Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7768-21
Intern Med 61: 1337-1343, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

Safety Profile of Ixazomib in Patients with Relapsed/Refractory Multiple Myeloma in Japan: An All-case Post-marketing Surveillance

Yoshihide Kakimoto[1], Miyako Hoshino[2], Mikiko Hashimoto[2], Masaya Hiraizumi[3], Kohei Shimizu[4] and Takaaki Chou[5,6]

Abstract:

Objective To evaluate the safety profile of ixazomib combined with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM) in clinical practice in Japan through an all-case post-marketing surveillance.

Methods This was a nationwide non-interventional observational study conducted in Japan. The study included all patients who received ixazomib from May 24 to September 24, 2017. Ixazomib was administered to RRMM patients according to the Japanese package insert. All enrolled patients were observed until the completion of the sixth treatment cycle or until ixazomib discontinuation. The patient treatment course, including adverse events (AEs), was reported.

Results The safety analysis set included 741 patients; the median age was 71 (range 35-92) years old, and the median number of prior treatment lines was 3 (range 1-30). Adverse drug reactions (ADRs) occurred in 572 (77.2%) patients, most commonly being thrombocytopenia (49.9%), diarrhea (29.2%), and nausea (12.4%). Serious ADRs occurred in 193 (26.0%) patients, most commonly being thrombocytopenia (9.9%) and diarrhea (5.9%). Thrombocytopenia, severe gastrointestinal disorders, infections, skin disorders, and peripheral neuropathy were prespecified as ADRs of clinical importance; the frequency of these ADRs (grade ≥3) were 28.5%, 9.4%, 7.4%, 2.2%, and 1.3%, respectively. Treatment discontinuation was most common with thrombocytopenia and severe gastrointestinal disorders (49 and 43 patients, respectively). Eleven patients died due to ADRs (16 events).

Conclusion These results suggest that ixazomib has a tolerable safety profile in clinical practice in Japan. However, close AE management for thrombocytopenia and gastrointestinal disorders should be considered.

Key words: multiple myeloma, ixazomib, proteasome inhibitor, post-marketing all-case surveillance, adverse drug reaction, safety

(Intern Med 61: 1337-1343, 2022)
(DOI: 10.2169/internalmedicine.7768-21)

Introduction

Every year, 5.9-6.2 per 100,000 people in Japan develop multiple myeloma (MM) (1). In the past decades, the prognosis of patients with MM has improved, from a median overall survival of 38.9 months in 1990-2000 to 60.6 months in 2001-2012 (2). At present, the Japanese Society of Hematology practical guidelines recommend the use of proteasome inhibitors (PIs) and immunomodulatory drugs,

[1]Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Limited, Japan, [2]Japan Medical Office, Japan Pharma Business Unit, Takeda Pharmaceutical Company Limited, Japan, [3]Pharmacovigilance, Takeda Development Center Japan, Takeda Pharmaceutical Company Limited, Japan, [4]Biostatistics, Takeda Development Center Japan, Takeda Pharmaceutical Company Limited, Japan, [5]Department of Internal Medicine, Niigata Cancer Center Hospital, Japan and [6]Niigata Kenshin Plaza, General Incorporated Foundation, Health Medicine Prevention Association, Japan

Received: April 14, 2021; Accepted: August 16, 2021; Advance Publication by J-STAGE: October 12, 2021
Correspondence to Miyako Hoshino, miyako.hoshino@takeda.com

and these agents have contributed to the significant improvement in the survival of patients with MM (2-5).

The TOURMALINE-MM1 study (MM1 study), a double-blind, placebo-controlled, Phase III trial, demonstrated that patients with relapsed/refractory MM (RRMM) who received the oral PI ixazomib combined with lenalidomide-dexamethasone (LenDex) had a significantly longer progression-free survival than those who received placebo plus LenDex (median 20.6 months vs. 14.7 months; hazard ratio, 0.74; p=0.01) (6).

