Tolerability and safety of real-world use of pomalidomide in patients with relapsed/refractory multiple myeloma

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Abstract. Pomalidomide (POM) is a second-generation immunomodulatory agent with proven efficacy in patients with relapsed/refractory multiple myeloma (RRMM) proven to be refractory to previous treatment with lenalidomide (LEN) and bortezomib. We herein conducted a retrospective analysis of 14 RRMM patients receiving POM to determine its tolerability and safety in the clinical setting. The median age of the patients was 72 years (range, 58-84 years), and 85.7% of the patients were aged >70 years. The most frequent treatment dose was 3 mg/day. POM dose reductions were required in 54.5% (6/11) of the patients. The patient data were compared among three age groups (<70, 70-75 and >75 years) and there was only significant difference in daily POM treatment dose. The tolerability of POM must be confirmed, particularly in elderly patients. Dose reduction from 4 to 3 mg occurred during the second cycle in 83.3% (5/6) of the patients. It is important to determine the tolerability of POM in the early phases of treatment. The most frequently reported grade 3/4 hematological adverse events were neutropenia (64.3%), anemia (64.3%) and thrombocytopenia (57.1%). Although the median number of treatment cycles was 4 (range, 1-13), 21.4% (3/14) of the patients with a performance status (PS) of 3 were administered only 1 treatment cycle. The tolerability of POM was low among patients with poor PS and an aggressive treatment introduction should be avoided. However, 21.4% (3/14) of the patients were able to continue treatment for >1 year and some patients received long-term therapy. POM does not require dose modification for renal function, and multiple capsule doses are available, which is an advantage of POM compared with LEN. POM may be administered to late-stage RRMM patients in a real-world clinical setting, but elderly patients or those with poor PS must be treated with caution. In this manner, the treatment options for RRMM patients may be expanded by assessing the tolerability and safety of POM.

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Introduction

Multiple myeloma (MM) is an incurable hematological malignancy caused by pathological proliferation of plasma cells. MM is a disease of older adults, with a median age at diagnosis of 66 years (1). The median survival of patients with MM has notably improved, from 3-4 years to ~7-8 years, due to the development of various new agents, such as immunomodulatory drugs (IMiDs), including thalidomide or lenalidomide (LEN), and proteasome inhibitors (PIs), such as bortezomib (BOR) (2,3). Patients who relapse after or become refractory to IMiDs and BOR have a very poor prognosis, with a median overall survival (OS) of 9 months, or only 3 months if no further treatment is administered (4). Recently, survival has been further prolonged with the introduction of new PIs (carfilzomib or ixazomib), histone deacetylase inhibitors (panobinostat) and monoclonal antibodies (elotuzumab or daratumumab) (5).

Pomalidomide (POM) is a second-generation IMiD with different antitumor mechanisms compared with those of LEN (6). IMiDs can be administered *per os*, which is convenient and may particularly benefit older patients. The evidence regarding POM efficacy in patients with relapsed/refractory MM (RRMM) is based on a phase 3 trial (MM-003) that compared POM plus low-dose dexamethasone (DEX) therapy to high-dose DEX alone (7). Based on the results of the phase 2 trial (MM-002) (8) and MM-003, POM was approved in the United States, European Union and other countries in 2013. A recent phase 3b trial (MM-010) proved the safety and efficacy of POM in a large population of RRMM patients refractory to LEN and BOR treatment (9,10).

However, real-world data are scarce. POM has been approved only for patients refractory to LEN and BOR, and it may be administered to late-stage RRMM patients. Clinical trial data may not always reflect real-world clinical practice and outcomes. Thus, a retrospective analysis of RRMM patients receiving POM was conducted to determine its tolerability and safety in a real-world clinical setting.

Patients and methods

Patients. The subjects of this study were RRMM patients who received POM at the Ogaki Municipal Hospital (Ogaki, Japan) between June 2015 and May 2018. POM was administered on days 1-21 of 28-day cycles with low-dose DEX on days 1, 8, 15 and 22.

Patient background. The characteristics of the patients treated with POM were investigated to determine their sex, age, time from diagnosis, estimate glomerular filtration rate (eGFR) and laboratory data at initiation of POM treatment, myeloma subtype, cytogenetic abnormalities, international staging system categorization at diagnosis and prior treatment.

