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ORIGINAL RESEARCH

Real-world Data on the Efficacy and Safety of Ixazomib-based Therapy in Multiple Myeloma: A Single-center Study in China

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Kai Ding*
Hong Yu*
Yuan-Yuan Shao
Li-Yan Li
Chao-Meng Wang
Jia Song
Li-Juan Li
Rong Fu

Department of Hematology, Tianjin Medical University General Hospital, Tianjin 300052, People's Republic of China

*These authors contributed equally to this work

Objective: To assess the short-term efficacy and safety of ixazomib in Chinese multiple myeloma (MM) patients in the real world.

Methods: Fifty-nine MM patients who received at least one cycle of ixazomib-based therapy between 1 June 2018 and 30 September 2019 were retrospectively analyzed in Tianjin Medical University General Hospital. Thirteen newly diagnosed MM (NDMM), 13 refractory/relapsed MM (RRMM) and 33 continuous therapy (27 bortezomib peripheral neuritis (PN) intolerant and six maintenance therapy) MM patients were included. The indicated overall response rate (ORR), time to overall response (TOR), and adverse events (AEs) were investigated.

Results: The ORR in NDMM was 76.9%, with one complete response (CR), five very good partial response (VGPR), four partial response (PR), median PFS, and TOR were 122 (66–272) days and 49 (22–108) days. The ORR in RRMM was 46.2%, with one CR, two VGPR, three PR, median PFS, and TOR were 79 (28–169) days and 59 (23–88) days. The ORR in continuous therapy MM patients was 100%, with nine stringent CR, 15 CR, six VGPR and three PR, median TOR was 75 (25–141) days. There were no significant differences regarding ORR between patients with cytogenetic high risk and standard risk in three subgroups (all $P>0.05$). The most frequent hematological AEs were anemia (13.6%) and thrombocytopenia (10.2%). The most common nonhematological AEs were PN (25.0%) and diarrhea (13.6%).

Conclusion: The real-world data demonstrated that ixazomib-based therapy was generally effective and safe in the short term for MM patients.

Keywords: multiple myeloma, ixazomib, real world, overall response rate, adverse events

Introduction

Multiple myeloma (MM) is a malignant clonal disease of plasma cells with poor prognosis and with a median survival of approximate five years, characterized by renal injury, osteolysis, hypercalcemia and anemia.[1,2] Myeloma often affects elderly patients aged more than 65 years.[3] A national population-based analysis data from 2012 to 2016 in China estimated that the standardized prevalence and incidence were 5.68 per 100,000 populations and 1.15 per 100,000 person-years, respectively.[4]

Presently, improvement in the prognosis of MM was observed with the increasing application of novel agents such as proteasome inhibitor (PI) and immunomodulatory drugs.[5] Both PI and immunomodulatory drugs have composed the backbone of newly

Correspondence: Rong Fu
Tel +86-18622008752
Email florai@sina.com

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diagnosed MM (NDMM) and relapse/refractory MM (RRMM) chemotherapy regimens.[1,6] Continuous therapy and maintenance as the long-term treatment approaches in MM offers prolonged disease control and improved progression-free survival (PFS) and overall survival (OS) compared with traditional fixed-duration approaches.[7] In order to optimize individual patient outcomes, the continuous therapy and maintenance treatment approaches are crucial for MM patients, which focus not only on efficacy and drug safety, but also on tolerability.

Ixazomib is the first oral bioavailable PI licensed by the China Food and Drug Administration for the treatment of MM in April 2018. Ixazomib is approved to be administered in combination with lenalidomide and dexamethasone (ixazomib-Rd) for the treatment of MM patients who have received at least one previous therapy. In the global Phase III TOURMALINE-MM1 study and China Continuation Study (CCS),[8,9] ixazomib-Rd demonstrated a significant improvement in PFS vs placebo-Rd, with good safety and tolerability in RRMM patients. Similar results were shown in global phase I/II clinical trials of NDMM patients and a phase III clinical trial of maintenance treatment of MM patients.[10,11] However, the real-world data on ixazomib-therapy for MM patients were seldom used in China.

The study aims to retrospectively evaluate the short-term efficacy and safety of ixazomib in therapy of MM patients in the real-world clinical practice in China.

Materials and Methods

This single-center, retrospective, observational study was conducted in Tianjin Medical University General Hospital, and approved by the Ethics Committee of the hospital with the ethical number of IRB2020-WZ-051.

