Regular Article

Factors Associated with Dose Modification of Lenalidomide Plus Dexamethasone Therapy in Multiple Myeloma

Yoko Kado,[a,b] Masayuki Tsujimoto,[c] Shin-ichi Fuchida,[d] Akira Okano,[d,†] Mayumi Hatsuse,[d] Satoshi Murakami,[d] Hikofumi Sugii,[b,‡] Kumi Ueda,[b] Yuki Toda,[a] Tetsuya Minegaki,[c] Kohshi Nishiguchi,[c] Yuichi Muraki,[e] Chihiro Shimazaki,[d] and Eishi Ashihara*[,a]

[a] *Department of Clinical and Translational Physiology, Kyoto Pharmaceutical University; 5 Nakauchi-cho, Misasagi, Ymashina-ku, Kyoto 607–8414, Japan:* [b] *Department of Pharmacy, Japan Community Health Care Organization, Kyoto Kuramaguchi Medical Center; 27 Shimofusa-cho, Koyama, Kita-ku, Kyoto 603–8151, Japan:* [c] *Department of Clinical Pharmacy, Kyoto Pharmaceutical University; 5 Nakauchi-cho, Misasagi, Ymashina-ku, Kyoto 607–8414, Japan:* [d] *Department of Hematology, Japan Community Health Care Organization, Kyoto Kuramaguchi Medical Center; 27 Shimofusa-cho, Koyama, Kita-ku, Kyoto 603–8151, Japan: and* [e] *Department of Clinical Pharmacoepidemiological, Kyoto Pharmaceutical University; 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607–8414, Japan.*

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Long-term combination treatment with lenalidomide and low-dose dexamethasone is important to achieve a curative effect in patients with multiple myeloma (MM). In this study, the plasma concentration of lenalidomide was measured at 3 h after oral administration, when the drug is in the elimination phase and can be easily measured in outpatients, to identify factors that may lead to the discontinuation of this combination therapy. Patients were assigned to continuation or discontinuation of therapy groups, and the baseline characteristics of patients, lenalidomide concentration, and concentration/dose (C/D) ratios reflecting oral clearance were compared between the two groups. The efficacy and severity of adverse events were also compared. The results showed that patients who discontinued or modified treatment had low plasma concentrations of lenalidomide and C/D ratios, indicating high oral clearance of lenalidomide. The estimated creatinine clearance rate was negatively correlated with the C/D ratio. The plasma concentrations of lenalidomide were independent from kidney function and differed significantly among patients. Taken together, the results indicate that low plasma concentrations of lenalidomide and low C/D ratios may lead to discontinuation of combination therapy in patients with MM. This suggests that early measurement of lenalidomide plasma continuation would help to prevent discontinuation of therapy or a delay in modifying the dose of lenalidomide.

Key words lenalidomide; plasma concentration; oral clearance; dose; therapy continuation

INTRODUCTION

Multiple myeloma (MM) is a malignancy characterized by the clonal proliferation of malignant plasma cells in the bone marrow.[1)] The characteristic clinical symptoms of MM are anemia induced by myeloma cells,[2)] osteolytic bone lesions,[3)] hypercalcemia associated with bone lesions, and monoclonal light chain-associated renal dysfunction.[4)] Patients with MM are susceptible to infection because of immunodeficiency.[5)] Although MM remains an incurable malignancy with a poor prognosis, survival rates have improved markedly with the emergence of novel targeted agents, such as thalidomide, lenalidomide, and bortezomib.[6)]

Lenalidomide, a thalidomide derivative known as an immunomodulatory drug, has significant clinical activity in patients with MM.[7)] Combination therapy with lenalidomide and low-dose dexamethasone is associated with high response rates,[8)] and this combination therapy, which can be administered orally, is used in both inpatient and outpatient settings. Long-term combination therapy with lenalidomide and low-dose dexamethasone extends progression-free survival.[9)] Therefore, continuous treatment using this combination is important to achieve a curative effect in patients with MM.

