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An Evaluation of the Clinical Efficacy and Safety of Ixazomib for Relapsed/Refractory Multiple Myeloma

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Abstract: *Objective:* To investigate the clinical efficacy and safety of ixazomib in the treatment of relapsed/refractory multiple myeloma (RRMM). *Methods:* The clinical data of 20 patients with RRMM admitted to the hospital from January 2020 to January 2022 were analyzed retrospectively. All patients were treated with ixazomib-based chemotherapy regimen (IRD regimen 13 cases; ID regimen 7 cases). The objective response rate (ORR) and adverse events (AEs) were observed. *Results:* All 20 patients received two to seven courses of treatment, in which the median was three courses. One patient had CR, four patients had VGPR, seven patients had PR, two patients had SD, and six patients had PD. The ORR was 60.00% (12/20), and 25.00% (5/20) of them had VGPR or more. The ORR of patients with previous treatment lines ≥ 3, ISS stage III, and high-risk cytogenetic was lower than that of patients with previous treatment lines < 3, ISS stage I/II, and low-risk cytogenetics. The main AEs include anemia, thrombocytopenia, neutropenia, nausea and vomiting, diarrhea, constipation, and respiratory tract infection, most of which are grade I/II. *Conclusion:* Ixazomib is effective in the treatment of RRMM in some patients, and the AEs are controllable. Patients who had received less than 3 lines of treatment in the past, with ISS stage I to II and low-risk cytogenetics had better treatment effect.

Keywords: Ixazomib; Relapsed/refractory multiple myeloma; Clinical efficacy; Adverse event

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1. Introduction

Multiple myeloma (MM) is one of the hematological malignancies. It originates from bone marrow hematopoietic cells and presents as clonal plasma cell dysplasia, resulting in multiple osteolytic lesions, anemia, kidney damage, and other organ or tissue damage [1]. With the advent of new anti-tumor drugs, the overall prognosis of MM patients has significantly improved, along with the remission rate and progression-free survival (PFS) [2]. However, hidden lesions and small residual lesions are still problems that cannot be fully resolved, and drug resistance is also a major problem in clinical treatment. Except for a few patients who may be cured by hematopoietic stem cell transplantation, most patients will eventually relapse and progress. The treatment of relapse/refractory multiple myeloma (RRMM) is still a major clinical problem, which needs to be solved urgently. As the first oral proteasome inhibitor, ixazomib has shown satisfactory results in the treatment of primary relapsed/refractory MM [3] and is in line with the new trend of treatment simplicity. This study retrospectively analyzed the clinical data of patients with RRMM who received ixazomib-based all-oral regimen in Shaanxi Provincial People's Hospital from January 2020 to January 2022 and evaluated its clinical efficacy and safety.

2. Data and methods

2.1. General information

Twenty patients with RRMM were admitted to the hospital from January 2020 to January 2022. Inclusion criteria: (1) patients who met the diagnostic criteria of MM and the definition of "relapsed/refractory" in "The Guidelines for the Diagnosis and Management of Multiple Myeloma in China (2020 Revision)" [4] and whose diagnosis was confirmed by bone marrow examination and imaging examination; (2) all patients were treated with ixazomib-based all-oral regimen and completed more than one course of treatment; (3) complete clinical data, including gender, age, physical fitness score, blood routine examination, blood biochemistry, laboratory examination, pathological examination, imaging examination, number of previous anti-bone marrow treatment lines, previous drug resistance, cytogenetic risk stratification, and revised international staging system. Exclusion criteria: (1) primary amyloidosis and secondary progression to plasma cell leukemia; (2) complicated with renal insufficiency, unstable cardiovascular disease, and other malignant tumors; (3) combined with central nervous system involvement; (4) ECOG score of > 2.

2.2. Treatment methods

The patients received ixazomib-based regimens (ID and IRD). The ID regimen includes oral ixazomib (Takeda Pharma A/S, H20180010) 4 mg, taken on the 1st-, 8th-, and 15th-day; oral dexamethasone 40 mg, taken on the 1st-, 8th-, 15th-, and 22nd-day, with 28 days as the course of treatment. The IRD regimen includes the doses of ixazomib and dexamethasone based on the ID regimen plus oral lenalidomide 25 mg, taken on the 1st- to 21st-day, with 28 days as the course of treatment. During the treatment, the dosages were adjusted accordingly based on the patient's age, creatinine clearance rate, and adverse reactions.