POM tolerability. The POM dosing information (exposure to POM, number of treatment cycles, daily treatment dose and initiation treatment dose) was examined. Patients were divided into three age groups (<70, 70-75 and >75 years), and laboratory data and POM treatment data were compared among these three groups.

POM safety. The adverse events (AEs) associated with POM treatment were recorded from electronic charts and medication management records. The reasons for POM dose reduction or interruption as a result of AEs were examined. The severity of AEs was classified according to the Common Terminology Criteria for Adverse Events, version 4.0 (11).

Statistical analysis. The data were analyzed using JMP software, version 5.0.1J (SAS Institute Japan Ltd., Tokyo, Japan). The Kruskal-Wallis test was used for comparisons among age groups. The recorded P-values were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient background. The baseline characteristics of 14 patients who received POM are listed in Table I. A total of 68 cycles were administered. The median age (range) of the patients was 72 (58-84) years, and the patients received a median of 3 (1-7) prior treatment regimens. A total of 85.7% (12/14) patients had been refractory to LEN and BOR treatment. Two patients had been treated with high-dose conventional therapy with autologous stem cell transplantation (HDT-ASCT), whereas the others were considered ineligible for HDT-ASCT.

POM tolerability. POM dosing information is shown in Table II. The median treatment duration and number of treatment cycles were 3.7 (0.9-14.3) months and 4 (1-13), respectively. A total of 21.4% (3/14) of the patients were able to continue treatment for >1 year. The median POM treatment dose was 3 (1-4) mg/day. The most frequent treatment doses were 3 mg/day (48.5% of the patients), and 4 mg/day (41.2% of the patients). The initiation POM treatment dose was 4 mg in 78.6% (11/14) of patients. Two patients were started on 3 mg due to a history of low tolerability (hematological AEs) or ileus caused by LEN; the remaining patient was started on 2 mg due to low tolerability (hematological AEs) caused by LEN. A comparison of laboratory data and POM treatment data among the three age categories (<70, 70-75 and >75 years) is presented in Table III. Although there was no significant difference in the baseline characteristics of the patients (performance status, prior treatment regimens, laboratory data or exposure to POM), there was a significant difference in the daily treatment dose ($P<0.01$).

POM safety. In the present study, the most frequently reported grade 3/4 hematological AEs were neutropenia (64.3%), anemia (64.3%) and thrombocytopenia (57.1%). Infection was the most frequent grade 3/4 non-hematological AE (42.9%), and fatigue occurred in 28.6% of the patients (Table IV). The reasons necessitating dose reduction or interruption of POM treatment are summarized in Table V. Dose reduction or interruption occurred in 50.0% of the patients, most commonly due to neutropenia (35.7%) and thrombocytopenia (14.3%). The rate of dose interruption due to fatigue was 21.4% (3/14). The rate of overall discontinuation due to AEs was 28.6% (4/14).

Discussion

We herein describe the real-world use of POM administered to 14 RRMM patients at Ogaki Municipal Hospital. In the present study, all the patients were considered as ineligible for HDT-ASCT when they received treatment with POM. Prior treatment comprised >3 regimens in almost all patients. POM was used at late-stage RRMM. The median patient age (range) was 72 (58-84) years, which was higher compared with that reported in other real-world or large-scale phase 3 trial data 59 (32-78) years in Sriskandarajah *et al* (12), 61 (41-82) years in Maciocia *et al* (13) and 66 (37-88) years in the MM-010 trial (9). In the present study, 85.7% of patients were aged >70 years, which was a higher rate compared with the other studies. The patient characteristics were analyzed among the three age groups (<70, 70-75, >75 years). There was no difference in treatment initiation dose, exposure to POM or number of treatment cycles. Although the initiation treatment dose was 4 mg/day in 78.6% (11/14) of the patients, the most frequent treatment dose was 3 mg/day (48.5% of total treatment courses). POM dose reductions were required in 54.5% (6/11) of the patients. The frequency of dose reduction was higher compared with that in the MM-010 (22.0%) and MM-011 (25.0%) trials. There was only a significant difference in daily treatment dose among age groups. The tolerability of POM must be particularly confirmed in elderly patients. In the present study, the reduction from 4 to 3 mg occurred during the second treatment cycle in 83.3% (5/6) of the patients. It is important to recognize the tolerability of each patient to POM in the early stages. Ailawadhi *et al* (14) reported long durations of treatment and response, higher response rates and fewer AEs with 2 mg POM. Therefore, the efficacy and safety of POM has been reported even at lower doses, and treatment dose must be reduced according to each patient's tolerability.

