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PHARMACOGENETICS

Effects of *ABCB1* and *ABCG2* polymorphisms on the pharmacokinetics of abemaciclib

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Abstract

Purpose Adverse events after the use of the CDK4/6 inhibitor abemaciclib are dose-dependent. However, its pharmacokinetics varies among individuals. Abemaciclib is reportedly transported by P-glycoprotein and breast cancer resistance protein. Therefore, we evaluated whether *ABCB1* and *ABCG2* polymorphisms are pharmacokinetic predictive factors of abemaciclib.

Methods A total of 45 patients with breast cancer taking abemaciclib (150 mg twice per day) for 2 weeks were evaluated to determine the associations among abemaciclib concentration; adverse events; and *ABCB1* 1236 T > C, 2677G > T/A, 3435C > T, and *ABCG2* 421C > A gene polymorphisms.

Results The trough concentration of abemaciclib was significantly higher in the group with grade 2 or greater neutropenia and thrombocytopenia than in those with grades 0 or 1. For *ABCB1* 2677G > T/A polymorphisms, the concentration of abemaciclib tended to be higher in the homozygous group (TT + AT) than in the wild-type + heterozygous group (GG + GA + GT) (median [range], 222.8 [80.5–295.8] ng/mL vs. 113.5 [23.6–355.2] ng/mL, $P = 0.09$), Moreover, the ABCB1 2677G > T/A homozygous group had a higher tendency of abemaciclib withdrawal or dose reduction within 4 weeks than the wild-type + heterozygous group (odds ratio, 4.22; 95% confidence interval, 0.86–20.7; $P = 0.08$). No significant association was observed among abemaciclib concentration; adverse reactions; and *ABCB1* 1236 T > C, 3435C > T, and *ABCG2* 421C > A polymorphisms.

Conclusion *ABCB1* 2677G > T/A polymorphism might be a predictor of the pharmacokinetics and tolerability of abemaciclib.

Keywords Abemaciclib · ABCB1 · ABCG2 · Pharmacokinetics · Polymorphisms

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Introduction

Abemaciclib is an orally administered inhibitor of cyclin-dependent kinase (CDK)-4 and CDK-6. When used in combination with a nonsteroidal aromatase inhibitor or fulvestrant, abemaciclib is effective in significantly improving overall survival against advanced breast cancer [1–4]. Abemaciclib is known to show side effects such as hematologic toxicity, diarrhea, and malaise, and approximately half of the patients need to withdraw or reduce the dose from the approved dose of 150 mg twice daily [1, 2]. Although the adverse events after abemaciclib consumption are dose-dependent [5], its pharmacokinetics varies among individuals [6].

We have previously reported the relationship between the blood concentrations of abemaciclib and its hematologic toxicity [7]. Therefore, identifying the predictive factors associated with abemaciclib concentration could be beneficial for possibly predicting its side effects and adjusting the dose.

Abemaciclib is primarily metabolized by cytochrome P450 isozyme (CYP)3A4 [8]. The substrates and/or inhibitors of CYP3A4 and P-glycoprotein (P-gp) are overlapping [9, 10]. In addition, abemaciclib may compete with transporter substrates to interact with the substrate-binding sites of P-gp and breast cancer resistance protein (BCRP) [11, 12]. This suggests that abemaciclib may be a substrate of P-gp and BCRP. These transporters (P-gp and BCRP) act as polymorphic efflux transporters that are located in the apical membrane of intestinal cells, the canalicular side of hepatocytes, and the luminal side of tubular cell in the kidneys [13]; they are encoded by *ABCB1* and *ABCG2* [14, 15].

In particular, three commonly investigated single-nucleotide polymorphisms (SNPs) in the protein-coding region, i.e., *ABCB1* 1236 T > C, 2677G > T/A, and 3435C > T, have been associated with changes in P-gp activity [14]. The *ABCG2* 421C > A allele is associated with decreased transportation activity of BCRP and increased bioavailability of drugs [16]. Therefore, similar to doxorubicin, which is a substrate for BCRP and P-gp [17, 18], these gene polymorphisms may be predictors of the pharmacokinetics of abemaciclib.