Based on the MM1 study, ixazomib was approved in Japan in March 2017 for the treatment of RRMM in combination with LenDex. The MM1 study also showed that the frequency of serious adverse events (SAEs) was similar in those who received ixazomib vs. placebo (47% and 49%), whereas grade 3/4 thrombocytopenia and rash occurred more frequently among patients who received ixazomib than among those who received placebo (19% vs. 9% and 36% vs. 23%, respectively). However, the number of Japanese patients included in the MM1 study was limited.

Therefore, the present all-case post-marketing surveillance aimed to evaluate the safety profile of ixazomib in combination with LenDex in patients with RRMM in clinical practice in Japan.

Materials and Methods

This was a nationwide non-interventional observational study conducted in Japan in accordance with the Declaration of Helsinki and Good Post-Marketing Study Practice (GPSP). Approvals from each institutional ethics committee and written informed consent from patients were not mandatory in this study, in accordance with GPSP. The study protocol was registered with the Japan Pharmaceutical Information Center-Clinical Trials Information (JapicCTI-173592) and ClinicalTrials.gov (NCT03169361).

The study included all patients who received ixazomib in Japan from May 24 to September 24, 2017. Ixazomib was administered to RRMM patients in accordance with the Japanese package insert, in which the recommended starting doses were 4 mg of ixazomib on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients who did not receive ixazomib, as indicated in the case report form, and those for whom the occurrence of adverse events (AEs) was unknown were excluded from the analysis.

All enrolled patients were observed from the start of ixazomib treatment until the completion of the sixth treatment cycle or until ixazomib discontinuation. During the observation period, the following variables were observed: starting doses, dose modifications (i.e., reductions, interruptions, and discontinuations), medications used as infection prophylaxis, any AE, and pregnancy status for women. All outcomes were recorded by the investigating physician on a standardized case report form. As the aim of this surveillance was to collect safety data for ixazomib in clinical practice in Japan, the collection of other data was not strictly enforced, and the duration of follow-up for AEs was not strictly defined. Reported AEs were coded using terminology from the Medical Dictionary for Regulatory Activities (MedDRA) ver. 22.0, and their severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0. AEs that were life-threatening or those leading to death, hospitalization, or permanent impairment of a bodily function were defined as SAEs.

AEs for which a causal relationship to ixazomib was at least considered possible (i.e. the relationship could not be ruled out) as deemed by the investigating physician were defined as adverse drug reactions (ADRs). Based on the safety results from the MM1 study, the following five events were pre-designated as ADRs of clinical importance: thrombocytopenia (including decreased platelet count), severe (grade ≥3) gastrointestinal disorders (diarrhea, nausea, vomiting, etc.), skin disorders, peripheral neuropathy (including sensory and motor), and infection.

Statistical analyses

Results were analyzed using descriptive statistics. Categorical variables were expressed as counts and frequencies, while continuous variables were expressed as medians and ranges or interquartile ranges, as appropriate. Based on the frequency of ADRs of clinical importance in the second interim analysis of the MM1 study (6), the target sample size was set at 480 patients.

Results

Of the 774 ixazomib-treated patients who were registered to the post-marketing surveillance, case report forms were collected for 743. The safety analysis set ultimately included 741 patients (Fig. 1).

The baseline characteristics of all enrolled patients are described in Table 1. The median age was 71 (range 35-92) years old, with 36.8% of patients ≥65 and <75 years old, and 38.5% ≥75 years old. The median duration from the initial diagnosis of MM until patient enrollment was 3.5 (range 0.1-22.4) years. The median number of prior treatment lines was 3 (range 1-30), with 89.3% of patients having received prior PIs and 89.9% having received immunomodulatory drugs. The proportions of patients with liver and kidney dysfunction as judged by the investigating physicians were 6.2% and 39.5%, respectively.