In the IFM2009-02 trial, 39.7% of the patients were able to continue treatment for >1 year. There was a significant difference between the two groups (≥1 vs. <1 year of treatment). The progression-free survival (PFS) was 20.7 vs. 4.6 months. Similarly, the OS rate was 100 vs. 66% at 12 months and 91 vs. 40% at 18 months, respectively (15). Sriskandarajah *et al* (12) reported a significant effect in 61.5% (24/39) of patients who were able to continue treatment for >5 cycles. Long-term treatment

Table I. Baseline characteristics of the patients.

Characteristics	No. (%) or median [range]	
Number of patients	14	
Sex		
Male	6	(42.9)
Female	8	(57.1)
Age (years)	72	[58-84]
≥70	12	(85.7)
>75	5	(35.7)
Time from diagnosis (years)	2.2	[0.7-14.2]
ECOG performance status		
0-1	9	(64.3)
2-3	5	(35.7)
eGFR at initiation of pomalidomide treatment (ml/min/1.73 m^2)		
eGFR ≥60	7	(50.0)
60> eGFR ≥30	4	(28.6)
30> eGFR	3	(21.4)
Laboratory data at initiation of pomalidomide treatment		
WBC (per μl)	4,560	[2,300-8,380]
Neutrophils (per μl)	2,759	[1,035-7,039]
Hemoglobin (g/μl)	9.4	[6.9-11.9]
Platelets (x10^4 per μl)	14.4	[6.1-29.9]
Myeloma subtype		
IgG	4	(28.6)
IgA	7	(50.0)
Light chain only	3	(21.4)
Cytogenetic abnormalities		
del (17p)	0	(0.0)
t (4:14)	0	(0.0)
t (14:16)	0	(0.0)
Other	3	(21.4)
International staging system at diagnosis		
I	4	(28.6)
II	6	(42.9)
III	4	(28.6)
Prior treatment		
Prior treatment regimens	3	[1-7]
>2 previous regimens	13	(92.9)
Dexamethasone	14	(100.0)
Lenalidomide	14	(100.00
Bortezomib	13	(92.9)
Thalidomide	2	(14.3)
Carfilzomib	3	(21.4)
Ixazomib	0	(0.0)
Cyclophosphamide[a]	4	(28.6)
Melphalan[b]	8	(57.1)
Stem cell transplantation	2	(14.3)
Refractory to prior therapies		
Lenalidomide	13	(92.9)
Bortezomib	13	(92.9)
Both lenalidomide and bortezomib	12	(85.7)

[a]Including cyclophosphamide that was administered for stem cell mobilization. [b]Including high-dose melphalan. ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; WBC, white blood cell; Ig, immunoglobulin. Data are presented as n (%) or median [range].

Table II. Pomalidomide dosing information.

	No. (%) or median [range]	
Exposure to pomalidomide (months)		
≤1	3	(21.4)
2-3	4	(28.6)
4-5	4	(28.6)
6-12	0	(0.0)
>12	3	(21.4)
Median treatment duration (months)	3.7	[0.9-14.3]
Median number of treatment cycles	4	[1-13]
Daily treatment dose, mg/day (n=68)		
4	28	(41.2)
3	33	(48.5)
2	5	(7.4)
1	2	(2.9)
Median daily treatment dose, mg/day	3	[1-4]
Initiation treatment dose, mg/day (n=14)		
4	11	(78.6)
3	2	(14.3)
2	1	(7.1)
1	0	(0.0)

continuity with POM has been shown to lead to prolonged PFS and OS. In the present study, only 21.4% of the patients were able to continue treatment for >1 year. Gueneau *et al* (16) reported POM effectiveness in the early recurrence phase. However, Palmas *et al* (17) reported its effectiveness in heavily pretreated patients. Therefore, the timing of POM treatment initiation must be individualized. Some patients were able to continue with long-term treatment, and POM may be expected to remain continuously effectiveness. However, 21.4% (3/14) of the patients could only tolerate 1 treatment cycle. These patients were unable to receive the next treatment due to the deterioration of their PS. One patient had first been diagnosed 14 years prior and was heavily pretreated. The other patients were refractory to carfilzomib. The PS of all three patients was 3 when they received

Table III. Comparison of laboratory data and pomalidomide treatment data between age categories.

