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ORIGINAL PAPER

Influence of *ABCB1* polymorphisms on the pharmacokinetics and toxicity of lenalidomide in patients with multiple myeloma

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Abstract

Individual diversity in plasma concentrations of lenalidomide occurs despite dosage modifications based on creatinine clearance (CCr), which can lead to unexpected toxicity. We have previously identified a cutoff value of area under the concentration–time curve ($AUC_{0–24}$) for lenalidomide to avoid severe toxicity. Here, we investigated the association between *ABCB1* polymorphisms and pharmacokinetics of lenalidomide in patients with multiple myeloma (MM) treated with lenalidomide and dexamethasone. Plasma concentrations of lenalidomide were analyzed using liquid chromatography–tandem mass spectrometry. Genotyping for *ABCB1* 1236C>T, 2677G>A/T, and 3435C>T polymorphisms was performed, and the effects of *ABCB1* polymorphisms on $AUC_{0–24}$ for lenalidomide were compared in 36 patients with MM who were administered lenalidomide according to the drug label based on CCr. Genotyping analysis showed that although there were no differences in $AUC_{0–24}$ in 1236C>T and 2677G>A/T polymorphisms. $AUC_{0–24}$ was significantly higher in patients with the T allele of 3435C>T ($n=15$) than in those without ($n=21$) (median 6324.6 ng h/mL vs. 2857.4 ng h/mL, $p=0.028$). The $AUC_{0–24}$ value exceeded the aforementioned cutoff value in 95% of the patients with the T allele of 3435C>T but in 60% with C/C genotype ($p=0.013$). Multivariate logistic analysis confirmed the significance of T allele of *ABCB1* 3435C>T as a factor due to which the $AUC_{0–24}$ cutoff value was exceeded (hazard ratio of 15.0, $p=0.019$). We show that lenalidomide pharmacokinetics is influenced by the *ABCB1* 3435C>T polymorphism, which could be useful to individualize dosage design and reduce unexpected toxicity.

Keywords Multiple myeloma · Lenalidomide · Pharmacokinetics · P-glycoprotein · *ABCB1* polymorphisms

Introduction

The prognosis of multiple myeloma (MM) has remarkably improved recently due to the integration of new drugs in therapy [1]. Lenalidomide is one of the key drugs used for the treatment of MM, and combination therapy with either a proteasome inhibitor or a monoclonal antibody can achieve deep remission [2–6]. However, lenalidomide is excreted in the urine, so dosage adjustment is generally required. Based on creatinine clearance (CCr), the suitable area under the concentration–time curve from 0 to 24 h ($AUC_{0–24}$) is generally adjusted [7, 8]. However, sometimes unexpected toxicity of lenalidomide occurs despite following the recommendations based on CCr [7].

We have previously reported the correlation between higher $AUC_{0–24}$ and severe toxicity from the phase II prospective clinical trial for lenalidomide–dexamethasone combination (Ld) therapy in newly diagnosed MM (NDMM) patients [9]. Furthermore, we clarified that the interindividual diversity in $AUC_{0–24}$ of lenalidomide exists despite following the drug label based on CCr from the results of our study so far. However, the factors that influence the interindividual diversity of $AUC_{0–24}$ were unknown.

In vitro analysis and drug–drug interaction data showed that lenalidomide is a known substrate of p-glycoprotein (P-gp), encoded by *ABCB1* [10, 11]. However, the correlation between *ABCB1* single nucleotide polymorphisms

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(SNPs) and $AUC_{0–24}$ of lenalidomide was unknown. Based on this background, we focused on the association between *ABCB1* SNPs and their correlation with the pharmacokinetics of lenalidomide in patients with MM.

Materials and methods

Patients

A total of 36 MM patients from eight major hospitals in Akita Prefecture, Japan, who were treated with Ld therapy according to the drug label of lenalidomide in a general practice were enrolled in this study. The lenalidomide dosage according to drug label was 25 mg daily for patients with CCr ≥ 60 mL/min; 10 mg daily for patients with CCr 30–60 mL/min, or 15 mg every other day for CCr < 30 mL/min. The study protocol was approved by the Ethics Committee of Akita University School of Medicine (No. 905). Informed consent was obtained from all individual participants included in the study. The body surface area (BSA) was calculated using the DuBois formula, and CCr was calculated using the Cockcroft–Gault formula.

