no significant differences (all P>0.05), indicating balanced baseline characteristics between the study groups (**Table 1**).

Comparison of clinical effectiveness

The evaluation revealed a significant difference in clinical outcomes between the two groups (P<0.05). The observation group exhibited a significantly higher ORR compared to the control group (P<0.05, **Table 2**).

Comparison of safety profile assessment

The incidence of adverse events, including fatigue, infections, gastrointestinal disturbanc-

Table 2. Comparison of clinical efficacy outcomes

Indicator	Control group (n=52)	Observation group (n=68)	χ^2	P
CR	14 (26.92)	25 (36.76)		
PR	16 (30.77)	27 (39.71)		
MR	11 (21.15)	11 (16.18)		
PD	11 (21.15)	5 (7.35)		
ORR	41 (78.85)	63 (92.65)	4.857	0.028

Note: CR, complete response; PR, partial response; MR, minimal response; PD, progressive disease; ORR, objective response rate.

Table 3. Comparison of safety profile

Indicator	Control group (n=52)	Observation group (n=68)	χ^2	P
Fatigue	2 (3.85)	4 (5.88)	0.257	0.612
Infections	2 (3.85)	1 (1.47)	0.682	0.409
Gastrointestinal disturbances	5 (9.62)	7 (10.29)	0.015	0.902
Peripheral neuropathy	6 (11.54)	12 (17.65)	0.862	0.353
Thrombocytopenia	8 (15.38)	14 (20.59)	0.533	0.465
Leukopenia	7 (13.46)	12 (17.65)	0.387	0.534

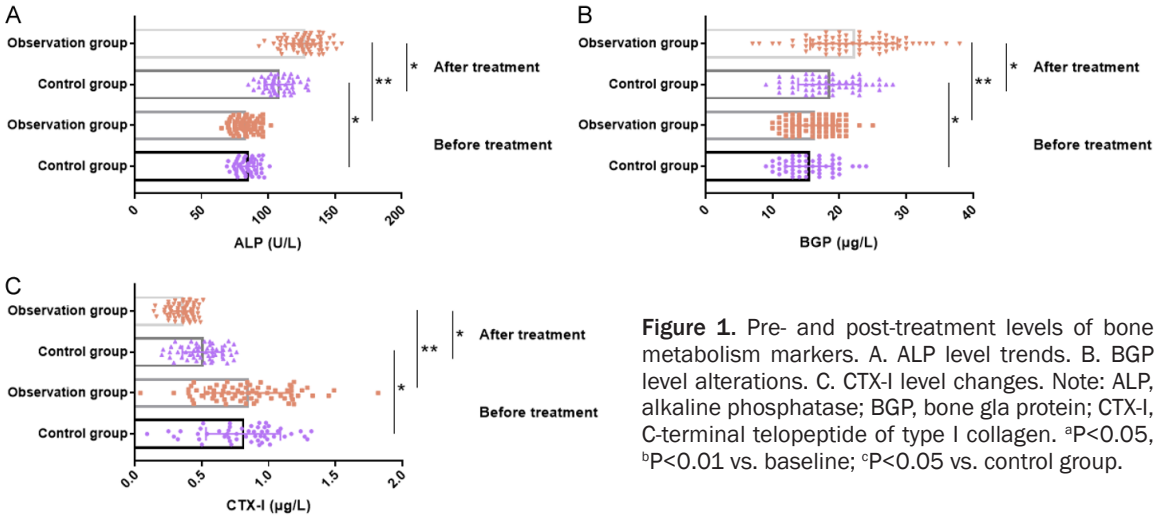

Figure 1. Pre- and post-treatment levels of bone metabolism markers. A. ALP level trends. B. BGP level alterations. C. CTX-I level changes. Note: ALP, alkaline phosphatase; BGP, bone gla protein; CTX-I, C-terminal telopeptide of type I collagen. [a]P<0.05, [b]P<0.01 vs. baseline; [c]P<0.05 vs. control group.

es, peripheral neuropathy, thrombocytopenia, and leukopenia, did not differ significantly between the groups (all P>0.05, **Table 3**).

Analysis of bone metabolism markers

Key bone metabolism indices - ALP, BGP, and CTX-I - were assessed. Baseline levels were similar between the groups (all P>0.05). Post-treatment, ALP and BGP levels increased, while CTX-I decreased in both groups (all P<0.05). The observation group exhibited significantly greater changes than the control group (all P<0.05, **Figure 1**).

Comparison of serum inflammatory markers

Serum inflammatory markers (CRP, IL-6, TNF-α) showed similar baseline levels between the groups (all P>0.05). Post-treatment, both groups demonstrated significant reductions, with greater decreases observed in the observation group (all P<0.05; **Figure 2**).