The median initial dose of ixazomib was 4 (range 2.3-4) mg, whereas the average single dose of ixazomib over treated cycles was a median of 3.0 (range 0.8-4.0) mg. The average single doses of lenalidomide and dexamethasone over treated cycles were a median of 10.0 (range 0-25.0) mg and 17.5 (range 0-71.7) mg, respectively. More than three-quarters of patients (77.3%) received prophylaxis for infections, including herpes zoster.

Of the 741 patients included in the analysis set,

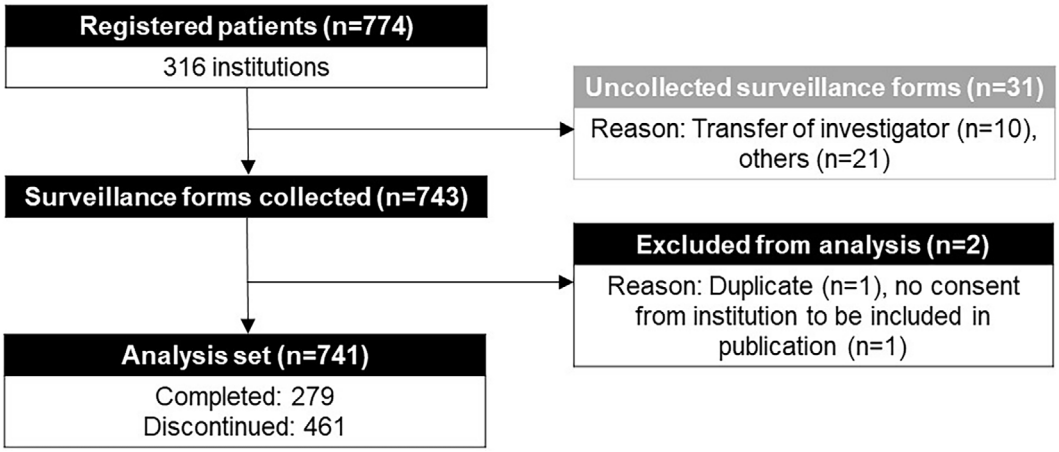

Figure 1. Patient flowchart of the analysis set (n=741). Data on the number of treatment cycles received were missing for one patient.

461 (62.2%) discontinued treatment on or before the sixth cycle, with data missing for 1 patient. The median number of cycles received by these patients was 2 (range 1-6). The most common causes of treatment discontinuation were AEs (243/741; 32.8%) and insufficient effectiveness (191/741; 25.8%). The most common AEs leading to discontinuation were thrombocytopenia (55/461; 11.9%), diarrhea (54/461; 11.7%), vomiting (21/461; 4.6%), nausea (17/461; 3.7%), and pneumonia (15/461; 3.3%).

SAEs occurred in 26.0% (193/741) of patients. The most common SAEs were thrombocytopenia (73/741; 9.9%) and diarrhea (44/741; 5.9%). Of the overall 741 patients, 48 (6.5%) died in this study; 28 (3.8%) died due to progression of the primary disease; and 11 (1.5%) died due to ADRs (16 events; Table 2).

Overall, ADRs occurred in 77.2% of patients (572/741 patients). ADRs reported in ≥1% of patients are reported in Fig. 2. The most common ADRs were thrombocytopenia (370/741; 49.9%), diarrhea (216/741; 29.2%), nausea (92/741; 12.4%), vomiting (68/741; 9.2%), rash (54/741; 7.3%), and peripheral neuropathy (52/741; 7.0%). Grade 3 and 4 ADRs occurred in 38.6% (286/741) and 15.4% (114/741) of patients, respectively.

Among the ADRs of clinical importance, the proportions of patients with grade ≥3 ADRs were 28.5% (211/741) for thrombocytopenia, 9.4% (70/741) for gastrointestinal disorders, 7.4% (55/741) for infections, 2.2% (16/741) for skin disorders, and 1.3% (10/741) for peripheral neuropathy.