Measurement of lenalidomide concentration in plasma

Whole-blood sampling was performed at 6–21 days after the initiation of lenalidomide oral uptake, which we estimated as the steady state of lenalidomide. Plasma was isolated by centrifugation at 1900 × *g* for 15 min and stored at − 40 °C until analysis. Plasma concentrations of lenalidomide were analyzed using liquid chromatography–tandem mass spectrometry, as described previously [12]. The maximum concentration (C_{max}) was defined as the greater of two concentrations between $C_{2\,h}$ and $C_{4\,h}$. $AUC_{0–4}$ was calculated from $C_{0\,h}$, $C_{2\,h}$, and $C_{4\,h}$. We predicted the $AUC_{0–24}$ of lenalidomide using a previously developed formula; $AUC_{0–24} = 37.1 \times C_{0\,h} + 6.4 \times C_{4\,h} - 32.1 \times CCr + 3265.6$ [12].

We measured the plasma concentrations of lenalidomide at 0 h ($C_{0\,h}$), 2 h ($C_{2\,h}$), 4 h ($C_{4\,h}$), 12 h ($C_{12\,h}$), and 24 h ($C_{24\,h}$) in 21 patients. Then, we validated the accuracy of the predicted $AUC_{0–24}$ against the measured $AUC_{0–24}$. As a result, the predicted $AUC_{0–24}$ showed the highest correlation with respect to measured $AUC_{0–24}$ ($r = 0.972$, $p < 0.001$). Therefore, we utilized the predicted formula to evaluate $AUC_{0–24}$ for lenalidomide in all the patients.

Genotyping

DNA was extracted from peripheral blood samples using the QIAamp blood mini kit (Qiagen, Tokyo, Japan) and stored at − 80 °C until analyzed. Genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism to identify the C and T alleles in exon 12 (1236C>T, rs1128503), the G and T/A alleles in exon 21 (2677G>T/A, rs2032582), and the C and T alleles in exon 26 (3435C>T, rs1045642) of the *ABCB1* gene [13–15].

Statistical analyses

Kolmogorov–Smirnov test was used to assess the distribution. Smirnov–Grubbs test was used to remove outlier data from $AUC_{0–24}$. The Pearson's correlation coefficient was used to assess the correlations between measured $AUC_{0–24}$ and predicted $AUC_{0–24}$. Fisher's exact test was used to examine differences in categorical data. Mann–Whitney *U* test and Student's *t* test was used to determine the significance of difference for $AUC_{0–24}$ between groups. Kruskal–Wallis test was used to determine the significance of difference for $AUC_{0–24}$ between three groups. To identify covariates that correlated with high $AUC_{0–24}$ of lenalidomide, univariate and multivariate logistic regression analyses were performed. Multivariate models were analyzed including all the variables examined in univariate model, which were then deleted in a stepwise manner from the model to exclude factors with a *p* value ≥ 0.05. Statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [16]. All *p* values were two-sided, and a *p* value ≤ 0.05 was considered statistically significant. For post hoc power analysis, the effect size was calculated in comparison with the AUC for lenalidomide between ABCB1 3435C>T genotypes. An effect size of greater than 0.5 was considered clinically meaningful [17]. Power was calculated using G*Power software ver.3.1.

Results

Patients and treatment

Patient demographics and baseline characteristics are listed in Table 1. The median age of patients was 69 years (range 34–92 years), and the male-to-female ratio was 24:12. The median body weight was 56.0 kg (range 33.1–82.0 kg), and BSA was 1.55 m^2 (range 1.09–1.92 m^2). Of all the patients, 18 (50% of patients, CCr ≥ 60 mL/min) were treated with a full dose of lenalidomide (25 mg) daily, 16 (44% of patients, CCr 30–60 mL/min) were treated with 10 mg lenalidomide daily, and 2 (6% of patients, CCr < 30 mL/min) were treated with 15 mg lenalidomide every other day. The subtype of M-protein was IgG in 22 (61%) patients and non-IgG in 14 (39%) of the 36 patients. Fourteen (39%) patients were treated with Ld during initial therapy and 22 (61%) patients had a previous treatment history of MM.