In this preliminary study, we evaluated the association between abemaciclib concentrations and adverse reactions and whether *ABCB1* and *ABCG2* polymorphisms could be used as pharmacokinetic predictive factors for abemaciclib in a small number of patients.

Methods

Patients

This observational study was conducted at the Aichi Cancer Center Hospital between July 2019 and March 2021. Patients were recruited if they fulfilled the following key inclusion criteria: (1) ≥ 20 years of age, (2) sufficient food intake, and (3) ER-positive, $HER2^-$ metastatic, or advanced breast cancer. There were no exclusion criteria.

Ethical considerations

This study was approved by the Ethics Committee of Aichi Cancer Center Hospital and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Procedures

All enrolled patients were prescribed abemaciclib (Eli Lilly, Ltd., Tokyo, Japan) at a dose of 150 mg twice per day by the attending physician. There were no regulations regarding the use of luteinizing hormone-releasing hormone (LH-RH) analog and the type or dose of endocrine therapy (nonsteroidal aromatase inhibitors or fulvestrant) to be used in combination with abemaciclib. The following data was collected over a period of 28 days: changes in laboratory values (hematologic and clinical) and adverse events reported according to the Common Terminology Criteria for Adverse Events, version 5.0 (Cancer Therapy Evaluation Program; National Cancer Institute, National Institutes of Health, Bethesda, MD, USA); and concomitant medications, including strong inhibitors and inducers of CYP3A4, BCRP, or P-gp [8, 19–21], and OCT2 and MATE substrates (such as metformin). We collected blood samples on days 12–16, a usual return visit day (at steady-state; blood collection was done only once), from participants who had been taking abemaciclib without withdrawal or dose reduction. Medication adherence was confirmed by the patients' self-reported diary. Abemaciclib serum concentrations and *ABCB1* and *ABCG2* polymorphisms were measured after the investigation period.

Measurement of serum abemaciclib concentrations

Serum abemaciclib concentration was measured as per a previously reported method [7]. The calibration range of abemaciclib was 5–1000 ng/mL with a good linearity (R^2 > 0.99). The accuracy and precision of the measurement of serum abemaciclib concentrations assay (n = 5) were 105.5–111.3% (relative error %) and 2.4–8.6% (relative standard error %), respectively. Serum samples were stored at −80°C in deep freezer, and all measurements were taken within 12 months after blood collection, when the stability of abemaciclib was confirmed [22].

ABCB1 and *ABCG2* genotyping

We extracted DNA from blood samples using the TaqMan Sample-to-SNP kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. All patients were genotyped for *ABCG2* 421C > A (rs2231142) and *ABCB1* 1236 T > C (rs1128503), 3435 C > T (rs1045642), and 2677G > T/A (rs2032582) using the TaqMan Drug Metabolism assays and ViiA 7 Real-Time PCR system (Thermo Fisher Scientific). Assay IDs were C_15854163_70 for rs2231142, C_7586662_10 for rs1128503, C_7586657_20 for rs1045642, and C_11711720C_30 and C_11711720D_40 for rs2032582.

Statistical analysis

We determined the correlation between body surface area and abemaciclib concentration using Spearman's rank correlation test. Differences in the adverse drug reaction variables between groups were analyzed using Fisher's exact test and multivariate logistic regression. Pharmacokinetics and laboratory data were analyzed using the Mann–Whitney *U* test. Data are expressed as median (range) and mean ± standard deviation. A *P* value of < 0.05 was considered statistically significant. All calculations were performed using EZR, version 1.54 (Saitama Medical Center, Jichi Medical University) [23].

Results

Table 1 summarizes the characteristics of the 55 patients enrolled in this study. The frequencies of *ABCB1* 1236 T > C, *ABCB1* 2677G > T, G > A, *ABCB1* 3435C > T, and *ABCG2* 421C > A, which are minor alleles, were 39%, 39%, 15%, 42%, and 31%, respectively, and were comparable to those reported in previous studies [16].