One factor preventing the continuity of combination therapy with lenalidomide and low-dose dexamethasone is an overdose of lenalidomide. Because lenalidomide is a renally excreted drug, the recommended initial dose is subject to dose reduction according to kidney function.[10)] However, despite dose adjustment according to kidney function, many patients discontinue lenalidomide therapy because of adverse events. In addition, an underdose of lenalidomide can lead to disease progression in MM. Therefore, early adjustment of the lenalidomide dose may allow MM patients to continue combination therapy with lenalidomide and low-dose dexamethasone.

Therapeutic drug monitoring (TDM) is a valuable tool for optimizing pharmacotherapeutics in the early stages. Studies indicate that the maximum concentration of lenalidomide is not related to efficacy, and patients with a high area under the time–plasma concentration curve (*AUC*) of lenalidomide have severe adverse events.[11)] Therefore, TDM should be a valuable tool for optimizing lenalidomide therapy early. However, the absorption rate of lenalidomide and the time to maximum concentration vary among individuals.[12)] Furthermore, determining the *AUC* of lenalidomide could be a burden for MM

† Present address: *Department of Hematology, Ohmihachiman Community Medical Center; 1379 Tsuchida-cho, Ohmihachiman, Shiga 523–0082, Japan.*

‡ Present address: *Department of Pharmacy, Biwako Ohashi Hospital; 5–1–29 Mano, Otsu, Shiga 520–0232, Japan.*

* To whom correspondence should be addressed. e-mail: ash@mb.kyoto-phu.ac.jp

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patients. An optimal index for TDM of lenalidomide that can be used in the clinical setting remains to be identified.

The purpose of this study was to identify factors preventing the continuation of combination therapy with lenalidomide and low-dose dexamethasone. The plasma concentration of lenalidomide was measured at 3 h after administration, when it is estimated to have reached the elimination phase for all patients and is easier to measure in an outpatient setting and analyzed in relation to the baseline characteristics of patients and oral clearance, as well as side effects of therapy.

PATIENTS AND METHODS

Patients This study was performed at the Japan Community Health care Organization of Kyoto Kuramaguchi Medical Center (Kyoto, Japan), and included 33 patients with relapsed and refractory MM who received oral lenalidomide and low-dose dexamethasone therapy between May 2013 and February 2017. Lenalidomide was administered orally midmorning on days 1–21 of each 28 d cycle, and dexamethasone was given on days 1, 8, 15, and 22. The initial dose of lenalidomide and continuation of combination therapy were determined by the attending physician. Patients who could not take lenalidomide daily and those who could not be evaluated for efficacy were excluded. Patients were divided into the following two groups: the continuous group, in which patients received three cycles of treatment without modifications, and the modifying group, which included patients requiring therapy modifications during the three cycles.

Measuring of the Plasma Concentration of Lenalidomide Blood was only collected on day 7 of the first cycle for measuring the plasma concentration of lenalidomide. Lenalidomide is the short half-life (about 2 h) and is that most patients reach peak concentration within 3 h.[12,13] That is to say, trough concentration of lenalidomide is not suitable to evaluate the individual difference of extent of bioavailability of lenalidomide, and the concentration of most patients reach the elimination-phase at 3 h after oral administration of lenalidomide. Therefore, we decided to collect blood from all patients at 3 h after oral administration of lenalidomide in order to evaluate the individual difference in not only the elimination phase but also the absorption phase. To avoid the effects of a meal, patients had taken no meal from the time of waking up to the blood collection. Blood was immediately centrifuged at $1670 \times \boldsymbol{g}$ for 10 min at 4°C to isolate plasma, which was stored at −80°C until analysis. The plasma concentration of lenalidomide was measured as described previously by Takahashi *et al.*[14] with modifications. Briefly, acetonitrile (50 μL), containing 50 μg/mL atenolol as an internal standard, and acetonitrile (5 mL) were added to 100 μL plasma, and the mixture was shaken at 300 cycles/min for 20 min. After centrifugation at $1630 \times \boldsymbol{g}$ for 20 min, the upper layer (4 mL) was collected and evaporated to dryness at 50°C under a stream of nitrogen. The residue was dissolved in the mobile phase (50 mM phosphate buffer, pH 2.5 : acetonitrile = 95 : 5). The sample was filtered through a Mini-UniPrep syringeless filter device (0.45 μm, polytetrafluoroethylene; GE Healthcare UK Ltd., U.K.) and injected into a HPLC apparatus using a column (Inertsil ODS-III, 5 μm, 250 × 4.0 mm i.d.; GL Sciences Inc., Tokyo, Japan). The absorbance was measured at 220 nm with a UV detector. Further, regarding the measurement of lenalidomide concentration, it has been confirmed that inter- and the intra-day variation are within 5%. The plasma sample of each patient was measured multiple times and the average values were used to ensure accuracy in this study.