Factors	Age categories (years) <70	70-75	>75	P-value
Number of patients	2	7	5	0.39
ECOG performance status	1 [0-1]	2 [0-3]	1 [0-3]	0.29
Time from diagnosis, median (years)	4.0 [1.6-6.3]	1.7 [0.7-14.2]	3.2 [0.8-9.3]	0.85
Prior treatment regimens	3 [2-3]	3 [2-6]	3 [1-7]	0.82
Laboratory data at initiation of pomalidomide treatment				
eGFR (ml/min/1.73 m^2)	64.2 [29.1-99.2]	57.1 [13.9-101.3]	64.6 [42.7-81.4]	0.93
WBC (per μl)	3,955 [2,980-4,930]	4,950 [2,830-7,040]	3,420 [2,300-8,380]	0.74
Neutrophils (per μl)	2,531 [1,788-3,352]	2,871 [1,330-5,914]	2,155 [1,035-5,698]	0.79
Hemoglobin (g/μl)	9.5 [7.6-11.4]	9.2 [6.9-11.9]	9.5 [8.8-10.6]	0.99
Platelets (x10^4 per μl)	15.3 [15.2-15.3]	13.5 [7.2-29.9]	11.5 [6.1-25.8]	0.79
Pomalidomide treatment				
Exposure to pomalidomide (months)	12 [9-12]	4 [1-14]	3 [1-11]	0.12
Number of treatment cycles	9 [5-13]	3 [1-13]	3 [1-12]	0.39
Daily treatment dose (mg/day) (n=68)	4 [2-4]	3 [3-4]	3 [1-4]	<0.01
Initiation treatment dose (mg/day) (n=14)	4 [4-4]	4 [3-4]	4 [2-4]	0.26
Dose reduction of pomalidomide	1 (50.0)	2 (28.6)	3 (60.0)	0.12
Dose interruption of pomalidomide	2 (100.0)	2 (28.6)	3 (60.0)	0.12
Overall discontinuation of pomalidomide	1 (50.0)	2 (28.6)	1 (20.0)	0.74

ECOG, eastern cooperative oncology group; eGFR, estimated glomerular filtration rate; WBC, white blood cell. Data are presented as n (%) or median [range].

Table IV. Adverse events associated with pomalidomide (n=14).

Adverse events	Grade 3/4 No.	(%)	All grades No.	(%)
Hematological				
Neutropenia	9	(64.3)	9	(64.3)
Anemia	9	(64.3)	11	(78.6)
Thrombocytopenia	8	(57.1)	9	(64.3)
Leukopenia	8	(57.1)	9	(64.3)
Febrile neutropenia	1	(7.1)	1	(7.1)
Non-hematological				
Infection	6	(42.9)	6	(42.9)
Pneumonia	2	(14.3)	2	(14.3)
Pyrexia	0	(0.0)	6	(42.9)
Fatigue	4	(28.6)	7	(50.0)
Peripheral neuropathy	0	(0.0)	2	(14.3)
Skin rash	0	(0.0)	5	(35.7)
Pruritus	0	(0.0)	4	(28.6)
Edema face	0	(0.0)	1	(7.1)
Increased serum ALT	1	(7.1)	4	(28.6)
Increased serum AST	0	(0.0)	5	(35.7)
Anorexia	0	(0.0)	3	(21.4)
Constipation	1	(7.1)	4	(28.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table V. Reasons for dose reduction or interruption of pomalidomide treatment.