Table 1 Patient demographics and baseline characteristics ($n=36$)

Characteristics	Median value (range) or *n* (%)
Age (years)	69 (34–92)
Male/female	24 (67)/12 (33)
Body weight (kg)	56.0 (33.1–82.0)
Body surface area (m^2)	1.55 (1.09–1.92)
Creatinine clearance (mL/min)	59.5 (14.6–223.7)
≥ 60	18 (50)
30–59	16 (44)
< 30	2 (6)
M-protein (subtype)	
IgG	22 (61)
Non-IgG	14 (39)
Prior therapy for multiple myeloma	
0	14 (39)
≥ 1	22 (61)

Plasma concentrations of lenalidomide

The median $AUC_{0–24}$ value was observed to be 4754.0 ng h/mL (range 186.3–27,246.9 ng h/mL), and high interindividual variability was observed despite dosage adjustments based on CCr. There were no significant differences in $AUC_{0–24}$ for lenalidomide in patients without renal insufficiency (RI, CCr ≥ 60 mL/min) and patients with RI (CCr < 60 mL/min) (median $AUC_{0–24}$ was 4754.0 ng h/mL in patients without RI and 4761.5 ng h/mL in patients with RI, $p=0.606$; Table 2).

Genotype and lenalidomide pharmacokinetics

The genotype frequencies for *ABCB1* polymorphisms and $AUC_{0–24}$ for lenalidomide in each *ABCB1* genotype are shown in Table 2. No correlation was observed between the *ABCB1* 1236C>T or 2677G>A/T genotypes and $AUC_{0–24}$ for lenalidomide. However, higher $AUC_{0–24}$ for lenalidomide was noted in patients with the T allele of 3435C>T (median $AUC_{0–24}$ was 2857.4 ng h/mL in patients with C/C genotype, 5278.4 ng h/mL in patients with C/T genotype, and 10,451.9 ng h/mL in patients with T/T genotype; $p=0.055$). Median $AUC_{0–24}$ was significantly higher in patients with the T allele of 3435C>T than in those with C/C genotype (6324.6 ng h/mL and 2857.4 ng h/mL, respectively, $p=0.028$). There were no significant differences in baseline characteristics except for BSA between the patients with C/C genotype and T allele of 3435C>T (median 1.61 m^2 and 1.46 m^2, respectively, $p=0.049$, Supplementary Table 1). In patients without RI (CCr ≥ 60 mL/min), the median C_{max} (1056 ng/mL and 265 ng/mL, respectively, $p=0.036$, effect size = 0.79) and $AUC_{0–4}$ (2484.8 ng h/mL and 596.3 ng h/

Table 2 Comparison of $AUC_{0–24}$ for lenalidomide in each genotype of *ABCB1* SNPs ($n=36$)

Variable	*n* (%)	Median $AUC_{0–24}$ (range)	*p* value
All patients	36 (100)	4754.0 (186.3–27,246.9)	
CCr ≥ 60 mL/min	18 (50)	4754.0 (186.3–23,284.7)	0.606[b]
CCr < 60 mL/min	18 (50)	4761.5 (2239.3–27,246.9)	
ABCB1 1236C>T			
C/C	9 (25)	9435.8 (2239.3–23,284.7)	0.188[a]
C/T	13 (36)	3385.3 (186.3–14,411.0)	
T/T	14 (39)	5852.8 (1666.6–27,246.9)	
C/C:C/T+T/T	9 (25):27 (75)	9435.8 (2239.3–23,284.7):4332.2 (186.3–27,246.9)	0.407[b]
ABCB1 2677G>T/A			
G/G	8 (22)	2315.7 (1542.4–23,284.7)	0.178[a]
G/A+G/T	17 (47)	9435.9 (186.3–27,246.9)	
A/A+A/T+T/T	11 (31)	4142.0 (1666.6–15,740.9)	
G/G:G/A+G/T+A/A+A/T+T/T	8 (22):28 (78)	2315.7 (1542.4–23,284.7):5852.8 (186.3–27,246.9)	0.193[b]
ABCB1 3435C>T			
C/C	15 (42)	2857.4 (186.3–23,284.7)	0.055[a]
C/T	16 (44)	5278.4 (2474.3–27,246.9)	
T/T	5 (14)	10,451.9 (4142.0–20,727.4)	
C/C:C/T+T/T	15 (42):21 (58)	2857.4 (186.3–232,847):6324.6 (2474.3–27,246.9)	0.028[b]

$AUC_{0–24}$ area under the plasma concentration–time curve of lenalidomide from 0 to 24 h, *SNPs* single nucleotide polymorphisms, *CCr* creatinine clearance

[a]Kruskal–Wallis test

[b]Mann–Whitney *U* test

mL, respectively, $p < 0.01$, effect size = 1.21) were significantly higher in patients with the T allele of 3435C>T than in those with C/C genotype (Supplementary Table 2). These data suggest that the absorption of lenalidomide from small intestine is significantly increased in patients with the T allele of 3435C>T than in those with the C/C genotype.