Table 3 shows the frequency of ADR events of clinical importance leading to treatment modification and/or discontinuation. Among these ADRs, the number of events leading to treatment discontinuation was highest with thrombocytopenia and severe gastrointestinal disorders (49 and 43 events, respectively).

Discussion

In this all-case post-marketing surveillance, we assessed the safety profile of ixazomib in patients with RRMM in the real-world clinical practice setting in Japan. We found that common ADRs experienced by patients treated with ixazomib combined with LenDex were thrombocytopenia, diarrhea, nausea, vomiting, rash, peripheral neuropathy, decreasing neutrophil count, decreasing white blood cell count, pneumonia, anemia, fatigue, loss of appetite, and herpes zoster. These ADRs were consistent with those reported previously in the MM1 study.

Approximately half of the patients in this study had thrombocytopenia, compared to 31% reported in the MM1 study (6). One possible reason for this difference is that the current study included patients who had platelet counts of < 75,000/mm^3; whereas in the MM1 study, such patients were not eligible. A second contributory factor may have been that the proportion of patients ≥65 years old was higher in this study than in the MM1 study (75.3% vs. approximately 53%). Owing to the presence of comorbidities and a decreased physiological function, elderly patients have a higher tendency to exhibit thrombocytopenia than younger patients (7). Another contributory factor might be the higher number of prior regimens in this study (median 3, range 1-30) than in the MM1 study (median 1, range 1-3). Previous studies on other PIs have shown that a higher number of prior regimens was associated with an increased risk of grade 3/4 thrombocytopenia (odds ratio 1.259; p=0.007) (8).

In the present study, dose reduction or interruption occurred in more than 35% of thrombocytopenia events, but such events resulted in discontinuation in <7% of all patients with thrombocytopenia (Table 3). These results are consistent with the safety data from the MM1 study (9), in which patients receiving ixazomib reported grade ≥3 thrombocytopenia twice as frequently as those receiving placebo, yet the frequency of treatment discontinuation was similar between the two groups. This suggests that the use of dose-modification guidelines was able to effectively reduce treatment discontinuation in clinical practice. According to Kumar et al. (2017), platelet counts should be monitored dur-

Table 1. Baseline Patient Characteristics.

Category	n=741*
Median age (range), years	71 (35-92)
Age groups, n (%)	
<65 years	183 (24.7)
≥65 and <75 years	273 (36.8)
≥75 years	285 (38.5)
Gender, n (%)	
Female	390 (52.6)
Male	351 (47.4)
Median weight (range), kg	52.7 (29.9-104.0)
Median BSA (range), m^2	1.5 (1.0-2.3)
Range of BSA, n (%)	
<1.4	149 (20.1)
≥1.4 and <1.6	254 (34.3)
≥1.6	302 (40.8)
International Staging System, n (%)	
Stage 1	140 (18.9)
Stage 2	259 (35.0)
Stage 3	290 (39.1)
Unknown	50 (6.7)
ECOG performance status, n (%)	
0	240 (32.4)
1	294 (39.7)
2	111 (15.0)
3	81 (10.9)
4	15 (2.0)
Liver dysfunction, n (%)	46 (6.2)
Kidney dysfunction, n (%)	293 (39.5)
Median time since initial diagnosis (range), years	3.5 (0.1-22.4)
Median number of prior regimens (range)	3 (1-30)
Number of prior regimens, n (%)	
1	142 (19.2)
2	167 (22.5)
3	107 (14.4)
≥4	318 (42.9)
Prior therapy, n (%)	
Proteasome inhibitors	661 (89.2)
Immunomodulatory drugs	665 (89.7)
Refractory to prior therapy, n (%)	
Any	582 (78.5)
Proteasome inhibitors	440 (59.4)
Immunomodulatory drugs	508 (68.6)
Proteasome inhibitors and immunomodulatory drugs	366 (49.4)

*Some categories do not include all the 741 patients.