2.3. Clinical efficacy and safety evaluation

The clinical efficacy of the treatment was evaluated based on the efficacy standard formulated by the International Myeloma Working Group (IMWG) [5], which can be divided into complete remission (CR), very good partial remission (VGPR), partial remission (PR), minimal remission (MR), stable disease (SD), and progressive disease (PD). The best curative effect during the treatment period was taken as the evaluation result. The objective response rate (ORR) is the sum of the ratios, excluding SD and PD. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [6] was used to evaluate the adverse events (grade I~IV) and the safety of treatment.

2.4. Statistical analysis

SPSS 23.0 was used for data analysis. The counting data were expressed in (%) and $\chi 2$ test; $p < 0.05$ signifies that the difference is statistically significant.

3. Results

3.1. Clinical characteristics and efficacy of treatment

By the end of the follow-up, the 20 patients had received two to seven courses of treatment, with a median of three courses. Thirteen patients were treated with IRD, while seven patients were treated with ID. One patient had CR, four patients had VGPR, seven patients had PR, two patients had SD, and six patients had PD. The ORR was 60.00% (12/20), and 25.00% (5/20) of them had VGPR or more. Fourteen patients continued to receive ixazomib, five patients received other treatment regimens due to disease progression, and one patient died due to multiple organ failure. The ORR of patients with previous treatment lines ≥ 3, ISS stage III, and high-risk cytogenetics was lower than that of patients with previous treatment lines < 3, ISS stage I or II, and low-risk cytogenetics ($p < 0.05$) (see **Table 1**).

Table 1. Correlation analysis between ixazomib efficacy and clinical characteristics

Clinical characteristics		Cases	ORR	*p*
Age (years)	18-64	11	6 (54.55)	0.784
	≥ 65	9	6 (66.67)	
Gender	Male	12	7 (58.33)	0.926
	Female	8	5 (62.50)	
ISS staging	I/II	14	12 (85.71)	0.035
	III	6	0	
Cytogenetic risk stratification	Low risk	11	11 (100.00)	0.030
	High risk	9	1 (11.11)	
Number of previous treatment lines	1/2 line(s)	13	12 (92.30)	0.020
	≥ 3 lines	7	0	
ECOG	1 point	9	7 (77.78)	0.465
	2 points	11	5 (45.45)	
Previous bortezomib	Yes	12	5 (41.67)	0.314
	No	8	7 (87.50)	
Previous lenalidomide	Yes	7	4 (57.14)	0.923
	No	13	8 (61.54)	
Previous autologous stem cell transplantation	Yes	5	4 (80.00)	0.612
	No	15	8 (53.33)	
Extramedullary focus	Yes	3	1 (33.33)	0.581
	No	17	11 (64.71)	
Treatment regimen	ID	7	4 (57.14)	0.923
	IRD	13	8 (61.54)	

3.2. Safety evaluation

The main adverse events (AEs) included anemia, thrombocytopenia, neutropenia, nausea and vomiting, diarrhea, constipation, and respiratory tract infection, most of which were grade I or II. After symptomatic treatment, they all improved without affecting the continued use of drugs (see **Table 2**).

Table 2. Analysis of hematological and non-hematological AEs after ixazomib treatment

AEs	I/II	III/IV	Overall incidence (%)
Hematological			
Anemia	4	1	25.00
Neutropenia	3	1	20.00
Thrombocytopenia	6	2	40.00
Lymphopenia	3	0	15.00
Non-hematological			
Nausea and vomiting	14	1	75.00
Weakness	15	0	75.00
Diarrhea	5	1	30.00
Constipation	4	0	20.00
Rash	2	0	10.00

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AEs	I/II	III/IV	Overall incidence (%)
Non-hematological			
Zoster	1	0	5.00
Joint pain	2	0	10.00
Peripheral neuropathy	3	0	15.00
Respiratory tract infection	4	1	25.00
Elevated creatinine	1	1	10.00
Elevated transaminase	1	0	5.00
Insomnia	1	0	5.00