Correlation between *ABCB1* genotypes and toxicity

We have previously conducted a prospective trial of Ld therapy for 40 NDMM patients and confirmed the correlation between AUC_{0-24} for lenalidomide and severe toxicity [9]. In the previous study, we clarified the cutoff value of AUC_{0-24} as 2613.5 ng h/mL for predicting severe toxicity and confirmed the significance of the cutoff value by multivariate analysis. In this study, we investigated the percentages of patients who exceeded the cutoff value in each *ABCB1* genotype. As a result, we noted no correlation between *ABCB1* 1236C>T, 2677G>A/T genotype, and the percentages of patients who exceeded the cutoff value. However, the percentages of patients who exceeded the cutoff value were significantly higher in patients with the T allele of 3435C>T (60% in patients with C/C vs. 95% in patients with T allele, $p = 0.013$, Table 3). Finally, univariate and multivariate logistic regression analyses were performed to evaluate the factors that were correlated with the AUC_{0-24} values higher than the cutoff value of 2613.5 ng h/mL (Table 4). As a result, age, BSA, and RI were deleted in a stepwise manner, and *ABCB1* 3435C>T T allele remained a significantly valuable marker for severe toxicity (odds ratio 15.0, $p = 0.019$).

Discussion

We have recently reported from the prospective trial of Ld therapy for NDMM patients that the higher AUC_{0-24} for lenalidomide leads to severe toxicity, and the cutoff value of AUC_{0-24} was identified as 2613.5 ng h/mL [9]. Moreover, we found that AUC_{0-24} differs despite dosage modifications based on CCr and investigated the factors that influence the pharmacokinetics of lenalidomide. In this study, a significant correlation was found between *ABCB1* 3435C>T polymorphism and AUC_{0-24} for lenalidomide. Furthermore, higher number of patients with T allele of *ABCB1* 3435C>T exceeded the cutoff value for severe toxicity compared to the 3435C/C genotype. The median AUC_{0-24} value for lenalidomide in patients with C/C genotype of *ABCB1* 3435C>T was 2857.4 ng h/mL, which supported the accuracy of recommended lenalidomide dosage based on renal function [18]. In contrast, the median AUC_{0-24} for lenalidomide in

Table 3 Relationship between *ABCB1* genotype and the AUC_{0-24} for lenalidomide exceeding the cutoff value associated with severe toxicity ($n = 36$)

Variable	*n* (%)	AUC_{0-24} < cutoff value, *n* (%)	AUC_{0-24} > cutoff value, *n* (%)	*p* value
All patients	36 (100)	7 (19)	29 (81)	
CCr ≥ 60 mL/min	18 (50)	5 (28)	13 (72)	0.402
CCr < 60 mL/min	18 (50)	2 (11)	16 (89)	
ABCB1 1236C>T				
C/C	9 (25)	1 (11)	8 (89)	0.878
C/T	13 (36)	3 (23)	10 (77)	
T/T	14 (39)	3 (21)	11 (79)	
C/T+T/T	27 (75)	6 (22)	21 (78)	0.652[a]
ABCB1 2677G>T/A				
G/G	8 (22)	3 (37)	5 (63)	0.134
G/A+G/T	17 (47)	1 (6)	16 (94)	
A/A+A/T+T/T	11 (31)	3 (27)	8 (73)	
G/A+G/T+A/A+A/T+T/T	28 (78)	4 (14)	24 (86)	0.167[b]
ABCB1 3435C>T				
C/C	15 (42)	6 (40)	9 (60)	0.044
C/T	16 (44)	1 (6)	15 (94)	
T/T	5 (14)	0 (0)	5 (100)	
C/T+T/T	21 (58)	1 (5)	20 (95)	0.013[a]

Fisher's exact test. The cutoff value of AUC_{0-24} was identified as 2613.5 ng h/mL for prediction of severe toxicity from the results of prospective study as we previously reported

AUC_{0-24} area under the plasma concentration–time curve of lenalidomide from 0 to 24 h

[a]CC versus CT/TT

[b]GG versus GA/GT/AA/AT/TT

Table 4 Univariate and multivariate analysis for predicting severe toxicity of lenalidomide ($n=36$)

Variable	Univariate model			Multivariate model		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (years)	1.03	0.97–1.09	0.403			
Body surface area < 1.55 m^{2a}	3.33	0.55–20.20	0.190			
Creatinine clearance (mL/min)	0.98	0.96–1.01	0.14			
ABCB1 3435C>T, T allele	13.3	1.39–128.0	0.025	15.0	1.55–145.0	0.019

The factors associated with higher AUC_{0-24} for lenalidomide > 2613.5 ng h/mL for the prediction of severe toxicity from the results of our previous study were analyzed

AUC_{0-24} area under the plasma concentration–time curve of lenalidomide from 0 to 24 h, *OR* odds ratio, *CI* confidence interval

[a]The cutoff point of body surface area was the median absolute number

patients with the T allele of *ABCB1* 3435C>T SNP was 2.5 times higher than 3435C/C genotype.