BSA: body surface area, ECOG: Eastern Cooperative Oncology Group

ing ixazomib treatment (weekly during the first three cycles and at least monthly thereafter), and if the count drops to <30,000/mm^3, ixazomib and lenalidomide should be withheld (9).

However, one in every three events of severe gastrointestinal disorders caused discontinuation (Table 3), accounting for the highest frequency of treatment discontinuation among ADRs of clinical importance. This might have contributed to patients' reluctance to continue treatment with ixazomib despite the potential feasibility of long-term treatment, as indicated by available safety data (9). To ameliorate nausea, the use of serotonin receptor antagonists prior to ixazomib dosing should be considered in patients who develop nausea (9). Anti-diarrheal mediation and laxative adjustments may also be used as needed; however, these are not recommended as prophylactics. Careful monitoring of gastrointestinal symptoms, interventions to relieve these symptoms, and appropriate prophylaxis are thus necessary for ensuring continuous treatment.

In an exploratory analysis of our study, the frequencies of

Table 2. Summary of Patients who Died Due to ADRs.

No.	Sex	Age group (years)	ECOG PS	Number of prior regimens	ADR leading to death (MedDRA preferred term)	Time (days) from treatment initiation to the occurrence of the ADR	Time (days) from treatment initiation to death
1	Female	≥75	3	3	Septic shock	20	21
					Plasma cell myeloma	21	-
2	Female	≥65 and <75	1	6	Death	44	44
3	Male	<65	1	5	Pancytopenia	42	43
					Septic shock	42	-
					Renal dysfunction	42	-
4	Male	≥75	1	2	Pneumonia	14	16
5	Male	≥75	1	3	Colisepticemia	15	20
6	Female	≥65 and <75	3	4	Pulmonary edema	17	17
7	Male	≥75	2	6	Vomiting of blood	5	5
8	Male	≥65 and <75	0	2	Bronchioloalveolar carcinoma	205	353
9	Female	≥75	3	4	Staphylococcal pneumonia	65	68
					Staphylococcal sepsis	65	-
10	Male	<65	0	4	Pneumonia	173	180
					C-reactive protein increase	172	-
11	Female	<65	4	6	Gastrointestinal necrosis	46	47

Coding with MedDRA Ver.22.0. When a single patient experiences several events, each event is counted but is counted as 1 case.
ADR: adverse drug reaction, ECOG: European Cooperative Oncology Group, MedDRA: Medical Dictionary for Regulatory Activities, PS: performance status