Patients

Fifty-nine patients hospitalized in the Hematology Department of Tianjin Medical University General Hospital between 1 June 2018 and 30 September 2019, with a diagnosis of NDMM or RRMM, or with bortezomib peripheral neuritis (PN) intolerant and maintenance therapy who received ixazomib-based chemotherapy were included. All patients were followed-up to October 30, 2019. Demographic characteristics and clinical data were collected and assessed. Patients were stratified by Durie–Salmon stage, International Staging System (ISS) disease stage and revised-ISS (R-ISS) stage respectively, and the risk stratification based on International Myeloma Working Group (IMWG) criteria—high risk mutation including del (17p), t (4, 14) and t (14, 16).[11,12] RRMM patients were identified by IMWG consensus.

Treatment Regimens

All patients received ixazomib on days 1, 8, and 15, in 28-day cycles. Ixazomib dose was 4 mg in patients with creatinine clearance (Clcr) ≥30 mL/min, and 3 mg in patients with Clcr <30 mL/min). The number of patients received ixazomib at first, second, third, and fourth-line therapy was 19, 30, 8, and 2 respectively. Ixazomib doublet- or triplet-drug regimens included: Id (ixazomib + dexamethasone 20 mg, days 1, 2, 8, 9, 15, 16, 22, 23, orally or intravenously) regimen; IRd (ixazomib + lenalidomide 25 mg, days 1–21, doses were modulated based on patients' Clcr + dexamethasone 20 mg, days 1, 2, 8, 9, 15, 16, 22, 23, orally or intravenously); ITd (ixazomib + thalidomide 100 mg, days 1–28 + dexamethasone 20 mg, days 1, 2, 8, 9, 15, 16, 22, 23, orally or intravenously); ICd (ixazomib + cyclophosphamide 300 mg/m^2, intravenously, days 1, 8, 15, 22 + dexamethasone 20 mg, days 1, 2, 8, 9, 15, 16, 22, 23, orally or intravenously) and IAd (ixazomib + liposomal doxorubicin 40 mg, day 1 + dexamethasone 20 mg, days 1, 2, 8, 9, 15, 16, 22, 23, orally or intravenously).

Efficacy and Safety Evaluation

The response/efficacy was evaluated using IMWG 2011 response criteria.[13] Blood samples and 24 h urine were collected for MM evaluation at baseline and after each cycle of chemotherapy. Bone marrow examination was undertaken in all patients at baseline, the clonal evolution was investigated at the time of disease progression, and minimal residual disease (MRD) was evaluated at the time of response to ≥complete remission (CR). The outcomes included stringent complete remission (sCR), CR, very good partial remission (VGPR), PR, minimal remission (MR), stable disease (SD), progressive disease (PD) and overall response rate (ORR: ≥PR). Adverse events (AEs) were assessed using the National Cancer Institute Common Toxicity Criteria for AEs, version 5.0.

Statistical Analysis

Baseline characteristics were assessed with descriptive statistical analysis; the mean and standard deviation (SD) or median (range) are presented for continuous variables and frequency distribution (n, %) presented for categorical variables and compared using the chi-squared test. All tests were

two-sided and a level of $P<0.05$ served as the threshold for statistical significance. All statistical analyses were performed in SPSS statistical software package (SPSS version 19.0, IBM Corporation, Armonk, NY, USA).

Results

Baseline Characteristics and Treatment

Among 59 MM patients, 13 were (22.0%) NDMM, 13 (22.0%) RRMM (four relapse, three refractory, six relapse and refractory), and 33 (55.9%) continuous therapy (all better than PR, six patients continued to maintenance after CR and 27 bortezomib PN intolerant). The median age was 67 (47–84) years and 59.3% of patients were male (Table 1).

Table 1 Baseline Characteristics of 59 MM Patients

Baseline Characteristics	n (%)
Age	
Median (range), years	67 (47–84)
<65 years	26 (44.1)
≥65–75 years	27 (45.8)
>75 years	6 (10.2)
Gender	
Male	35 (59.3)
Female	24 (40.7)
NDMM	13 (22.0)
Continued to therapy	33 (55.9)
Bortezomib PN-intolerant (≥PR)	27 (45.8)
RRMM	13 (22.0)
Relapse	4 (6.8)
Refractory	3 (5.1)
Relapse and refractory	6 (10.2)
ECOG PS	
0–1	12 (20.3)
2	19 (32.2)
≥3	28 (47.5)
ISS disease stage	
I	8 (15.7)
II	13 (22.0)
III	38 (64.4)
R-ISS disease stage	
I	6 (11.8)
II	30 (50.8)
III	23 (39.0)
Durie–Salmon stage	
I	3(5.1)
II	10(16.9)
III	46 (78.0)
M-protein subtype IgG λ	19 (32.2)
IgG	32 (54.2)
IgA	12 (20.3)
IgE	1 (1.7)
IgG/A	1 (1.7)
λ light chain	11 (18.6)
κ light chain	2 (3.4)
ClCr, mL/min	
<30	12 (20.30)
30–<60	13 (22.0)
60–<90	13 (22.0)
≥90	21 (35.6)
IMWG myeloma frailty status	
Fit	8 (13.6)
Intermediate	30 (50.8)
Frail	21 (35.6)