Ethics Committee Approval and Patient Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the Institutional Review Boards of the Japanese Community Health care Organization of Kyoto Kuramaguchi Medical Center (IRB number: H25.04.11) and Kyoto Pharmaceutical University (Kyoto, Japan; IRB number: 13-07).

Comparison of Plasma Concentrations at 3 h after Oral Administration and Plasma Concentration/Dose Ratios of Lenalidomide between the Continuous and Modifying Groups The plasma concentration of lenalidomide at 3 h after oral administration and the plasma concentration/dose (C/D) ratio, which is the inverse of oral clearance, of lenalidomide were compared between the continuous and modifying groups.

Effect of Kidney Function on the C/D Ratio and the Relationship between Plasma Concentration and Lenalidomide Dose The correlation between estimated creatinine clearance (e*CL*cr) calculated using the Cockcroft–Gault equation[15] and the C/D ratio was analyzed. Patients were classified into normal function (≥60 mL/min), mild dysfunction (30–59 mL/min), and severe dysfunction (<30 mL/min) groups according to e*CL*cr values, and the effect of kidney dysfunction on the correlation between plasma concentration and lenalidomide dose was analyzed.

Comparison of Treatment Efficacy and the Severity of Adverse Events between the Continuous and Modifying Groups Attending physicians evaluated the efficacy of lenalidomide and low-dose dexamethasone therapy on each cycle according to International Myeloma Working Group criteria,[16] and the best response in three cycles was defined as efficacy in this study. Attending physicians and pharmacists evaluated the severity of adverse events according to the Common Terminology Criteria for Adverse Events Version 4.0, and the highest grade of all adverse events in three cycles was defined as the grade of severity of adverse events in this study. However, the modifying groups were evaluated the best response and the severity of adverse events until the modification of lenalidomide.

Statistical Analysis Differences in continuous variables and comparison of plasma concentrations and C/D between groups were evaluated using the Mann–Whitney *U*-test, and differences in categorical variables were evaluated using Fisher's exact test. The relationship between C/D ratio and e*CL*cr was determined according to the Pearson correlation coefficient, and that between lenalidomide dose and plasma concentration was determined by the Spearman rank correlation coefficient. The level of significance was set at $p < 0.05$.

RESULTS

Patients The study enrolled 33 patients between May 2013 and February 2017 (Fig. 1). Two patients were excluded, and 31 patients met the eligibility criteria. Of these, 23 patients

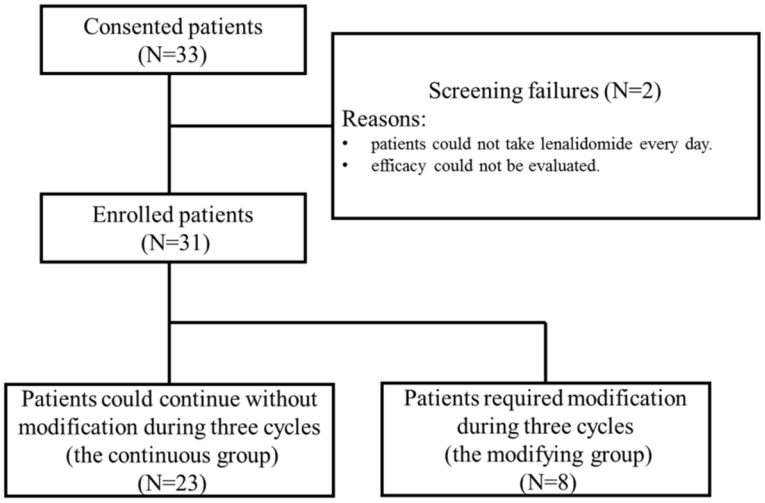

Fig. 1. Flowchart of Patient Enrollment

Thirty-three patients were initially recruited and two patients were excluded. Twenty-three patients were included in the continuous group, and eight patients were included in the modifying group.