Comparison of additional serum biochemical markers

Other biochemical markers (ESR, M protein, β_2-MG) also showed no significant differences

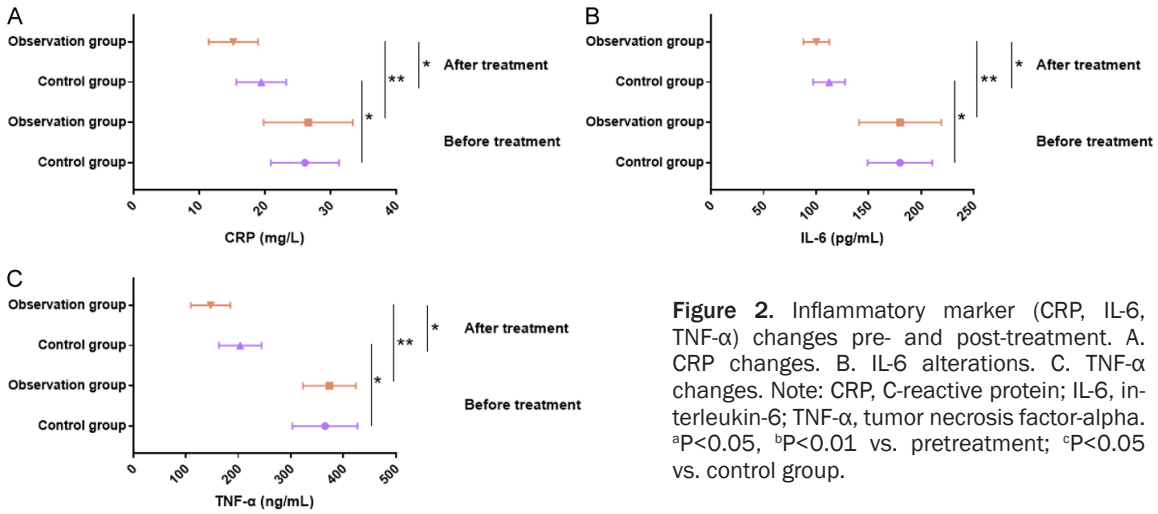

Figure 2. Inflammatory marker (CRP, IL-6, TNF-α) changes pre- and post-treatment. A. CRP changes. B. IL-6 alterations. C. TNF-α changes. Note: CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha. [a]P<0.05, [b]P<0.01 vs. pretreatment; [c]P<0.05 vs. control group.

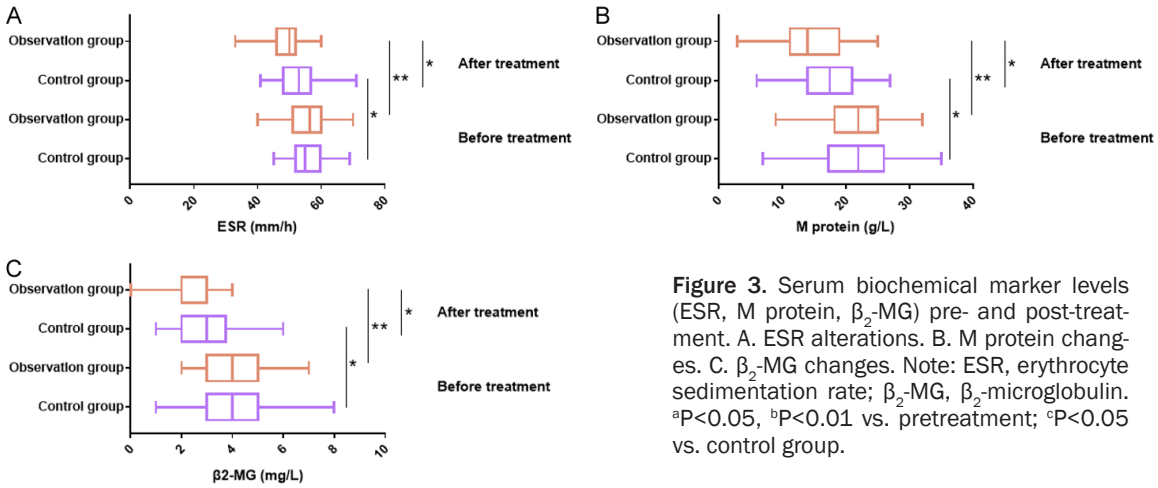

Figure 3. Serum biochemical marker levels (ESR, M protein, β_2-MG) pre- and post-treatment. A. ESR alterations. B. M protein changes. C. β_2-MG changes. Note: ESR, erythrocyte sedimentation rate; β_2-MG, β_2-microglobulin. [a]P<0.05, [b]P<0.01 vs. pretreatment; [c]P<0.05 vs. control group.

at baseline (all P>0.05). Post-treatment, all markers significantly decreased, with the observation group showing lower levels than the control group (all P<0.05; **Figure 3**).