(*Continued*)

Efficacy

NDMM Patients

The median follow-up from first ixazomib dose was three (1–11) months. The ORR was 76.9% (10/13), with one patient obtaining CR, five VGPR, and four PR. MRD was positive in the patient with CR. The median time to response was 49 (22–108) days (Table 2). The median PFS was 122 (66–272) days. In 13 patients (four younger and nine older than 65 years) the ORR were 100% and 66.7% respectively, the median number of cycles to response of ixazomib were 2.5 (1–4) and 2.0 (1–4) respectively. In eight frail patients, all received Id regimens, the ORR was 62.5%, with three VGPR, two PR (Supporting information in Table S1).

RRMM Patients

The median follow-up was four (2–10) months. The ORR in RRMM patients was 46.2% (6/13), with one CR, two VGPR, three PR. MRD was positive in the patient with CR. The median time to response was 59 (23–88) days (Table 2). The median PFS was 79 (28–169) days. Of them, six patients received IRd regimen, three IAd, three ICd and one ITd regimen. The ORR in nine bortezomib resistant patients was 33.3% (3/9), with one VGPR (received IAD), two PR (received IAD and IRD). The median response time was 70 (28–112) days.

Continuous Therapy Patients

The median follow-up was six (2–11) months. The ORR in 33 continuous therapy patients was 100%, with nine sCR, 15 CR, six VGPR, three PR. MRD was negative in three of nine patients with sCR and six of 15 patients with CR. The median time to response was 75 (25–141) days (Table 2).

Table 1 (Continued).

Baseline Characteristics	n (%)
Cytogenetic profile	
Standard risk	48 (81.4)
High risk[a]	11 (18.6)
Prior treatment (except NDMM)	
Median cycle of treatment (range)	3 (1–14)
PI	17 (37.0)
IMiD	3 (6.5)
PI+IMiD	26 (56.5)

Note: [a]High-risk cytogenetic was defined as any of del17p, t (4; 14), or t (14; 16).
Abbreviations: NDMM, newly diagnosed multiple myeloma; RRMM, refractory/relapsed multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; R-ISS, revised International Staging System; ClCr, creatinine clearance rate; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

Twenty-seven patients responded better than PR after prior triplet- bortezomib-based therapy, however, they were intolerant to bortezomib PN; Of them, 10 patients (37.0%) received improved response, the median number of treatment cycles was three (one to five). Afterwards, these patients with bortezomib PN intolerant substituted ixazomib therapy for bortezomib, of whom 16 patients received IRd, five IAd, four ICd and two ITd. In other six patients received Id regimen as maintenance therapy, the median treatment duration was four (two to six) cycles, two (33.3%) received improved response to sCR, and all responded better than CR after ≥4 cycles of prior therapies (two patients received PAd, one VRd and three RAd). At the end of follow-up, no relapse or PDs were reported. Across the entire study, the median PFS was not reached for patients with continuous therapy.

Table 2 Efficacy Evaluation of 59 MM Patients

Items	NDMM (n=13) n (%)	RRMM (n=13) n (%)	Continuing Therapy (n=33) n (%)
Median follow-up (months)	3 (1–11)	4 (2–10)	6 (2–11)
Median time to response (days)	49 (22–108)	59 (23–88)	75 (25–141)
sCR	–	–	9 (27.3)
CR	1 (7.7)	1 (7.7)	15 (45.5)
VGPR	5 (38.5)	2 (15.4)	6 (18.2)
PR	4 (30.8)	3 (23.1)	3 (9.1)
MR	1 (7.7)	0 (0,0)	0 (0,0)
SD	1 (7.7)	1 (7.7)	0 (0,0)
PD	1 (7.7)	6 (46.2)	0 (0,0)
ORR	10 (76.9)	6 (46.2)	33 (100)
<65 years	4 (100.0)	9 (69.2)	25 (75.8)
≥65 years	6 (66.7)	4 (30.8)	8 (24.2)
Cytogenetic high risk	3 (100.0)	2 (50.0)	4 (100.0)
Cytogenetic standard risk	7 (70.0)	4 (44.4)	29 (100.0)

Abbreviations: NDMM, newly diagnosed multiple myeloma; RRMM, refractory/relapsed multiple myeloma; sCR, stringent complete remission; CR, complete remission; VGPR, very good partial remission; PR, partial remission; MR, minimal remission; SD, stable disease; PD, progressive disease; ORR, overall response rate (≥PR).

