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Case Report

A long-term favorable response and effective control of neutropenia obtained by low-dose pomalidomide treatment in a patient with relapsed refractory multiple myeloma: a case report

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Abstract: In June 2011, a 66-year-old woman was diagnosed as multiple myeloma (IgG-k type). In July 2011, she received bortezomib and dexamethasone therapy with a 5-week cycle. After the third treatment cycle, the patient showed disease progression to secondary plasma cell leukemia. In September 2011, lenalidomide and dexamethasone therapy was initiated with a 4-week cycle; however, the patient remained refractory to treatment. In October 2011, the therapy regimen was switched to vincristine/doxorubicin/dexamethasone with a 3-week cycle. Partial response (PR) was achieved after the first cycle. In December 2011 and April 2012, autologous peripheral blood stem cell transplantations were performed. Stringent complete remission was achieved in December 2011 and was sustained for about 3 years. Disease relapse occurred in January 2015. There was a temporary response to melphalan and prednisolone (MP) therapy; however, the patient eventually developed progressive disease. In September 2015, MP therapy was switched to pomalidomide 4 mg q.d. plus dexamethasone 40 mg once weekly. Because neutropenia developed, the dose of pomalidomide was reduced in stages to 1 mg on alternate days followed by a 7-day washout period from day 22 to day 28. Despite this being below the recommended minimum dose, there was a favorable response: the total leukocyte count and neutrophil count were maintained at ≥1000/μL and ≥500/μL, respectively, obviating the need for continued administration of granulocyte-colony stimulating factor. As of late December 2015, PR was maintained while the patient received a third cycle of alternate-day treatment with 1 mg pomalidomide.

Keywords: Relapsed refractory multiple myeloma, alternate-day low-dose pomalidomide administration, leukopenia, neutropenia

Introduction

Development of a new treatment strategy is needed for patients with relapsed refractory multiple myeloma (RRMM) resistant to therapy with bortezomib (Bor) and lenalidomide (Len). Such patients have a grave prognosis with a median survival time as short as 9 months [1]. Pomalidomide (Pom) is an immunomodulatory drug that is structurally analogous to thalidomide. It was developed by Celgene (Summit, NJ, USA) as Pomalyst (formerly CC-4047) [2].

The mechanisms underlying the antitumor activity of Pom are diverse. They include a direct antitumor effect on myeloma cells [3, 4], inhibition of regulatory T cell activity, activation of natural killer cells and T cells mediated by cytokine stimulation, and suppression of osteoclast function [5]. Pom is reportedly effective for the treatment of multiple myeloma (MM) refractory to treatment with Bor and Len [6-10]. Pom was administered at doses of ≥1 mg daily on consecutive days in practically all previously reported cases (i.e., Pom was typically