Overall, 23 (42%) patients stopped or reduced the dose of abemaciclib within 4 weeks due to adverse effects. Diarrhea was the most frequent cause of reduction and/or withdrawal of abemaciclib in 10 (18%) patients, followed by hematotoxicity in 7 (12%) patients (Table 2). Nine of these were unable to consume abemaciclib for 2 weeks because of nonhematologic toxicity for 2 weeks and one of the nine patients had to undergo emergency hospitalization due to nausea. These patients stopped abemaciclib or received a reduced dose before undergoing blood sampling for drug concentration measurement. Moreover, the blood sample of one patient could not be collected at 2 weeks; therefore, these ten patients were excluded from the pharmacokinetic analysis.

For the 45 whose blood concentrations could be measured, no significant correlation was observed between the steady-state serum concentration of abemaciclib and body surface area, age, albumin, and serum creatinine (body surface area, $r = 0.189$, $P = 0.21$; age, $r = 0.241$, $P = 0.11$; albumin, $r = -0.116$, $P = 0.46$; serum creatinine, $r = -0.053$, $P = 0.73$).

Adverse reactions

Figure 1 shows the relationship between adverse drug reactions and serum concentration of abemaciclib over a 4-week period. The trough concentrations were higher in the group with grade 2 or greater neutropenia, anemia, and thrombocytopenia than in the groups with grades 0 or 1 (neutropenia, 150.0 [31.0–349.7] ng/mL vs. 94.0 [23.6–355.2] ng/mL, $P = 0.04$; anemia, 228.4 [74.8–349.7] ng/mL vs. 115.8 [23.6–355.2] ng/mL, $P = 0.07$; thrombocytopenia, 249.0 [121.7–339.6] ng/mL vs. 113.5 [23.6–355.2] ng/mL, $P = 0.05$, respectively.). Consistent with these results, the concentration of abemaciclib tended to be higher in the patients who required withdrawal or dose reduction within 4 weeks than in those who did not require the same (222.8 [70.4–349.7] ng/mL vs. 115.8 [23.6–355.2] ng/mL, $P = 0.13$). Among all the enrolled patients, there was no association detected between the incidence of grade 2 or greater adverse events or tolerability and patient profile, such as age, body surface area, serum albumin level, and serum creatinine level.

Polymorphisms

One of the 45 patients was consuming strong CYP3A4 inducer (carbamazepine) and was excluded from the investigation of the effects of gene polymorphism on pharmacokinetics.

No significant association was observed between *ABCB1* 1236 T > C and 3435C > T polymorphisms and the concentration of abemaciclib. As for *ABCB1* 2677G > T/A polymorphism, the abemaciclib concentration tended to be higher in the minor allele homozygous group (TT + AT) than in the wild-type + heterozygous group (GG + GA + GT) [222.8 (80.5–295.8) ng/mL vs. 113.5 (23.6–355.2) ng/mL, $P = 0.09$] (Table 3). Moreover, the *ABCB1* 2677G > T/A homozygous group had a higher tendency of abemaciclib withdrawal or dose reduction within 4 weeks than the wild-type + heterozygous group (odds ratio, 4.22; 95% confidence interval, 0.86–20.7, $P = 0.08$) (Table 4).

In the examination of *ABCB1* 1236 T > C, 2677G > T/A, and 3435C > T haplotypes, the TT(A)T/TT(A)T haplotype did not affect the abemaciclib concentration, incidence of grade 2 or greater adverse events, or tolerability (Supplementary Table 1).

We found no association among *ABCG2* 421C > A polymorphism, abemaciclib concentration (Table 3), and tolerability (Table 4).