Univariate analysis of treatment response predictors in RRMM

Univariate analysis identified R-ISS classification, IL-6, ESR, M protein, and treatment protocol as significant predictors of treatment response (all P<0.05). Other variables showed no association with treatment response (all P>0.05, **Table 4**).

Multivariate analysis of treatment response predictors

Significant variables from univariate analysis were included in a binary logistic regression model, with treatment response as the dependent variable. Multivariate analysis confirmed M protein (OR: 4.560) as an independent predictor of treatment efficacy (P<0.05, **Tables 5**, **6**).

Discussion

Recent cancer registry reports indicate that the burden of MM in China reached significant levels in 2022, with an estimated 23,000 new cases and approximately 18,000 related deaths [16]. Despite advances in MM therapies, many patients exhibit suboptimal responses to initial treatment or experience disease relapse [17]. This underscores the need for novel therapeutic strategies for RRMM to improve clinical outcomes while ensuring patient safety [18].

Table 4. Univariate analysis of treatment response predictors in RRMM

Indicator	n	Ineffective group (n=16)	Effective group (n=104)	χ^2	P
Sex				0.085	0.771
Male	71	10 (62.50)	61 (58.65)		
Female	49	6 (37.50)	43 (41.35)		
Age (years)				0.129	0.719
<55	65	8 (50.00)	57 (54.81)		
≥55	55	8 (50.00)	47 (45.19)		
Disease duration (years)				1.093	0.296
<3	67	7 (43.75)	60 (57.69)		
≥3	53	9 (56.25)	44 (42.31)		
Body mass index (kg/m^2)				1.816	0.178
<24	71	7 (43.75)	64 (61.54)		
≥24	49	9 (56.25)	40 (38.46)		
R-ISS classification				4.261	0.039
II	51	3 (18.75)	48 (46.15)		
III	69	13 (81.25)	56 (53.85)		
Prior treatment regimen				3.586	0.167
First-line therapy	61	5 (31.25)	56 (53.85)		
Second-line therapy	38	6 (37.50)	32 (30.77)		
Third-line/other therapies	21	5 (31.25)	16 (15.38)		
ALP (U/L)				2.527	0.112
<85	68	12 (75.00)	56 (53.85)		
≥85	52	4 (25.00)	48 (46.15)		
BGP (μg/L)				3.343	0.068
<16	57	11 (68.75)	46 (44.23)		
≥16	63	5 (31.25)	58 (55.77)		
CTX-I (μg/L)				2.596	0.107
<0.85	60	11 (68.75)	49 (47.12)		
≥0.85	60	5 (31.25)	55 (52.88)		
CRP (mg/L)				1.484	0.223
<27	62	6 (37.50)	56 (53.85)		
≥27	58	10 (62.50)	48 (46.15)		
IL-6 (pg/mL)				4.314	0.038
<180	59	4 (25.00)	55 (52.88)		
≥180	61	12 (75.00)	49 (47.12)		
TNF-α (ng/mL)				1.955	0.162
<365	57	5 (31.25)	52 (50.00)		
≥365	63	11 (68.75)	52 (50.00)		
ESR (mm/h)				4.025	0.045
<56	58	4 (25.00)	54 (51.92)		
≥56	62	12 (75.00)	50 (48.08)		
M protein (g/L)				5.140	0.023
<22	54	3 (18.75)	51 (49.04)		
≥22	66	13 (81.25)	53 (50.96)		
β_2-MG (mg/L)				0.070	0.792
<4	41	5 (31.25)	36 (34.62)		
≥4	79	11 (68.75)	68 (65.38)		

Treatment protocol				4.857	0.028
Lenalidomide-dexamethasone	52	11 (68.75)	41 (39.42)		
Ixazomib-lenalidomide-dexamethasone	68	5 (31.25)	63 (60.58)		

Note: RRMM, relapsed/refractory multiple myeloma; R-ISS, Revised International Staging System; ALP, alkaline phosphatase; BGP, bone gla protein; CTX-I, C-terminal telopeptide of type I collagen; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; ESR, erythrocyte sedimentation rate; β_2-MG, β_2-microglobulin.

Table 5. Variable assignments

Indicator	Variable	Assignment
R-ISS classification	X1	II=0, III=1
IL-6 (pg/mL)	X2	<180=0, ≥180=1
ESR (mm/h)	X3	<56=0, ≥56=1
M protein (g/L)	X4	<22=0, ≥22=1
Treatment protocol	X5	Lenalidomide-dexamethasone =0, Ixazomib-lenalidomide-dexamethasone =1
Efficacy	Y	Effective (CR, PR, or MR)=0, ineffective (PD)=1

Note: R-ISS, Revised International Staging System; IL-6, interleukin-6; ESR, erythrocyte sedimentation rate; CR, complete response; PR, partial response; MR, minimal response; PD, progressive disease.