continued treatment without modification of lenalidomide dose during the initial three cycles, whereas eight patients required lenalidomide dose increase or decrease, discontinuation, or modification of the treatment during the initial three cycles. The causes of modification were an increase of serum creatinine or C-reactive protein, rash, infection symptoms, tolerability, the progression of MM, and ventricular outflow tract obstruction. One patient with the progression of MM could not complete the initial three cycles.

Patient Baseline Characteristics There were no significant differences in renal and liver function, blood cell count, and M protein types before combination therapy between the continuous and modifying groups. The International Staging System stage progressed significantly in the modifying group compared with that in the continuous group. The daily initial lenalidomide dose was lower in the modifying group than in the continuous group (Table 1).

Comparison of Plasma Concentrations at 3 h after Oral Administration and Plasma Concentration/Dose Ratios of Lenalidomide between the Continuous and Modifying Groups Figure 2 shows the comparison of plasma concentrations and C/D ratios between the continuous and modifying groups. The plasma concentration of lenalidomide at 3 h after oral administration, expressed as median (range), was significantly higher in the continuous group [366.3 (172.5–560.9) ng/mL] than in the modifying group [188.5 (126.8–278.4) ng/mL; $p = 0.001$]. The C/D ratio, expressed as median (range), was significantly higher in the continuous group [21.8 (8.1–43.5) (ng/mL)/(mg/day); $p = 0.034$] than in the modifying group [13.1 (8.5–18.7) (ng/mL)/(mg/day)].

Effect of Kidney Function on C/D Ratio and the Relationship between Plasma Concentration and Lenalidomide Dose The C/D ratio was negatively correlated with the e*CL*cr ($r = 0.562$; $p = 0.010$; Fig. 3). There was no correlation between plasma concentration of lenalidomide and dose ($r = 0.331$; $p = 0.154$). The plasma concentration of lenalidomide showed marked variation among patients who received the same dose of lenalidomide and had similar kidney function (Fig. 4).

Comparison of Treatment Efficacy and the Severity of Adverse Events between the Continuous and Modifying Groups There were no significant differences in efficacy between the continuous and modifying groups. However, the modifying group included one patient with progressive disease (PD). There were no significant differences in the severity of adverse events between the two groups (Table 2). The major adverse events were leukopenia and neutropenia both in the continuous group and the modifying group and they were the same rate, 16 (69.6%), and 4 (50.0%), respectively.

DISCUSSION

In this study, we showed that patients with low plasma concentrations of lenalidomide at 3 h after oral administration on day 7 of the first cycle are unable to receive continuous combination therapy with lenalidomide and low-dose dexamethasone. Oral clearance of lenalidomide was significantly higher in patients who required modification of therapy than in those who received continuous combination therapy.

The plasma concentrations of lenalidomide were significantly lower in the modifying group than in the continuous group (Fig. 2A). Although lenalidomide plasma concentration depended partially on kidney function (Fig. 3), no differences in kidney function were observed between the continuous and modifying groups (Table 1). Therefore, the difference in lenalidomide concentration between the two groups cannot be explained by the difference in kidney function alone. One reason for the low plasma concentration of lenalidomide in the modifying group may be a high score of ISS, that is, doctors tend to begin the treatment of low-dose lenalidomide on the patients with advanced stage. In fact, one patient with an initial dose of 15 mg had low plasma concentration (160.9 ng/mL). This patient obtained very good partial response (VGPR) without severe adverse effects after the increase of lenalidomide dose. These results suggest that low concentrations of lenalidomide associated with an excessive decrease in the initial dose is one of the causes of lenalidomide treatment failure.