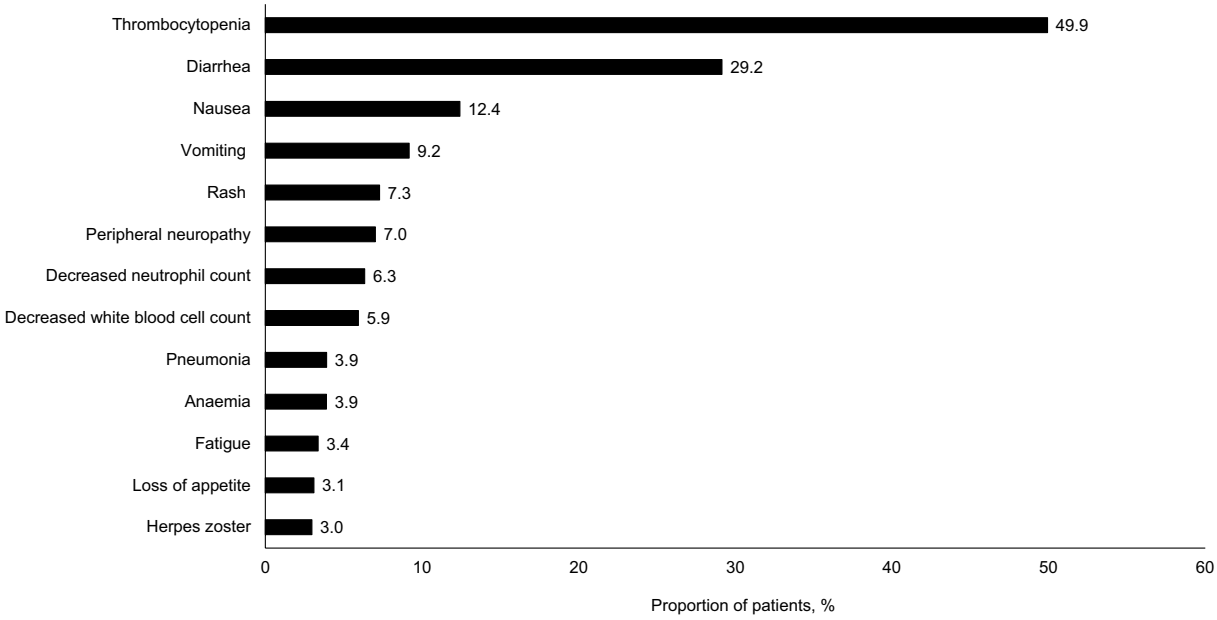

Figure 2. Adverse drug reactions reported in ≥3% of all patients (n=741). When a single patient experienced several events of the same preferred term, one patient was counted for all events. Any Common Terminology Criteria for Adverse Events missing value was counted as unknown.

thrombocytopenia and diarrhea were numerically higher by more than 5% in patients ≥75 years old than in younger patients (≥65 and <75 years old, and <65 years old) (data not shown). Based on a previous pharmacokinetics analysis (10), severe renal impairment, end-stage renal disease requiring dialysis, and moderate-to-severe hepatic impairment are associated with increased total systemic exposure to ixazomib, and the increased drug exposure may lead to increased incidence of known ADRs (grade ≥3, anemia and thrombocytopenia; grade ≥2, diarrhea, fatigue, nausea, peripheral neuropathy, and rash) in these patients. Therefore, close monitoring and dose modification should be considered for patients with an older age, severe renal impairment, and moderate-to-severe hepatic impairment.

Two deaths were due to septic shock, and two were due to pneumonia. The increased susceptibility to infections may also have been related to the underlying immunodeficiency due to the primary disease and the presence of other concomitant therapies (11-13).

Based on these findings, the results of this all-case sur-

Table 3. ADRs of Clinical Importance Leading to Treatment Dose Modification or Discontinuation.

ADR	Total no. of events	Events leading to ixazomib dose modification or discontinuation, n (%)				
		Reduction	Interruption	Discontinuation	Reduction and interruption	(Reduction and/or interruption) and discontinuation
Thrombocytopenia	710	23 (3.2)	129 (18.2)	39 (5.5)	51 (7.2)	10 (1.4)
Severe GI disorders*	117	13 (11.1)	13 (11.1)	39 (33.3)	20 (17.1)	4 (3.4)
Skin disorders**	138	5 (3.6)	17 (12.3)	13 (9.4)	14 (10.1)	2 (1.4)
Peripheral neuropathy	58	6 (10.3)	4 (6.9)	7 (12.1)	4 (6.9)	4 (6.9)
Infections***	133	0	67 (50.4)	24 (18.0)	8 (6.0)	0

*Includes diarrhea, nausea, emesis, abdominal pain, constipation, GI necrosis, obstruction, melena, stomatitis, axial volvulus, mechanical ileus, bleeding.

**Includes rash, pruritus, erythema, exanthem, acute febrile neutrophilic dermatosis, eczema, purpura, alopecia, acne, papules, nail disorder.

***Includes herpes; ear, nose, and throat infections; respiratory infections; GI tract infections; cystitis; bacteremia.

ADR: adverse drug reaction, GI: gastrointestinal

veillance are consistent with the safety profile of ixazomib observed in the clinical study in combination with LenDex in patients with RRMM (6). It should be kept in mind that thrombocytopenia is an expected ADR, as indicated in the ixazomib package insert.