4. Discussion

RRMM has low remission rate and short median survival time. Its treatment has always been the focus and issue in clinical practice. Proteasome inhibitors (PIs) are one of the mainstays of treatment for MM [7], but their long-term use is limited by parenteral administration and treatment-related toxicity [8]. Ixazomib is a reversible PI, which acts on the catalytic center of 20S proteasome [9]. With lower drug concentration in the body, it selectively binds and interacts with proteasome β5 subunit, thus inhibiting chymotrypsin-like protease activity; with higher drug concentration in the body, it interacts with β1 and β2 subunits, thus inhibiting glutamyl peptide hydrolase and trypsin-like protease activities and inducing cell apoptosis [10-12]. In terms of the mechanism of action, ixazomib is similar to bortezomib. However, the half-life of ixazomib is short, about one-sixth of bortezomib [13], and there are only a number of factors that affect the pharmacokinetics. Fixed dose medication can be used to ensure the rigor of the treatment [14]. Intolerable peripheral neuropathy is a major limitation in the use of bortezomib. As a new PI, ixazomib has a much lower incidence of peripheral neuropathy than bortezomib [15]. Additionally, patients receiving ixazomib have better compliance than those receiving intravenous injection drugs, and these patients can be treated for a longer time. Mouse studies have also confirmed that ixazomib can better control tumor cells compared to bortezomib; moreover, it has an effect on bortezomib-resistant myeloma cells.

The use of ixazomib in combination with lenalidomide and dexamethasone is approved for the treatment of MM patients who have received treatment at least once. A number of clinical trials and real-world studies at home and abroad have confirmed that ixazomib-based regimens have good efficacy and safety for RRMM patients. In a study [16], Avet-Loiseau confirmed that IRD is beneficial to RRMM patients with high-risk and standard risk cytogenetics, and it can prolong the progression free survival of patients compared with placebo RD. In another study [17], 90 RRMM patients who received eight cycles of IRD were observed; the results showed that the total effective rate was 51.1%; 23.3% reached CR or VGPR, 10% reached MR, and the clinical benefit rate was 61.1%; the effective rate, PFS, and overall survival (OS) were similar in patients with or without t(4;14) and/or del(17p); however, the PFS and OS were significantly shortened in patients with 1q21 gain; multiple regression analysis showed that the gain of 1q21 is the most critical factor related to OS [17]. A multicenter retrospective analysis showed that the PFS and OS of IgG patients were significantly better than those of non-IgG patients [18]. In this study, among the 20 patients, one patient achieved CR, four patients achieved VGPR, and seven patients achieved PR; the ORR was 60.00%, and 25.00% achieved VGPR or more; 14 patients continued to receive ixazomib treatment, five patients received other treatment regimen due to disease progression, and one patient died due to multiple organ failure. This shows that ixazomib has good curative effect on some patients. The correlation analysis between the clinical characteristics and drug efficacy showed that the ORR of patients with previous treatment lines ≥ 3, ISS stage III, and high-risk cytogenetics was lower than that of patients with previous treatment lines < 3, ISS stage I/II, and low-risk cytogenetics.

Drug-related peripheral neuropathy is a common AE with first generation PIs. It has a reported incidence of about 40%, which may seriously affect the quality of life and treatment compliance of patients [19,20]. In this study, the incidence of peripheral neuropathy with ixazomib treatment was only 15.00%, which confirmed that ixazomib has significantly lower neurotoxicity compared to bortezomib. The main AEs in this study included anemia, thrombocytopenia, neutropenia, nausea, vomiting, diarrhea, constipation, and respiratory tract infection, most of which were grade I/II. After symptomatic treatment, they all improved and did not affect the continued use of drugs.

In conclusion, ixazomib is effective in the treatment of RRMM in some patients, and its AEs are controllable. Patients who had received less than three lines of treatment in the past with ISS stage I/II and low-risk cytogenetics achieved better treatment effect. However, compared with large clinical studies, the sample size of this study is small. The effectiveness and safety of ixazomib still require further confirmation by expanding the sample size, extending the follow-up time, and conducting more thorough clinical studies.

Disclosure statement

The authors declare no conflict of interest.

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