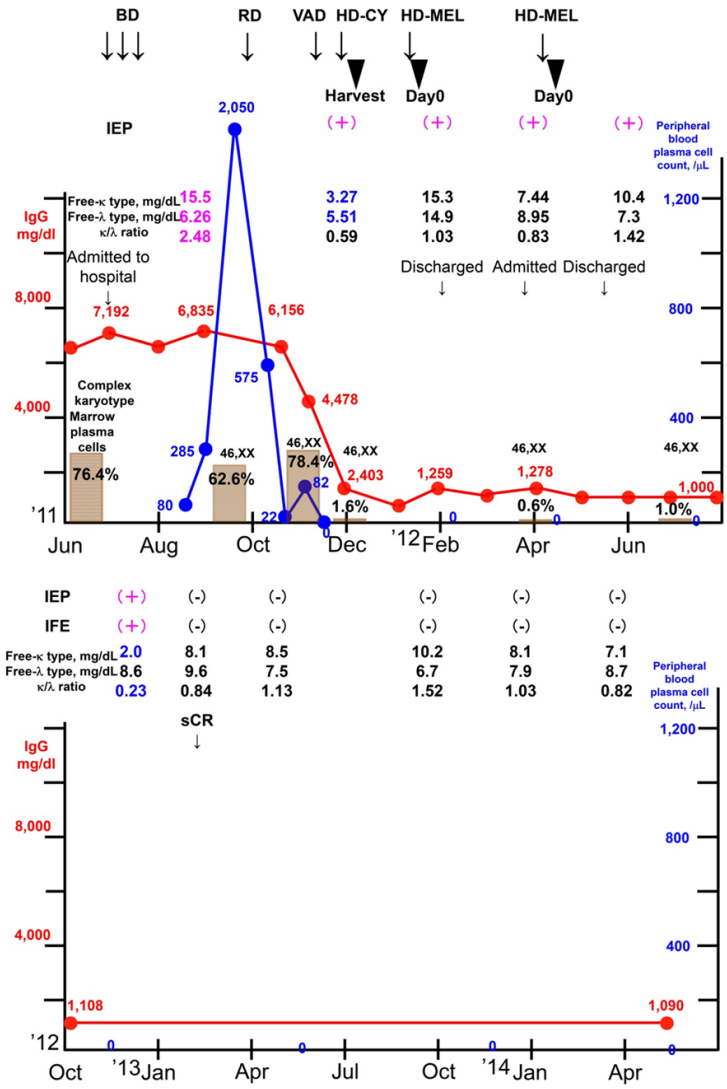

Figure 1. Clinical progress up to initiation of Pom therapy. Bortezomib and dexamethasone (BD) therapy was started in July 2011. The disease progressed to secondary plasma cell leukemia after the third cycle of this therapy. The regimen was therefore switched to lenalidomide and dexamethasone (RD) therapy in September 2011. However, because the disease remained refractory to RD therapy, vincristine/doxorubicin/dexamethasone (VAD) therapy was initiated in October 2011. This treatment led to a rapid disappearance of plasma cells from the peripheral blood, with marked reduction of the bone marrow plasma cell count to 1.6% during the first cycle. The response was accompanied by normalization of the karyotype as assessed by chromosomal G-band analysis; thus partial response (PR) was achieved. Autologous peripheral blood stem cell transplantation (auto-PBSCT) was performed in December 2011. Because the PR was maintained, a second auto-PBSCT was performed 3 months later, i.e., in April 2012. Stringent complete response (sCR) was achieved 8 months later (in December 2012) and was sustained thereafter. HD-CY, high-dose cyclophosphamide; HD-MEL, high-dose melphalan; IEP, immunoelectrophoresis; IgG, Immunoglobulin G; Harvest, autologous peripheral blood stem cell hrvest; Day 0, autologous peripheral blood stem cell transplantations; IFE, immunofixation electrophoresis.

administered on day 1 to 21 followed by a 7-day washout period, or on days 1 to 28 without any washout).

Significant clinical benefit with respect to MM may be expected in patients who, despite experiencing adverse events within a permissible range, are still capable of tolerating sufficient doses of Pom. However, for patients unable to tolerate consecutive daily administration of Pom at ≥1 mg, there is no evidence of low dose levels being effective, nor are there recommendations on the optimal regimen for administration. Furthermore, the prognosis of patients with RRMM treated with low-dose Pom is unclear. The only information that is clearly available in this regard is that dose reduction to <1 mg is not recommended [11] and that the drug should be discontinued if an adverse event occurs at a dose of 1 mg/day [12, 13].

At Juntendo University Urayasu Hospital (Chiba, Japan), we encountered a case of MM in which treatment was administered with Pom1 mg/day on alternate days (days 1, 3, 5, 7, 9...21), followed by a 7-day washout period, plus dexamethasone (DEX) 40 mg once weekly (days 1, 8, 15, and 22); this regimen enabled continuation of the treatment and partial response (PR) to be maintained, along with effective control of an adverse event (neutropenia) that had appeared in response to previous treatment with Pom at 4, 3, 2, and 1 mg/day. A report of this case is considered valuable for future exploration of the dose levels and optimum regi-

men for Pom so as to avoid adverse events and maintain clinical benefits.

Case report

The patient

The patient was a 66-year-old woman referred to the Juntendo University Urayasu Hospital for initiation of pomalidomide administration. Her medical history included pneumothorax and myoma uteri at the age of 40 years and a cervical vertebral fracture and costal fracture at the age of 42. At the age of 58, the patient was diagnosed as having type II diabetes mellitus. She suffered from cellulitis of the right thigh 2 years later and lumbar spinal canal stenosis a year after that. The family history was non-contributory.

The present illness

In June 2011, the patient presented to another hospital with the chief complaint of low back pain and was noted as having hyperproteinemia (10.3 g/dL, normal range 6.7-8.3 and hyperimmunoglobulinemia G (6384 mg/dL, normal range 870-1700); therefore, she was referred to our hospital for further medical investigations. Bone marrow analysis revealed a plasma cell count of 76.4% (normal range <10%). Based on these findings, the patient was diagnosed as having MM, IgG-k type, Durie-Salmon stage IIIA (multiple bone lesions), International Staging System stage 2 (serum albumin 2.6 g/dL, serum β2-microglobulin 3.0 mg/dL). Chromosomal G-banding analysis revealed a complex karyotype with (11, 14) translocation and 13q deletion.