Table 1 Patient characteristics

	Patients with eligibility	Patients analyzed for pharmacokinetics
n	55	45
Age (years), median (range)	52 (34–77)	52 (34–77)
Female, *n* (%)	55 (100)	45 (100)
Menopause, *n* (%)	33 (60)	26 (58)
BSA (m^2)	1.50 (1.24–1.93)	1.50 (1.24–1.93)
ECOG-PS (*n*)		
0/1	51 / 4	42 / 3
LH-RH analog, *n* (%)		
Leuprorelin	6 (11)	5 (11)
Goserelin	20 (36)	15 (33)
Combination therapy, *n* (%)		
Fulvestrant	30 (55)	25 (56)
Aromatase inhibitor	24 (43)	19 (42)
Tamoxifen	1 (2)	1 (2)
WBC (/μL)	5400 (3110–8530)	5440 (3110–8470)
Hemoglobin (g/dL)	13.0 (10.1–16.3)	13.0 (10.1–16.3)
Platelet (10^4/μL)	21.6 (10.3–35.1)	21.3 (10.3–32.7)
Albumin (g/dL)	4.2 (3.3–4.8)	4.3 (3.5–4.8)
ALP (U/L)	237 (106–649)	235 (106–649)
LDH (U/L)	184 (119–301)	183 (135–301)
AST (U/L)	23 (16–79)	22 (16–79)
ALT (U/L)	16 (7–90)	17 (7–90)
T.bil (mg/dL)	0.6 (0.3–1.6)	0.6 (0.4–1.6)
SCr (mg/dL)	0.66 (0.38–1.03)	0.66 (0.38–0.87)
eCCr (mL/min)	84.1 (39.5–158.0)	83.5 (49.3–158.0)
ABCB1 1236 T > C		
TT	18 (33)	13 (29)
TC	31 (56)	28 (62)
CC	6 (11)	4 (9)
ABCB1 2677G > T/A		
GG	10 (18)	10 (22)
GA	8 (15)	6 (13)
GT	22 (40)	18 (40)
AT	9 (16)	7 (16)
TT	6 (11)	4 (9)
ABCB1 3435C > T		
CC	18 (33)	16 (36)
CT	28 (51)	23 (51)
TT	9 (16)	6 (13)
ABCG2 421C > A		
CC	30 (55)	24 (53)
CA	16 (29)	14 (31)
AA	9 (16)	7 (16)

Data are presented as mean ± standard deviation

BSA body surface area, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *ALP* alkaline phosphatase; *LDH* lactate dehydrogenase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T.bil* total bilirubin, *SCr* serum creatinine, *eCcr* estimated creatinine clearance (Cockcroft–Gault), *LH-RH* luteinizing hormone-releasing hormone

Table 2 Reason for dose reduction and/or withdrawal of abemaciclib

Patients (*n*)	55
Dose reduction and/or withdrawal of abemaciclib due to AEs, *n* (%)	23 (42)
Within 2 weeks, *n* (%)	9 (16)
Diarrhea (*n*)	5
Nausea (*n*)	3
Malaise (*n*)	2
Anorexia (*n*)	2
Dyspnea (*n*)	1
Fever (*n*)	1
Within 2–4 weeks	14 (25)
Hematotoxicity (*n*)	7
Diarrhea (*n*)	5
Nausea (*n*)	2
Rash (*n*)	2
Malaise (*n*)	1
AST and ALT increased (*n*)	1

There is a duplicate count if there are multiple reasons for dose reduction and/or withdrawal

AE adverse event, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Discussion

We investigated the relationship between steady-state serum abemaciclib concentration, adverse events, and *ABCB1* and *ABCG2* polymorphisms as well as the predictive factors influencing the pharmacokinetics of abemaciclib. In this study, we observed a significant relationship between serum abemaciclib concentration and hematologic toxicity, as has been previously reported [7]. As a predictor of abemaciclib concentration, homozygous (TT + AT) *ABCB1* 2677 G > T/A polymorphism tended to be associated with a higher abemaciclib concentration and a higher incidence of abemaciclib withdrawal and dose reduction within 4 weeks than the wild and heterozygous types (GG + GA + GT group). Presumably, this result was due to the increase in abemaciclib exposure associated with the decrease in the intestinal and hepatic excretory function of abemaciclib via P-gp in the *ABCB1* 2677G > T/A polymorphism carrier.