Subgroup Analysis in Different Cytogenetic Risk Patients

The ORR between patients with cytogenetically high risk and standard risk were respectively NDMM (100%, 70%), RRMM (50.0%, 44.4%), continuous therapy (100%, 100%). The differences between the two groups were all without statistical significance (all $P>0.05$). The results were shown in Table 2.

13.6% of patients suffered gene lq21 abnormality, 8.5% undergone gene 17p- mutation. The proportions of gene t (14,16), t (11,14) and t (4,14) abnormalities were 5.1%, 5.1% and 3.4%, respectively (Table 3).

Safety

The most frequently reported hematological AEs were anemia (13.6%) and thrombocytopenia (10.2%). The most common nonhematological AEs were peripheral neuritis (25.0%) and diarrhea (13.6%). Grade 3/4 AEs were reported in nine cases (15.3%). The most commonly reported grade 3/4 AEs were thrombocytopenia (3.4%) and cardiac events (3.4%).The results were shown in Table 4. However, these AEs can be relieved and improved via symptomatic treatment.

Discussion

Ixazomib,when combined with dexamethasone and lenalidomide, has shorter dissociation half-life, better pharmacokinetics, more powerful anti-MM efficacy, even in bortezomib-resistant cells, compared with first generation

Table 3 The Cytogenetically Risk Profile of All 59 Patients

Cytogenetic Abnormality	n (%)
1q21	8 (13.6)
17p-	5 (8.5)
t (14,16)	3 (5.1)
t (11,14)	3 (5.1)
t (4,14)	2 (3.4)
Other mutations	7 (11.9)
More than two mutations	12 (20.3)
Negative	19 (32.2)

Table 4 Safety Analysis of 59 MM Patients

	Any Grade	Grade 3/4
Hematological adverse events		
Anemia	8 (13.6)	1 (1.7)
Thrombocytopenia	6 (10.2)	2 (3.4)
Neutropenia	5 (8.5)	–
Nonhematological adverse events		
PN[a] (32 patients)	8 (25.0)	1(3.1)
Diarrhea	8 (13.6)	1 (1.7)
Infection	5 (8.5)	–
Cardiac events	4 (6.8)	2 (3.4)
Liver dysfunction	2 (3.4)	–
Nausea and vomit	2 (3.4)	–
Skin rash	2 (3.4)	1 (1.7)
Fatigue	2 (3.4)	–
Edema	1 (1.7)	–
Cerebropathy	1 (1.7)	1 (1.7)
Constipation	1 (1.7)	–

Note: [a]Because it is hard to attribute PN to ixazomib or prior-bortezomib treatment, the 27 bortezomib PN intolerant patients in continuing therapy group were excluded here, and analyzed separately in the discussion part.
Abbreviation: PN, peripheral neuritis.

PI.[14,15] A few studies indicated that ixazomib monotherapy, or doublet-/triplet-drug regimens with dexamethasone or/and lenalidomide, were effective in patients with NDMM,[10] RRMM,[8,9] and MM maintenance therapy after autologous stem cell transplantation.[11] In this study, 56.0% of MM patients were older than 65 years, 10.2% were older than 75 years. As known, age is one of the most important prognostic factors in the treatment of MM.[16] A published study reported that approximately one-third of MM patients were older than 75 years at the time of diagnosis.[17]

In our study, the ORR was 76.9% in NDMM. Moreover, the ORR in patients who were younger than 65 years was higher than those who were older (100% vs 66.7%). It was possible that the frail patients in the group of younger than 65 years were fewer than those in the group of older than 65 years (50.0% vs 66.7%). A published phase II study demonstrated that the ORR was 92% in patients with previously untreated MM with IRd regimen.[18] However, 92% NDMM patients were treated with Id doublet regimens in our study. In addition, the median PFS was almost four months, which was much shorter than the 35.4 months reported in a long-term follow-up study in patients with NDMM.[19] Different study population, treatment regimen, treatment duration and variety study design probably led to differences in multiple studies.