Treatment

In July 2011, the patient began to receive bortezomib and DEX (BD) therapy (**Figure 1**). The regimen was bortezomib 1.3 mg/m^2 i.v. on days 1, 8, 15, and 22, followed by a 7-day washout period, plus DEX 20 mg/day orally on days 1, 2, 8, 9, 15, 16, 22, and 23; cycle length, 5 weeks). After the third cycle of BD therapy, the disease progressed to secondary plasma cell leukemia (peripheral blood plasma cell count: 2050 cells/μL). The bone marrow plasma cell count was 62.6%. The patient was thus judged to be refractory to BD therapy. Treatment was then was switched to lenalidomide and DEX (RD) therapy from September 2011. The regimen was lenalidomide 25 mg/day orally on days 1-21, followed by a 7-day washout period, plus DEX 40 mg/day orally on days 1, 8, 15, and 22; cycle length, 4 weeks). Although there was a decrease of the peripheral blood plasma cell count following the initiation of RD therapy, the patient's condition remained refractory to this therapy also: bone marrow examination performed on completion of the first cycle of RD therapy showed an increased marrow plasma cell count of 78.4%. In October 2011, vincristine, doxorubicin, and DEX (VAD) therapy was started. The regimen was vincristine 0.4 mg on days 1-4, doxorubicin 10 mg/m^2 on days 1-4, and DEX 40 mg on days 1-4, days 9-12, and days 17-20). The response was a rapid disappearance of plasma cells from the peripheral blood and a marked reduction of the marrow plasma cell count to 1.6% during the first cycle of VAD therapy. The response was accompanied by normalization of the karyotype as assessed by chromosomal G-banding analysis; thus, PR was achieved.

In November 2011, after the first cycle of VAD therapy, the patient became depressed and expressed strong reluctance to continue treatment. Consequently, we were compelled to discontinue VAD therapy. In December 2011, autologous peripheral blood stem cell transplantation (auto-PBSCT) was performed after pretreatment with high-dose melphalan (200 mg/m^2). Because PR was sustained until April 2012, i.e., 3 months after the first auto-PBSCT, a second auto-PBSCT was carried out. Stringent complete remission (sCR) was achieved in December 2012, i.e., 8 months after the second auto-PBSCT. sCR was maintained for 3 years thereafter; however, in January 2015, the patient presented with pancytopenia. A bone marrow examination revealed an increased plasma cell count of 42.2%; therefore, progressive disease (PD) was diagnosed. As a result, melphalan and prednisolone (MP) therapy (melphalan 8 mg/m^2 plus prednisolone 60 mg/m^2) was started in February 2015. This combination regimen proved effective: the serum IgG level decreased from 2153 to 1552 mg/dL and the marrow plasma cell count decreased to 10.0%. However, the patient also showed evidence of marked myelosuppression, which necessitated frequent blood transfusions and administration of granulocyte colony-stimulating factor (G-CSF). Therefore, the sec-