In all, 23 (42%) patients stopped or reduced the abemaciclib dose within 4 weeks due to adverse events. This incidence was similar to that reported in previous large-scale clinical trials [1, 2]. Most of the reasons for withdrawal and dose reduction within 2 weeks were grade 3 or higher serious nonhematologic events, such as diarrhea, nausea, and vomiting. Notably, one patient was admitted to the hospital for nausea on the third day of abemaciclib consumption. Therefore, we were unable to collect blood samples at 2 weeks for these patients with severe nonhematologic toxicity or adequately examine them in terms of the relationship between early severe nonhematologic toxicity and abemaciclib concentration. On investigating patients who consumed abemaciclib for 2 weeks, the association between abemaciclib concentration and hematotoxicity was confirmed as the steady-state abemaciclib concentration was significantly higher in grade 2 or higher hematotoxicity-expressing group than in grades 0 or 1 group. In addition, as per previous large-scale clinical trials [1, 2], patients who stopped or reduced their dose because of severe diarrhea or nausea and vomiting might be able to manage these adverse

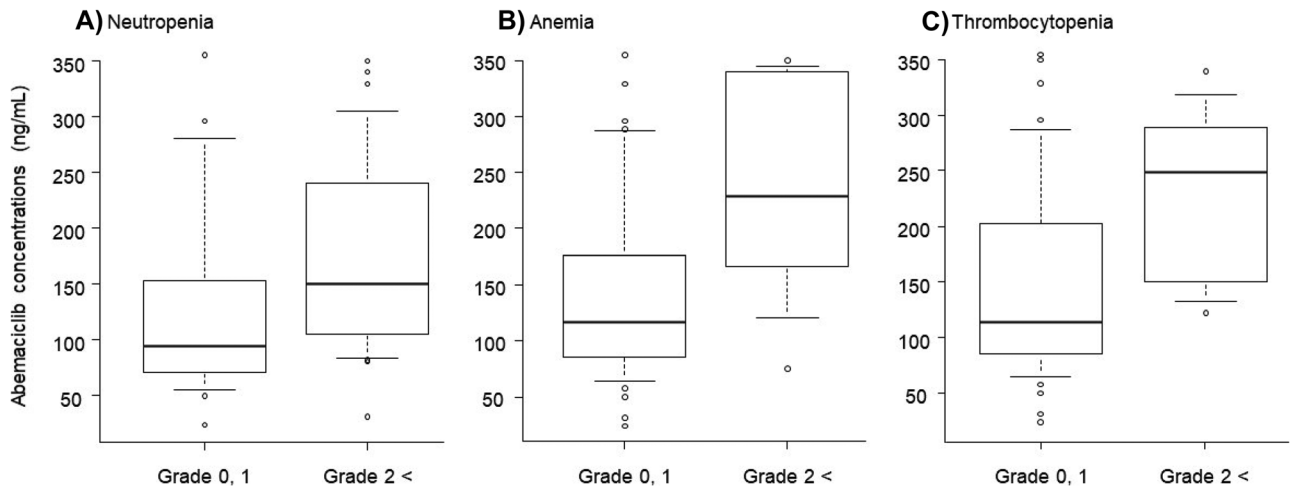

Fig. 1 Comparison of abemaciclib concentrations and treatment-related grade 2 or greater hematotoxicity. The lines within the boxes represent the median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively ($n = 45$)

Table 3 Comparison of abemaciclib concentrations between the *ABCB1* and *ABCG2* polymorphism groups

	ABCB1 1236 T > C			*ABCB1* 2677G > T/A			*ABCB1* 3435C > T			*ABCG2* 421C > A		
	TT + TC ($n = 40$)	CC ($n = 4$)	*P* value	GG + GA + GT ($n = 34$)	TT + AT ($n = 10$)	*P* value	CC + CT ($n = 38$)	TT ($n = 6$)	*P* value	CC + CA ($n = 37$)	AA ($n = 7$)	*P* value
Abemaciclib concentrations (ng/mL)	132.4 (23.6–349.77)	90.6 (82.1–355.2)	0.62	113.5 (23.6–355.2)	222.8 (80.5–295.8)	0.09	126.9 (23.6–355.2)	187.9 (70.4–328.9)	0.77	126.3 (49.5–355.2)	127.5 (23.6–234.6)	0.38

Abemaciclib concentrations are presented as mean (range)

events after dose reduction, suggesting that the identification of abemaciclib pharmacokinetic predictors is clinically important for avoiding side effects.