The large variation in plasma lenalidomide concentrations associated with the different doses indicated that

Table 1. Patient Baseline Characteristics

	The continuous group	The modifying group	*p*-Value
Median age, years (range)	69 (48–87)	67.5 (44–82)	0.529[a)]
Sex: Male/Female, number (%)	9 (39.1)/14 (60.9)	2 (25.0)/6 (75.0)	0.678[b)]
Height (cm)	153.2 (144.8–182.0)	155 (145–174.3)	0.521[a)]
Weight (kg)	58.5 (40.1–84.0)	53.4 (37–88)	0.513[a)]
AST (U/L)	19 (15–56)	20.5 (12–45)	0.505[a)]
ALT (U/L)	15 (5–74)	12.5 (8–59)	0.567[a)]
TP (g/dL)	7.1 (4.4–11.5)	7.4 (6.4–8.8)	0.145[a)]
ALB (g/dL)	3.8 (1.9–4.4)	3.5 (2.4–4.9)	0.543[a)]
WBC ($\times 10^3/\mu$L)	4.36 (0.66–24.07)	3.49 (2.41–6.50)	0.508[a)]
Hb (g/dL)	11.8 (6.4–13.9)	10.2 (8.4–12.3)	0.518[a)]
PLT ($\times 10^3/\mu$L)	161.0 (82.0–259.0)	207.5 (7.0–297.0)	0.086[a)]
NEUT ($\times 10^3/\mu$L)	2.57 (0.6–21.45)	1.59 (1.20–4.33)	0.158[a)]
e*CL*cr, number (%)			
≥60 mL/min	16 (69.6)	4 (50.0)	0.543[b)]
30–59 mL/min	6 (26.1)	4 (50.0)	
<30 mL/min	1 (4.3)	0 (0.0)	
Median (range)	66.6 (22.7–138.2)	63.8 (38.1–127.4)	0.523[a)]
Body surface area, number (%)			
≥1.4 m^2	20 (87.0)	5 (62.5)	0.161[b)]
<1.4 m^2	3 (13.0)	3 (37.5)	
Median (range)	1.52 (1.26–1.97)	1.49 (1.23–1.99)	0.551[a)]
M protein subtype, number (%)			
IgG	15 (65.2)	7 (87.5)	0.155[b)]
IgA	4 (17.4)	0 (0.0)	
IgD	0 (0.0)	1 (12.5)	
BJP	4 (17.4)	0 (0.0)	
ISS, number (%)			
I	12 (52.2)	0 (0.0)	0.023*, b)
II	5 (21.7)	3 (37.5)	
III	4 (17.4)	3 (37.5)	
Unknown	2 (8.7)	2 (25.0)	
Previous treatment history, number (%)			
1	6 (26.1)	2 (25.0)	0.968[b)]
2	8 (34.8)	3 (37.5)	
3	4 (17.4)	2 (25.0)	
4	3 (13.0)	0 (0.0)	
5	2 (8.7)	1 (12.5)	
Median	2	2	
Thalidomide, number (%)			
+	3 (13.0)	1 (12.5)	1.000[b)]
−	20 (87.0)	7 (87.5)	
Bortezomib, number (%)			
+	20 (87.0)	5 (62.5)	0.161[b)]
−	3 (13.0)	3 (37.5)	
Autologous transplantation, number (%)			
+	7 (30.4)	3 (37.5)	1.000[b)]
−	16 (69.6)	5 (62.5)	
Initial lenalidomide dose/d, number (%)			
25 mg	10 (43.5)	0 (0.0)	0.052[b)]
20 mg	1 (4.3)	1 (12.5)	
15 mg	8 (34.8)	6 (75.0)	
10 mg	4 (17.4)	1 (12.5)	

a) Mann–Whitney *U*-test (*$p < 0.05$), *b*) Fisher's test. AST: aspartate transaminase; ALT: alanine transaminase; TP: total protein; ALB: albumin; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; NEUT: neutrophil; e*CL*cr: estimated creatinine clearance; ISS: International Staging System; Ig: immunoglobulin; BJP: Bence Jones protein.