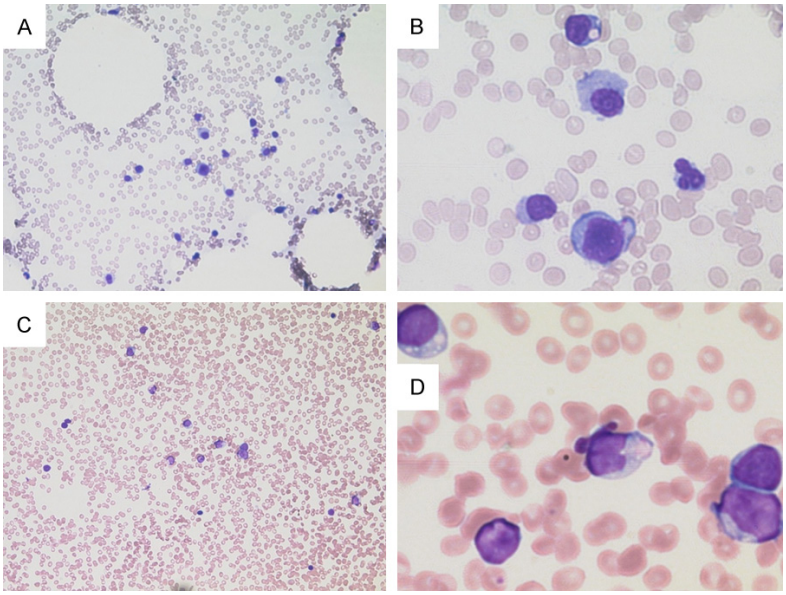

Figure 2. Bone marrow smears (Wright-Giemsa staining) viewed under a microscope. A: A marked increase (86.8%) in plasma cell count was noted prior to the start of Pom therapy (×100). B: An increase in the number of relatively immature plasma cells with high nucleus-to-cytoplasm (N/C) ratios was observed before the start of Pom therapy (×400). C: A decrease in the plasma cell count (58.4%) became evident after completion of the first cycle of Pom therapy at 1 mg/day on alternate days (×100). D: A therapeutic response was evident with a decrease in the number of relatively immature plasma cells with high N/C ratios after completion of the first cycle of Pom therapy at 1 mg/day on alternate days (×400).

ond cycle of MP therapy was administered from May 2015 with the drug doses reduced to 60% of the original dose levels (i.e., melphalan 4.8 mg/m^2 plus prednisolone 36 mg/m^2). However, the need for frequent blood transfusions and G-CSF administration continued. The third cycle of MP therapy was started in August 2015, again with doses at 60% of the original dose levels. There was no decrease in the size of the M protein band, and bone marrow suppression was still evident. The treatment response was rated as PD because the results of bone marrow examination revealed a rebound increase of the plasma cell count to 86.8% (**Figure 2A**, **2B**). The laboratory findings at that time are presented in **Table 1**.

The case was judged as being refractory to MP therapy, and, consequently, treatment with Pom 4 mg daily was started in combination with DEX 40 mg once weekly (days 1, 8, 15, 22, and 28) in early September 2015 (**Figure 3**). Pom was then discontinued after 3 days of treatment because the neutrophil count fell to ≤400/μL (Grade 4 according to the CTCAEv4.0 criteria). The therapy was resumed at 3 mg/day after the neutrophil count recovered to ≥1000/μL in response to administration of G-CSF. After 2 days of resumption of the medication at the lower dose, the neutrophil count again decreased to 312/μL, necessitating discontinuation of Pom. Pom therapy was resumed again at 2 mg/day after the neutrophil count recovered to ≥1000/μL in response to administration of G-CSF. After 2 days of resumption of Pom, the neutrophil count decreased again to 224/μL, necessitating discontinuation of Pom. The therapy was resumed again at 1 mg/day after the neutrophil count recovered to ≥1000/μL following administration of G-CSF. However, once again, the neutrophil count decreased to 432/μL after 3 days of administration of Pom, and the drug was again discontinued. During this course of Pom treatment, thrombocytopenia was evident and required a platelet transfusion; additionally, there was progression of anemia. The serum IgG level decreased from 2013 mg/dL to 1111 mg/dL, indicating the efficacy of Pom. A washout period of about 1 month was required for bone marrow recovery; during the washout period, hyperimmunoglobulinemia G relapsed to a level of 2072 mg/dL.

In late October 2015, Pom therapy was resumed at a reduced dose of 1 mg on alternate days (i.e., Pom 1 mg on days 1, 3, 5, 7, 9...19, and 21, followed by a 7-day washout period from day 22 to day 28, plus DEX 40 mg/day on days 1, 8, 15, and 22). The total leukocyte count and neutrophil count were then maintained consistently at ≥1000/μL and ≥500/μL, respectively, precluding the need for further G-CSF administration. Bone marrow examination showed a decrease of the plasma cell count to 58.4% (**Figure 2C**, **2D**). After the planned 7-day washout period, the ensuing two