In this study, there were large individual differences between serum abemaciclib concentrations, which is in accordance with a previous report [6]. The differences in serum concentration among individuals may be attributable to differences in physique; however, we observed no correlation between body surface area, age, albumin and serum creatinine levels, and serum concentration in this study. In general, previous studies have reported that a decrease in performance status and metabolic activity due to advanced age and the change of distribution volume due to hypoalbuminemia are factors affecting drug pharmacokinetics [24–26]. However, we clarified through this study that these factors were not associated with abemaciclib pharmacokinetics.

Another study identified advanced age (> 70 years) as significantly associated with an increased risk of abemaciclib-induced grade 3 of higher diarrhea [27]. Our study included six patients aged ≥ 70 years; 3 (50%) of these withdrew or reduced their dose within 4 weeks due to anorexia or hematotoxicity. This finding suggests that elderly patients poorly tolerate 150 mg abemaciclib, twice daily. However, this was a small number of patients, and further investigation is required to determine the drug tolerability in elderly patients.

Abemaciclib is primarily metabolized by cytochrome CYP3A4 [8]. The substrates and/or inhibitors of CYP3A4 and P-gp are overlapping [9, 10]. Although abemaciclib might be the substrate for BCRP and P-gp, *ABCG2* 421C > A, which is associated with loss of function of BCRP, is not associated with abemaciclib concentration, and *ABCG2* 421C > A might not be a predictor of side effects. Conversely, among the gene polymorphisms of *ABCB1* 1236 T > C, 2677G > T/A, and 3435C > T that are related to P-gp function, *ABCB1* 2677G > T/A homozygous type (TT + AT group) tended to be associated with a higher abemaciclib concentration. It was also associated with the incidence of drug withdrawal and dose reduction within 4 weeks compared with the wild and heterozygous types (GG + GA + GT group; $P = 0.08$). Moreover, one patient who was urgently hospitalized due to nausea on day 3 after starting abemaciclib showed homozygous type *ABCB1* 2677G > T/A, suggesting that *ABCB1* 2677G > T/A polymorphism predicts abemaciclib tolerability.

A large-scale study of palbociclib, another CDK4/6 inhibitor, reported that *ABCB1 1236C > T* was an independent risk factor for early occurrence of grade 3/4 neutropenia [28]. Though this study did not investigate the effects of *ABCB1* 2677G > T/A and haplotypes, the results suggests that the pharmacokinetics and adverse events of the CDK4/6 inhibitor are influenced by P-gp polymorphism.

Previous researchers have reported that it is important to examine the effect of SNPs for *ABCB1* using haplotype based

Table 4 Comparison of tolerability between the *ABCB1* and *ABCG2* polymorphism groups

	Withdrawal of abemaciclib due to AEs within 2 weeks				**Dose reduction and/or withdrawal of abemaciclib due to AEs within 4 weeks**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ABCB1 1236 T > C								
CC (vs TT + TC)	2.85 (0.22–25.0)	0.26	3.60 (0.47–27.3)	0.22	1.51 (0.18–12.5)	0.68	1.97 (0.31–12.7)	0.48
ABCB1 2677G > T/A								
TT + AT (vs GG + GA + GT)	1.53 (0.21–8.76)	0.68	1.69 (0.24–11.9)	0.60	3.64 (0.88–16.9)	0.06	4.22 (0.86–20.7)	0.08
ABCB1 3435C > T								
TT (vs CC + CT)	1.54 (0.13–10.8)	0.63	1.54 (0.17–14.3)	0.70	2.03 (0.38–11.8)	0.47	1.26 (0.20–7.98)	0.80
ABCG2 421C > A								
AA (vs CC + CA)	1.54(0.13–10.8)	0.63	1.46 (0.22–9.8)	0.70	3.53 (0.65–24.8)	0.14	4.14 (0.82–20.8)	0.09

OR odds ratio, *CI* confidence interval, *AEs* adverse events

on *ABCB1* 1236 T > C, 2677G > T/A, and 3435C > T and that T-T (A)-T carriers are especially known to reduce P-gp function [17, 29, 30]. However, in our study, patients homozygous for TT(A)T/TT(A)T were not significantly associated with higher abemaciclib concentrations and higher incidence of grade 2 or greater adverse events or drug tolerability within 4 weeks. Hence, *ABCB1* 2677G > T/A polymorphism might be a more beneficial factor in predicting the pharmacokinetics and adverse events of abemaciclib than T-T(A)-T homozygosity. However, as the number of patients homozygous for TT(A)T/TT(A)T was small, further investigation is needed to determine the effect of haplotype on pharmacokinetics.