This study showed that the ORR was 46.2% of RRMM patients and the median time to response was 59 days. The results were similar with a published abstract of the real-world study that included 27 Chinese patients with ixazomib-based therapy in MM (with 12 NDMM and 15 RRMM) which demonstrated that the ORR of RRMM was 53.3% and the median time to response was 1.76 months.[20] Moreover, a published retrospectively real-world study which focused on the effectiveness and safety of lenalidomide plus dexamethasone (RD) in 546 patients with RRMM at 25 university hospitals in South Korea between October 2009 and December 2016 found that the ORR of RRMM patients who received median seven cycles of RD was 64.2%, with CR 13.1% and VGPR 19.9%.[21] The rate in our study was slightly lower than that demonstrated in the Korean study. In addition, the ORR in our study was significantly lower than 78%, which was reported for RRMM patients in the TOURMALINE-MM1 study.[8] In our study, 76.9% patients received ixazomib as more than third-line therapy, and 69.2% of patients were bortezomib-resistant who were excluded in the TOURMALINE-MM1 trial, which might lead to a lower ORR. Furthermore, the median PFS was 2.6 months in our study, however, median PFS have been reported as 10–18 months in other retrospective studies and 6.7 months in a phase 3 randomized controlled trial.[9,21] The results varied from kinds of therapeutic drugs and treatment duration, different diagnosis and treatment environment, diverse health status of patients, and variety of sample size. The possible causes need further analysis.

Thirty-seven percent of continuing therapy patients received improved response after a median three cycles of ixazomib therapy in our study. The ORR of patients with continuous therapy was 100%, the median response time was 75 days. However, most (81.8%) of them were bortezomib PN-intolerant. Afterwards, the physician substituted bortezomib for ixazomib because of its slight PN-adverse events.[8,9] An open-label phase 1/2 study suggested that ixazomib-based therapy had improvement in depth of response in patients continuing with maintenance therapy.[18]

The most common hematological AEs were thrombocytopenia (13.6%) and anemia (15.3%) in our study which were in line with the incidences (18.4% and 8.2%) reported in a real-world study of lenalidomide and dexamethasone therapy for RRMM patients.[21] Despite transient blood transfusion needed in three patients, no discontinuation was reported because of hematological AEs. PN is the most common AE of first-generation PI, the incidence was approximate 40%,[22] which decreased the life quality of

patients and treatment compliance. Nevertheless, our study reported lower incidence (25.0%) and less severity (grade 3/4 3.1%) of PN. This may have been due to missing data and small sample size. In 27 PN-intolerant but sensitive patients, 11.1% had PN aggravated, 29.6% had PN stable and 59.3% had PN relieved gradually, which suggested good safety of PN with ixazomib therapy.

In our study, 86.4% (51/59) of patients (11 of 13 patients with NDMM could not be included, four patients with myocardial amyloidosis and ECOG ≥3, five with ECOG ≥3, and two with Clcr ≤30 mL/min; 13 patients with RRMM could not be enrolled, 10 patients with greater than third-line treatment and three patients with bortezomib resistance; among 33 patients with continuous treatment, 27 patients with bortezomib PN intolerance had grade 1/2 pain could not be enrolled) were ineligible for the inclusion criteria in the TOURMALINE-MM1 study, who composed a large part of MM patients in China, similarly worldwide. Our study also has some limitations. Firstly, it was retrospective and had a small sample size in a single institution. Secondly, the follow-up was too short to measure OS and entire PFS. Thirdly, comparisons between different treatments were not conducted because of limited numbers of patients. In addition, some information might not be recorded and lost due to the retrospective design. However, the advantage of this study was that NDMM, RRMM and continuous therapy patients were all enrolled and stratified analysis was performed. We will continue to have a longer follow-up and continue to expand the sample size in each subgroup. Therefore, our study demonstrates the efficacy and safety of ixazomib-based therapy in the real-world clinical setting and should provide useful information to physicians treating patients with MM in clinical practice.

Conclusions

The study indicated that ixazomib-based treatments were proved to be effective in the short term for MM patients, also well-tolerated and safe in Chinese real-world practices. And the longer follow-up, larger sample size and case-controlled clinical study of ixazomib-based therapy for MM patients in the real-world also deserved to be performed in the future.

Ethical Approval

The study was approved by the Ethics Committee of Tianjin Medical University General Hospital, with the ethical number of IRB2020-WZ-051. All authors declare that patient data were covered confidentiality. All authors affirm that the guidelines outlined in the Declaration of Helsinki were met.

Consent to Participate

The need for informed consent was waived by the Ethics Committee of Tianjin Medical University General Hospital because the retrospective study involved existing data and records at the time of investigation, and the study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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