Table 1. Laboratory findings immediately prior to the initiation of Pom therapy

Peripheral blood			
WBC	1000/μL↓	Hb	10.0 g/dl↓
Band	4.0%	Ht	30.5%↓
Seg	54.0%	MCV	101.6 fl↑
Ly	36.0%	MCH	33.2 pg↑
Mono	6.0%↓	Plt	2.3 p^4/μL↓
RBC	301 p^4/μL↓	Reti	0.4%
Biochemistry			
T.P.	7.5 g/dL	T-Bil	0.6 mg/dL
Alb	4.5 g/dL	BUN	15 mg/dL
AST	20 IU/L	Cr	0.57 mg/dL
ALT	20 IU/L	Uricacid	3.6 mg/dL
LDH	202 IU/L	CRP	0.3 mg/dL
ALP	179 IU/L	Ferritin	2346.0 ng/mL↑
γ-GTP	48 IU/L↑		
Findings on bone marrow smears			
Nucleated cell count	3.0lea^4/μL↓	Plasma cellcount	86.8%↑
Mega karyocyte count	≤15/μL↓		
Marrow blood flow cytometry			
CD19	7.5%	CD56	89.3%↑
CD20	33.8%↑	CD138	72.3%↑
CD45	37.3%↑	MPC-1	49.6%↑
CD49e	16.5%	κ	69.9%↑
CD54	65.4%↑	λ	2.8%↓
Blood Coagulation			
PT	100%	Fbg	236 mg/dL
APTT	20.1 s	FDP	≤5.0 μg/mL
Immunoserological findings			
IgG	2013 mg/dL↑	Free-λ type	5.3 mg/L↓
IgA	20 mg/dL↓	κ/λ ratio	22.83↑
IgM	20 mg/dL↓	IEP (specific antiserum)	IgG-κ positive type↑
Serum β2 MG	2.2 mg/dL↑	IEP (urinary BJP)	BJP-κ positive type↑
Free-κ type	121.0 mg/L↑		

Urinalysis revealed no abnormality. Marrow blood chromosome analysis (G-banding) indicated 46, XX, 20/20. The findings included pancytopenia, serum IgG elevation, and low serum IgA and IgM levels. Increased serum β2 microglobulin concentration and an increased serum κ/λ ratio were also noted. Bone marrow examination revealed a markedly increased plasma cell count of 86.8%.↑, upper limit; ↓, lower limi; WBC, white blood cells; Seg, segment; Ly, lymphocyte; Mono, monocyte; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular cell volume; MCH, mean corpuscular cell hemoglobin; Plt, platelets; Reti, reticulocytes; T.P., total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-guanosine triphosphate; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; CD, cluster of differentiation; MPC-1, mitochondrial pyruvate carrier 1; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; FDP, fibrin fibrinogen degradation; IgG, Immunoglobulin G; MG, microglobulin; IEP, immunoelectrophoresis; BJP, Bence Jones protein.

cycles of Pom therapy at 1 mg on alternate days were begun in late November. After the start of alternate-day treatment with Pom at 1 mg, there was no need for G-CSF administration, and the hemoglobin level was maintained consistently at ≥9 mg/dL. There was also no need for the washout period to be extended beyond the specified 7-day period. At the end of the second course of alternate-day treatment with Pom 1 mg, the serum IgG level had decreased to 1155 mg/dL. As of late December 2015, the patient was pursuing an unev-