Abemaciclib is a hepatically metabolized oral drug, and thus a decrease in hepatic intrinsic clearance may have a significant effect on pharmacokinetics. Abemaciclib is primarily metabolized by CYP3A4 with the formation of three active metabolites: *N*-desethylabemaciclib, hydroxyabemaciclib, and hydroxy-N-desethylabemaciclib [8]. In fact, abemaciclib concentration in a patient taking carbamazepine (a strong inducer of CYP3A4), who was excluded from our pharmacogenomics analysis, was low (91.7 ng/mL), although she carried the *ABCB1* 2677G > T/A minor allele. This makes it necessary to investigate the potential effects of *CYP3A4* and *CYP3A5* polymorphisms on the pharmacokinetics and safety/tolerance of abemaciclib. However, it is known that the frequency of gene polymorphisms that affect the activity of CYP3A4 is extremely rare in Asians [31–33], and the effects of *CYP3A5* polymorphisms on the safety/tolerance of the drug have been seldom reported except for tacrolimus. Therefore, we did not measure these gene polymorphisms in this study. Additionally, the active metabolites are also reported to be transported by BCRP and P-gp [12]. Therefore, it is possible that the effect of *ABCB1* 2677G > T/A polymorphism on the pharmacokinetics of metabolites also affected tolerability of this drug.

One of the main limitations of the present study was the single-point measurement of abemaciclib concentration as this value could be influenced by interday (intrasubject, interoccasion) variability. Conventionally, when examining drug exposure, it is important to use the area under the curve. However, it has been reported that the maximum and minimum concentrations of abemaciclib are approximately the same after repeated administration [6]. This may be explained by the distinctive pharmacokinetic characteristics of abemaciclib, such as long elimination half-life and slow absorption [5]. Therefore, when examining abemaciclib pharmacokinetics, it is possible to estimate the total drug exposure from its serum concentration at one point.

Second, 9 (16%) patients stopped or reduced the dose of abemaciclib due to nonhematologic toxicity, such as diarrhea, nausea, and vomiting, within 2 weeks. Therefore, the abemaciclib concentrations in these patients showing early intolerance could not be evaluated. In this study, we could not confirm a significant association between nonhematologic toxicity and abemaciclib concentration; this could be due to the failure in validating abemaciclib concentration in these patients. The usefulness of predicting the pharmacokinetics of abemaciclib will be further increased by clarifying the influence of abemaciclib pharmacokinetics in patients showing early intolerance.

In conclusion, we were able to reconfirm a significant association between serum concentration of abemaciclib and its hematotoxicity as previously reported [7]. A statistically significant predictor of the steady-state concentration of abemaciclib has not been identified by the patients' profiles and *ABCB1* and *ABCG2* polymorphisms. However, *ABCB1* 2677G > T/A homozygous type was associated with a higher tendency of abemaciclib withdrawal and dose reduction as well as a tendency for higher abemaciclib concentration. Therefore, *ABCB1* 2677G > T/A polymorphism might be a predictor of abemaciclib tolerability and pharmacokinetics.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00228-022-03331-0.

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Author contribution All authors contributed to the study conception and design. Material preparation was performed by Akimitsu M. Data collection was performed by Akimitsu M, Naoya H, Hiroji I, and Masataka S. Analysis was performed by Hitoshi A, Kei I, Jun-ichi M, Shoji F, and Hiromichi E. The first draft of the manuscript was written by Akimitsu M, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets during and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval All procedures performed in this study that involved human participants were conducted in accordance with the standards of the Ethics Committee of Aichi Cancer Center Hospital (No.: 2018–2-27) and the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Competing interests Hitoshi Ando had received a grant from Eli Lilly Japan. Hiroji Iwata had received honorarium for educational lectures and advisor from Eli Lilly Japan. All other authors declare no competing interests.

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