P-gp is an efflux transporter which is expressed in the small intestine, brain, liver, kidney and other tissues [19]. P-gp is located on the apical site of the plasma membrane and plays an important role in cellular excretion of the drug substrates. Therefore, P-gp expression influences the oral bioavailability and the renal excretion of P-gp substrates. It is known that the *ABCB1* 3435C>T SNP is associated with the expression levels of P-gp [20]. Digoxin is the most extensively studied P-gp substrate. It has been reported that interindividual variations in the intestinal expression of P-gp can result in a sevenfold change in the oral bioavailability of digoxin [21]. Therefore, plasma concentration of digoxin is significantly higher in individuals with the 3435T/T genotype than in individuals with the 3435C/C genotype, and is associated with toxicity [22, 23]. The *ABCB1* 3435C>T allele frequency differs by ethnicity. The frequency of T allele in *ABCB1* 3435C>T is around 40–70% in European, American, and Asian populations, including Japanese population compared to around 10–20% in the African populations [24]. Therefore, there may be a racial difference in the frequency of toxicity observed upon lenalidomide administration.

In a previous study, clinically significant pharmacokinetic interactions between lenalidomide and substrates or inhibitors of P-gp were not found [25]. However, the other studies reported that lenalidomide is a substrate of P-gp [26, 27]. We also confirmed that lenalidomide is a substrate of P-gp by the concomitant use of P-gp inhibitors, clarithromycin or itraconazole, which increased the absorption of lenalidomide from small intestine by in vitro assays and drug–drug interactions [10, 11]. In this study, our observations based on the C_{max} and AUC_{0-4} for the SNP validated the previous findings that the P-gp is involved in the intestinal absorption of lenalidomide. It has also been reported that lenalidomide was not the substrate for human breast cancer resistance protein (BCRP), multidrug resistance proteins (MRP1, MRP2, MRP3), organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1 and OCT2), human organic cation transporter novel 1 and 2 (OCTN1 and OCTN2), multidrug and toxin extrusion (MATE1), and organic anion-transporting polypeptide (OATP1B1) [27]. These findings suggest the possibility that preevaluation of *ABCB1* polymorphisms could determine the individualized dosage of lenalidomide and reduce the unexpected toxicity [28].

There are, however, some limitations of this study. A recent study from another group reported that the time to progression was significantly longer in patients carrying the 1199A variant in *ABCB1* 1199G>A SNPs than in those without [29]. In this study, we could not evaluate the correlation between *ABCB1* SNPs and Ld efficacy, because study design was not expected to evaluate the efficiency of Ld therapy, and this is pharmacokinetic analysis in general practice data. Additionally, due to the small sample size, further studies are needed to validate and clarify the correlation between *ABCB1* 3435C>T polymorphism and AUC_{0-24} for lenalidomide and other clinical parameters, including toxicity profile. However, we investigated the validity of the sample size from the study and found that the effect sizes for the AUC_{0-4} for lenalidomide between ABCB1 3435C>T genotypes were 1.21, supporting the clinical significance of these results. The results of randomized phase 3 FIRST trial [30] reported that the 80% of NDMM patients treated with Ld therapy experienced severe toxicity. Our data is in line with these results in that 81% of patients in this study exceeded the cutoff value for AUC_{0-24}. We also noted that the 95% of the patients with the T allele of 3435C>T exceed the cutoff value. Therefore, our data indicate the possibility of incorporation of *ABCB1* SNPs investigation for individualized lenalidomide-based therapy in patients with MM.

Conclusion

In this study, we revealed that AUC_{0-24} for lenalidomide was significantly higher in patients with the T allele of *ABCB1* 3435C>T than the C/C genotype, which also correlated with

the cutoff values of severe toxicity. A prospective study in large number of patients is further required to evaluate the correlation between pharmacokinetic parameters, clinical outcomes, and *ABCB1* 3435C>T SNPs in MM patients treated with lenalidomide-based therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the Ethics Committee of Akita University School of Medicine (No. 905) and with the 1964 Helsinki Declaration.

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