the difference of plasma lenalidomide concentrations involves factors other than kidney function (Fig. 4). For example, plasma lenalidomide concentration varied over a large range (202.4–560.9 ng/mL) in patients with normal kidney function (e*CL*cr ≥ 60 mL/min) treated with 25 mg Lenalidomide. The plasma concentration of lenalidomide was lower in some patients with mild kidney dysfunction (30 < e*CL*cr < 60 mL/min) than in those with normal kidney function (e*CL*cr ≥ 60 mL/min) receiving the same dose. A previous study showed that the *AUC* of plasma concentration-

time shows a >10-fold variation range (955–11841 ng/mL) despite adjustment of lenalidomide dose according to kidney function.[17] These results indicate that factors other than kidney function strongly affect the plasma concentration of lenalidomide.

This study showed that the C/D ratios were lower in the modifying group than in the continuous group (Fig. 2B), which suggests that oral clearance of lenalidomide was significantly greater in the modifying group. Because kidney function was comparable between the two groups (Table 1), this result could be attributed to decreased bioavailability in patients in the modifying group. Lenalidomide is a substrate of the efflux transporter P-glycoprotein (P-gp), which is expressed functionally in intestinal epithelial cells.[14] The 3435 C>T polymorphism of P-gp is associated with variation in lenalidomide concentration.[18] That is, one of the reasons of high oral clearance in the modifying group may be polymorphisms of P-gp. In addition, another possibility may be the decrease in the intestinal absorption of lenalidomide in patients with advanced stage, because M-protein deposited in intestine reduces the intestinal absorption of nutrients.[19] Therefore, variation in the intestinal absorption of lenalidomide caused by polymorphisms of P-gp and the progression of MM may decrease oral clearance and cause treatment failure. Further research may clarify the effects of polymorphisms of P-gp and the progression of MM on high oral clearance of lenalidomide.

The plasma concentration of lenalidomide at 3 h after oral administration on day 7 of the first cycle in the continuous group was >172.5 ng/mL (Fig. 2A). This suggests that the lenalidomide dose should not be reduced more than necessary in patients with kidney dysfunction. In addition, it is necessary to increase the dose of lenalidomide according to the condition in patients with high oral clearance of lenalidomide, which is indicated by low concentration, in the combination therapy with low-dose dexamethasone. Early measuring the plasma concentration of lenalidomide at 3 h after oral administration is important to identify patients with high oral clearance.

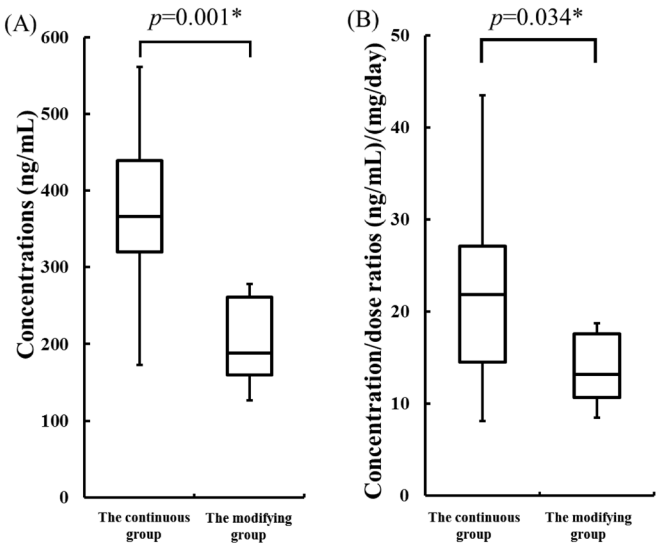

Fig. 2. Comparison of Plasma Concentrations at 3 h after Oral Administration (A) and Plasma Concentration/Dose Ratios of Lenalidomide (B) between the Continuous and Modifying Groups

Concentration/dose ratio is an indicator of oral clearance of lenalidomide. *Mann–Whitney *U*-test.