Of note, the results of this surveillance should be evaluated alongside a thorough consideration of several study limitations, including the non-blinded, non-randomized, non-controlled study design, which lends inherent risks for bias. Furthermore, the patients were observed only until the end of the sixth treatment cycle or until treatment discontinuation (whichever came first); therefore, the study was unable to detect any long-term ADRs.

Conclusion

This analysis showed an acceptable safety profile of ixazomib for RRMM patients in clinical practice in Japan. The ADRs observed in this post-marketing surveillance were similar to those reported in the MM1 study despite patients in this study being older and heavily pre-treated. Thrombocytopenia was frequent, and this should be managed with appropriate dose modification or interruption if warranted. Gastrointestinal symptoms require appropriate prophylaxis and symptomatic therapy for continuous treatment.

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within three months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Author's disclosure of potential Conflicts of Interest (COI).
Yoshihide Kakimoto: Employment, Takeda Pharmaceutical. Miyako Hoshino: Employment, Takeda Pharmaceutical. Mikiko Hashimoto: Employment, Takeda Pharmaceutical. Masaya Hiraizumi: Employment, Takeda Pharmaceutical. Kohei Shimizu: Employment, Takeda Pharmaceutical. Takaaki Chou: Honoraria, Takeda Pharmaceutical, Janssen Pharmaceuticals, Celgene and BMS.

Financial Support

This study was funded by Takeda Pharmaceutical.

Medical writing support was provided by Ivan Olegario of MIMS Pte, Ltd., which was funded by Takeda Pharmaceutical Company Limited (Tokyo, Japan), and complied with Good Publication Practice 3 ethical guidelines (Battisti et al. Ann Intern Med 163: 461-464, 2015).

Acknowledgement

We thank the patients who participated in this study, their families, and all participating investigators. We also thank Ichirou Nakayama for providing valuable advice on the interpretation of the study data.

References

1. Cancer Information Service, National Cancer Center, Japan. Cancer Registry and Statistics. [Internet]. Ministry of Health, Labour and Welfare, National Cancer Registry. 2016-2017 [cited 2021 Jun]. Available from: https://ganjoho.jp/reg_stat/statistics/dl/ (in Japanese)
2. Ozaki S, Handa H, Saitoh T, et al. Trends of survival in patients with multiple myeloma in Japan: a multicenter retrospective collaborative study of the Japanese Society of Myeloma. Blood Cancer J **5**: e349, 2015.
3. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood **111**: 2516-2520, 2008.
4. Ozaki S. Treatment algorithms for multiple myeloma in Japan. Rinsho Ketsueki (Jpn J Clin Hematol) **58**: 1014-1023, 2017.
5. Iida S, Ishida T, Murakami H, et al. JSH practical guidelines for hematological malignancies, 2018: III. Myeloma-1. Multiple myeloma (MM). Int J Hematol **109**: 509-538, 2019.
6. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med **374**: 1621-1634, 2016.
7. Mehta J, Cavo M, Singhal S. How I treat elderly patients with myeloma. Blood **116**: 2215-2223, 2010.
8. Lonial S, Waller EK, Richardson PG, et al. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed,

refractory multiple myeloma. Blood **106**: 3777-3784, 2005.
9. Kumar S, Moreau P, Hari P, et al. Management of adverse events associated with ixazomib plus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma. Br J Haematol **178**: 571-582, 2017.
10. Gupta N, Hanley MJ, Xia C, Labotka R, Harvey RD, Venkatakrishnan K. Clinical pharmacology of ixazomib: the first oral proteasome inhibitor. Clin Pharmacokinet **58**: 431-449, 2019.
11. Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. Rheum Dis Clin North Am **42**: 157-176, ix-x, 2016.
12. Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica **100**: 107-113, 2015.
13. Ying L, YinHui T, Yunliang Z, Sun H. Lenalidomide and the risk of serious infection in patients with multiple myeloma: a systematic review and meta-analysis. Oncotarget **8**: 46593-46600, 2017.