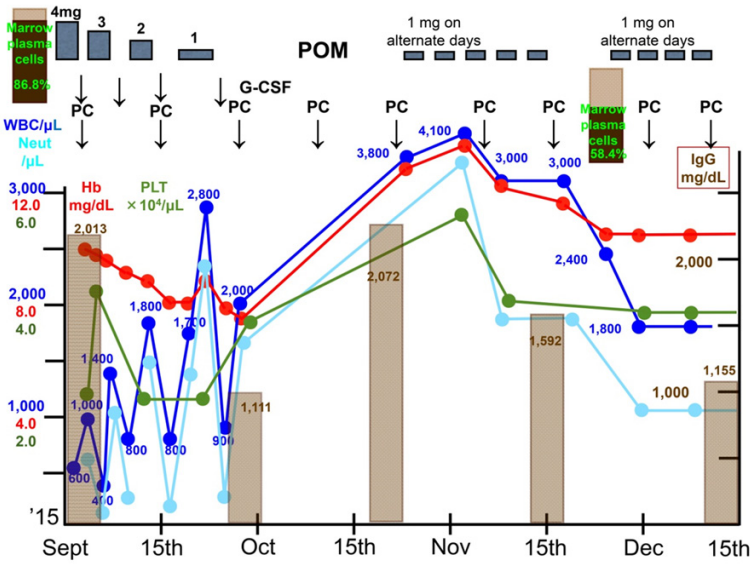

Figure 3. Clinical progress after the initiation of Pom therapy. The first cycle of melphalan and prednisolone (MP) therapy was initiated after the patient was diagnosed with progressive disease (PD) in January 2015. The serum IgG level decreased from 2153 mg/dL to 1552 mg/dL; however, there was also evidence of marked myelosuppression. Therefore, the second cycle of MP therapy was started in May with the component drug doses reduced to 60% of their initial dose levels. The third cycle was started at the beginning of August 2015. PD was diagnosed based on a bone marrow examination that revealed a rebound increase of the plasma cell count to 86.8%. The patient was begun on Pom 4 mg daily in combination with DEX 40 mg once weekly in early September 2015. The dosage of Pom then had to be quickly reduced because of an adverse event (neutropenia, <500/μL). Neutropenia (<500/μL) could not be avoided despite reduction of the Pom dose and concomitant administration of granulocytecolony-stimulating factor (G-CSF). In late October 2015, therefore, the dose of Pom was further reduced to 1 mg on alternate days. The neutrophil count was subsequently maintained consistently at ≥500/μL, precluding the necessity of continued G-CSF administration. As of late December 2015, the patient was pursuing an uneventful and favorable course while maintaining PR with alternate-day treatment with Pom 1 mg. PC, platelet concentrate; WBC, white blood cell; Neut, neutrophil; Hb, hemoglobin; PLT, platelet. On the y-axis, the scale for the neutrophil count is the same as that for the WBC count.

entful and favorable course while continuing to receive alternate-day treatment with Pom 1 mg.

Discussion

The present case was previously described in a case report of MM refractory to novel drugs (i.e., BD, RD) in which sCR was consistently maintained for about 3 years with VAD therapy and auto-PB-SCT alone [14]. Pom 4 mg/day was administered when the disease relapsed after BD, RD, VAD, auto-PBSCT, and MP therapy. However, the occurrence of an adverse event (neutropenia) made it necessary to reduce the dose. Dose reductions to 3, 2, and then to 1 mg/day were all followed by neutropenia, making it impossible to continue with Pomtherapy at the minimum recommended dose (1 mg/day). However, a subsequent dosage reduction to Pom 1 mg on alternate days yielded a sustained PR and did not result in neutropenia. Consequently, we considered that a further updated report of this case was warranted.

The most common adverse event associated with Pom therapy is grade 3-4 myelosuppression, with neutropenia being especially frequent. The incidence of grade 3-4 neutropenia was 41% in the MM-002 study (carried out in the USA) [8], 62% in the IFM-200902 study (carried out in France) [9], 48% in the MM-003 study (carried out in Australia, Canada, Europe, Russia, and the USA) [10], and 67% in the MM-04 study, a phase I clinical trial carried out in Japanese subjects [15]. It follows that administration of Pom in adequate doses may often be impracticable, or Pom therapy may often be discontinued, because of the development of neutropenia. Furthermore, it has been suggested that Japanese patients are more prone to developing neutropeniathan are Caucasians [15].

All reported dose-limiting toxicities (DLT) of Pom are related to neutropenia [2, 16, 17], and the recommended dosages based on the DLT is Pom 2 mg/day for 28 consecutive days [2, 6, 7, 18], Pom 4 mg/day for 21 days followed by a 7-day washout period (days 1 to 21/28) [8-10, 15, 17], or Pom at 5 mg on alternate days [16]. The dose levels for RRMM in all previous reports dealing with Pom monotherapy (including those with concomitant DEX therapy) [2, 6-10, 16-18] or combination treatment [19-25] are 1 mg q.d. or more. There is currently no evidence establishing a mini-

mal dose for Pom to treat RRMM. The only relevant information available at present is that the Expert Panel Consensus Statement recommends against dose reduction to <1 mg [11] and package inserts recommend discontinuation of the drug if the dose needs to be reduced to <1 mg [12, 13].

An extensive search of the literature in regard to Pom therapy at <1 mg/day for RRMM revealed five case reports of patients treated with the drug at 1 mg/day on alternate days [16]; hence, the current report is the sixth case in the world and the first report from Japan. The therapeutic responses in the six reported cases of alternate-day treatment with Pom 1 mg included very good PR in one case, PR in two cases, stable disease in one case and PD in two cases. PD seemed somewhat more common among these six cases than among not an alternate-day treatment. Close attention must be paid to indications for dosage reduction and follow-up observation because the therapeutic response tends to be positively correlated with the drug dose [17]. However, in cases in which even the lowest recommended dose of 1 mg/day of Pom cannot be tolerated despite concurrent use of G-CSF, a further dose reduction to 1 mg on alternate days may be considered. This option should be explored, particularly in Japanese patients who seem to commonly develop neutropenia as an adverse event of Pom [15]. Evaluation of the data from accumulated patients treated with 1 mg of Pom on alternate days, along with analysis of the relevant plasma drug concentrations, is warranted.

Disclosure of conflict of interest

None.

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