Table 6. Multivariate analysis of treatment response predictors in RRMM

Indicator	B	SE	Wald	P	OR	95% CI
R-ISS classification	1.186	0.709	2.799	0.094	3.275	0.816-13.144
IL-6 (pg/mL)	0.891	0.616	2.095	0.148	2.438	0.729-8.150
ESR (mm/h)	0.671	0.631	1.130	0.288	1.956	0.568-6.743
M protein (g/L)	1.517	0.699	4.714	0.030	4.560	1.159-17.943
Treatment protocol	-0.882	0.633	1.944	0.163	0.414	0.120-1.430

Note: RRMM, relapsed/refractory multiple myeloma; R-ISS, Revised International Staging System; IL-6, interleukin-6; ESR, erythrocyte sedimentation rate.

In this study, the IRd regimen demonstrated significantly superior efficacy compared to the Rd regimen, with an ORR of 92.65% versus 78.85%. These findings are consistent with previous studies. For instance, Batinić et al. [19] reported an ORR of 65.8% for Croatian RRMM patients treated with single-agent ixazomib, highlighting its favorable effectiveness and tolerability. The IRd regimen has shown high response rates (ORR: 95.7%) in newly diagnosed MM patients, as reported by Perrot et al. [7], which was also confirmed in our study. In RRMM treatment, ixazomib's potent antitumor effects may be attributed to its promotion of lenalidomide-induced apoptosis through NF-κB signaling inhibition and tumor cell death through endoplasmic reticulum stress activation [20-22], likely contributing to its superior tumor-killing effects compared to Rd.

Both groups demonstrated a clinically comparable safety profile, with no significant differences in adverse events such as fatigue, infections, gastrointestinal disturbances, peripheral neuropathy, thrombocytopenia, and leukopenia. This suggests that the addition of ixazomib in the IRd regimen does not significantly worsen adverse reactions. Bonnet et al. [23] found that ixazomib, whether used alone or in combination with other drugs, exhibits favorable safety and manageable adverse effects, which aligns with our findings. Furthermore, real-world evidence supports the safety and efficacy of the IRd regimen in Asian and elderly RRMM populations, consistent with our results [24].

In addition, IRd therapy outperformed Rd in improving bone metabolism (greater elevations in ALP and BGP levels and reduced CTX-I) and inflammation (more significant reductions in CRP, IL-6, and TNF-α) in RRMM patients. These findings indicate that IRd therapy more effectively restores the osteolytic-osteogenic balance and maintains the inflammatory microen-

vironment. This may be attributed to ixazomib's role in maintaining the anabolic balance of bone formation by enhancing osteoblast activity and inhibiting osteoclast differentiation, as well as its potent modulation of the inflammatory microenvironment, which likely contributes to its bone-protective effects [25].

Moreover, notable reductions in ESR, M protein, and β_2-MG levels were observed in RRMM patients receiving IRd. Univariate analysis identified significant associations between therapeutic efficacy and R-ISS classification, IL-6, ESR, M protein, and treatment protocol. Binary logistic regression analysis confirmed M protein as an independent predictor of treatment response, suggesting its potential as a biomarker for efficacy. As established in the literature, IRd is most effective in RRMM when used prior to third-line therapy or in patients receiving ≤2 prior therapies [26]. Gupta et al. [27] found a link between higher ixazomib exposure and reduced lenalidomide dose intensity, which may impact the Rd regimen dosing. However, the clinical effects of varying ixazomib doses on Rd regimen modifications require further investigation.

This study has a few limitations. First, it did not explore the optimal efficacy of different IRd therapy doses; future dose-response analyses could help optimize treatment strategies. Second, the absence of a risk stratification model highlights the need for predictive tools to identify treatment-refractory RRMM cases, thereby improving clinical decision-making. Additionally, the economic efficiency of the two therapies was not assessed, and incorporating such data could further support the clinical applicability of IRd.

In conclusion, the IRd regimen demonstrates superior clinical effectiveness compared to Rd in RRMM treatment without significantly increasing adverse events. It also effectively maintains bone metabolic balance, suppresses excessive serum inflammation, and reduces ESR, M protein, and β_2-MG levels. Furthermore, M protein serves as an independent predictor of treatment outcomes, with elevated levels correlating with a higher risk of treatment failure. These findings offer comprehensive insight to optimize RRMM treatment.

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Disclosure of conflict of interest

None.

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