Reasons for modification	Patients (n=14), n (%)		Occasions (n=68), n (%)	
Dose reduction	7	(50.0)	11	(16.2)
Neutropenia	5	(35.7)	8	(11.8)
Thrombocytopenia	2	(14.3)	4	(5.9)
Fatigue	1	(7.1)	1	(1.5)
Infection	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)
Skin rash	0	(0.0)	0	(0.0)
Increased serum ALT or AST	2	(14.3)	2	(2.9)
Dose interruption	7	(50.0)	15	(22.1)
Neutropenia	5	(35.7)	6	(8.8)
Thrombocytopenia	2	(14.3)	2	(2.9)
Fatigue	3	(21.4)	3	(4.4)
Infection	1	(7.1)	0	(0.0)
Pneumonia	1	(7.1)	1	(1.5)
Skin rash	1	(7.1)	1	(1.5)
Increased serum ALT or AST	2	(14.3)	2	(2.9)
Overall discontinuation due to AEs	4	(28.6)		

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

POM. The tolerability of POM is generally low in patients with poor PS. Thus, aggressive treatment introduction should be avoided. There is a wide range of patients who may be treated by POM in the real-world setting, including patients with a high age or in a poor condition. It is important to determine tolerability and safety. In the present study, the patients who were unable to continue long-term treatment were switched to treatments including carfilzomib, daratumumab or panobinostat. The therapeutic options for patients with late-stage disease continue to expand, with continuous introduction of new treatments, including elotuzumab and ixazomib. These new agents have further prolonged the OS of RRMM patients. The most notable advantage of IMiDs is that they may be administered orally. This route of administration is convenient and particularly beneficial for older patients. Therefore, it is important to select treatment for RRMM patients taking into consideration patient convenience and treatment cost (18,19).

In the present study, the incidence of grade 3/4 hematological AEs was compared with that of the MM-010 trial for neutropenia (64.3 vs. 49.7%), anemia (78.6 vs. 33.0%) and thrombocytopenia (64.3 vs. 24.1%) (9). Compared with the Japanese clinical trial (MM-011), the incidence of neutropenia was comparable (64.3 vs. 63.8%). However, anemia (78.6 vs. 41.7%) and thrombocytopenia (64.3 vs. 31.4%) were more frequent in the present study (20). Except for 3 patients who received only 1 treatment cycle, POM dose reduction or interruption occurred in 63.6% (7/11) of the patients. Therefore, we should confirm the incidence of hematological AEs carefully in a real-world setting.

LEN requires dose modification according to renal function. However, POM is indicated and is efficacious and safe even in patients with severe renal impairment (21). Maciocia *et al* (13) reported no significant difference in response, survival, or tolerability by renal function. Therefore, POM is easier to use compared with LEN for patients with renal impairment. However, POM may only be used in patients who have received at least 2 prior therapies, including LEN and BOR. This affects the timing of treatment initiation due to patient restrictions. It may also be necessary to consider introducing POM in early myeloma treatment.

The capsule dosing of POM is convenient for patients. There are 2 types of capsules (2.5 and 5 mg) in LEN. The usual dose of LEN is 25 mg for MM patients; therefore, the patient must take 5 capsules, which may be inconvenient. By contrast, POM is available in 4 doses (1, 2, 3 and 4 mg). Therefore, patients must only take 1 capsule, which may contribute to improved compliance due to the convenience. However, when POM dose reduction is required, it is necessary to change to a different capsule. If the patients have not completed one cycle of treatment, they are not able to take the remaining POM. With regard to inventory, it is difficult to continuously stock all 4 expensive dose types of POM in the hospital or pharmacy, and the expiration date of POM is only 4 years. As we previously experienced having to discard expired POM in our hospital, Thus, the patient condition must be carefully determined and a close communication with the prescribing physician must be maintained.

In conclusion, we herein conducted a retrospective analysis of RRMM patients treated with POM to describe its tolerability and safety in a real-world clinical setting. The age of the patients receiving POM was higher compared with that reported in the clinical trials. The incidence of grade 3/4 hematological AEs was high and the tolerability of POM was low for patients with poor PS. The most frequent treatment dose was 3 mg/day. POM dosage should be reduced in the early phases, but POM may be administered to frail patients in a real-world setting. It is crucial that we pay close attention to elderly or poor PS patients in particular. In that manner, we

may expect an expansion of the treatment options available to RRMM patients by assessing the tolerability and safety of POM. Our real-world experience may provide confirmatory support for further research on POM. However, the number of patients included in this study was small, real-world data from multiple centers must be accumulated to confirm our results.

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Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

EU and MK designed the study and prepared the manuscript. EU and ST observed the patients' condition and collected clinical data. EU and MI analyzed the data. HT and TY interpreted the data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was performed according to the principles set out in the 1964 Declaration of Helsinki and all subsequent revisions, and was approved by the Ethics Committee at Ogaki Municipal Hospital (20180628-6).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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