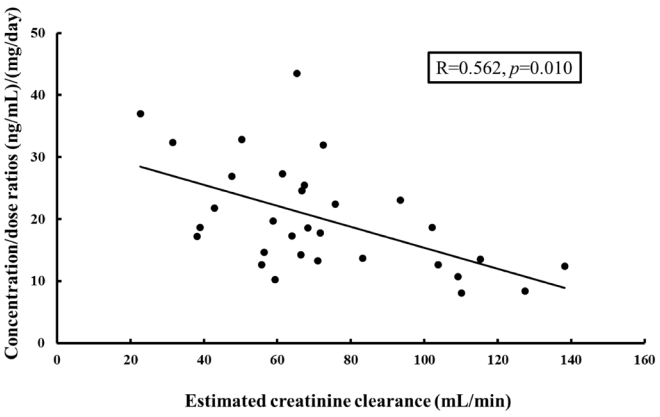

Fig. 3. Effect of Kidney Function on the Plasma Concentration/Dose Ratios of Lenalidomide

The concentration/dose ratio was negatively correlated with estimated creatinine clearance (Pearson correlation coefficient).

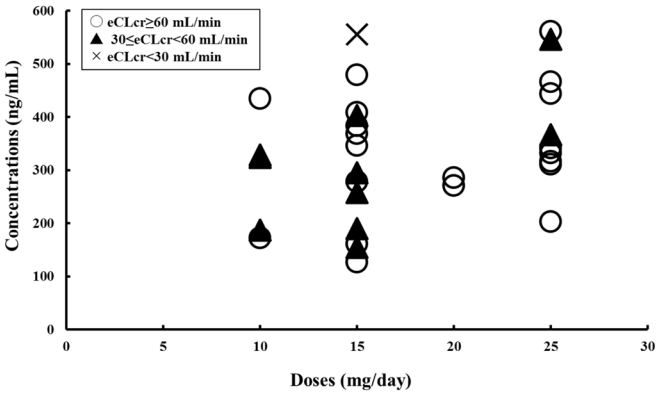

Fig. 4. Relationship between Lenalidomide Plasma Concentration and Dose

There was no correlation between dose and plasma concentration of lenalidomide (Spearman rank correlation coefficient). Estimated creatinine clearance was calculated using the Cockcroft–Gault formula. e*CL*cr: estimated creatinine clearance.

Table 2. Efficacy and Severity of Adverse Events

Efficacy	The continuous group	The modifying group	*p*-Value
PR/CR	11 (47.8)	3 (37.5)	0.6980*
PD/SD	12 (52.2)	5 (62.5)	
Severity of adverse events	The continuous group	The modifying group	*p*-Value
Grade 1/2	15 (65.2)	4 (50.0)	0.6757*
Grade 3/4	8 (34.8)	4 (50.0)	

*Fisher's test. PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

The present study had several limitations. First, the sample size was small because of the single-institution design of the study. So, it was difficult to subdivide and evaluate adverse events. Second, we cannot deny that the patients with high scores of ISS may modify lenalidomide treatment, regardless of their plasma concentration and plasma concentration/dose ratio. Third, the initial dose of lenalidomide was not always adjusted according to kidney function because of decisions made by attending physicians according to various factors such as progression of MM. However, whether determining the lenalidomide dose according to kidney function would affect the results showing that plasma concentration of lenalidomide and C/D ratio were associated with continuation of combination therapy remains unclear.

CONCLUSION

The present study showed that some patients with a low plasma concentration and a high C/D ratio of lenalidomide at 3 h after oral administration on day 7 of the first cycle were unable to continue combination therapy with lenalidomide and low-dose dexamethasone. Therefore, early optimization of lenalidomide therapy by measuring plasma concentration may help to prevent discontinuation of therapy leading to PD. In future, it is necessary to clarify the relationship between the plasma concentration of lenalidomide and efficacy and the severity of adverse events.

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Author Contributions YK designed the study, performed research, analyzed data, interpreted data, and wrote the manuscript. MT and YM performed research, analyzed data, and interpreted data. SF, AO, MH, SM, YT, TM, and KN performed experiments. CS interpreted data. EA was responsible for the original conception of the study, designed the study, and interpreted data. All authors revised the manuscript.

Conflict of Interest Yuichi Muraki received an honorarium for lecturing from Pfizer Japan, Inc. Other authors have no conflict of interest to declare.

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