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Adverse Effects Induced by Osimertinib Based on the Dose per Body Constitutional Parameters: A Retrospective Observational Study

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Background: Osimertinib is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor treatment for non-small-cell lung cancer. Area under the blood concentration-time curve (AUC) of osimertinib can be related to the development of adverse events (AEs). Furthermore, the dose-per-body constitutional parameters (BCPs), such as body weight, body surface area (BSA), or lean body mass (LBM), are closely related to the AUC. However, BCPs other than weight have not been considered in clinical trials. Therefore, in this retrospective study, we investigated the association between doses per BCP (Dose/BCPs) and AEs of osimertinib. Method: Forty-two patients who received osimertinib between January 2010 and December 2020 were investigated. Differences in Dose/BCPs were compared between patients with and without AEs. Results: Among the patients, 54.8%, 38.1%, and 28.6% developed thrombocytopenia, neutropenia, and leukopenia, respectively. The Dose/BSA and Dose/LBM were significantly higher in patients who developed leukopenia than in those who did not ($p < 0.05$). The cutoff values of Dose/BSA and Dose/LBM associated with leukopenia were 50.0 mg/m² and 1.86 mg/kg, respectively. Conclusion: This study suggests that Dose/BCPs are associated with the development of leukopenia. Now, fixed dose regardless of BCPs is approved on almost of oral molecular targeting agents. However, the patients with low BCPs can be also received these medications in clinical practices. Therefore, although the sample size is small, the results of this study suggests the potential risk on the fixed dose. Moreover, Dose/BSA or Dose/LBM may be a useful parameter for assessing the risk of leukopenia with osimertinib.

Key words osimertinib, body constitutional parameters, body surface area, lean body mass, adverse event

INTRODUCTION

Several molecular targeted anticancer agents are available for the treatment of various cancer types, including hematological and non-hematological diseases. They have been shown to be more effective than conventional chemotherapies in terms of treatment outcomes.[1)] Tumor shrinkage or extension of survival after treatment with tyrosine kinase inhibitors (TKI) has been observed in patients with epidermal growth factor receptor (EGFR) gene mutations in non-small cell lung cancer (NSCLC). Consequently, clinical guidelines recommend EGFR-TKIs as a first-line treatment of advanced/metastatic diseases or as adjuvant treatment after radical surgery for NSCLC.[2–4)] Adverse events (AEs) in some cases caused by EGFR-TKI treatment are clinically problematic, although these treatments are generally tolerable.[5–11)] Therefore, treatment interruptions need to be avoided and successful outcomes achieved by managing AEs before they become serious.

Osimertinib is a third-generation EGFR-TKI used in primary and adjuvant treatments of NSCLC. Osimertinib doses were determined based on the results of the AURA study, a phase I clinical trial.[12)] This study revealed that the incidence of AEs in patients receiving a dose of > 80 mg was higher than that in patients receiving a dose of 80 mg; however, no clinical efficacy differences were observed between the two groups. In addition, subgroup analysis, including patients who were divided into six groups based on body weight (BW) (≥ 90, 89–73, 72–62, 61–53, 52–43, and <43 kg) in phase I and phase II clin-

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ical trials,[12,13] indicated that the incidence of AEs was similar among the groups. Based on these results, the approved dose of osimertinib is globally fixed at 80 mg, regardless of the individual's body size.

The largest effect on clearance of osimertinib was related to BW in population pharmacokinetic models.[14] Osimertinib is predominantly metabolized in the liver by cytochrome P450 (CYP) 3A4/5.[15,16] However, genetic polymorphisms in CYP3A4/5 did not affect the area under the blood concentration-time curve (AUC) of osimertinib in Japanese patients with NSCLC.[17] These reports suggest that BCPs such as BW may be factor related to blood concentration or AUC of osimertinib in clinical practice.

In addition, previous studies have suggested an association between AUC of osimertinib and AEs.[14] Moreover, a pharmacokinetic study of afatinib, a second-generation EGFR-TKI, reported an association between high blood concentrations and AEs.[18,19] The patients with severe AEs such as stomatitis, diarrhea, and skin disorders that necessitated dose reduction had high blood concentrations. Moreover, the development of mucositis and diarrhea is not only associated with BW but also with body surface area (BSA). Patients with relatively low lean body mass (LBM) or small BSA (<1.58 m^2) are more susceptible to dose reduction.[20,21] As BSA and LBM are associated with AEs of afatinib, BW and other BCPs may also be associated with AEs of osimertinib. However, only BW was considered for osimertinib, and other BCPs were not considered in clinical trials, as mentioned above.

We hypothesized that differences in Dose/BCPs may affect the occurrence of AEs in clinical practice, because BCPs may affect blood concentration and AUC, which are also associated with AEs. To the best of our knowledge, there is no reported evidence of an association between the dose of osimertinib per BCPs and AEs. The aim of this study was to investigate the association between osimertinib dose per BCP and AEs.

MATERIALS AND METHODS

Patients This was a retrospective case-control study. The medical records of patients with NSCLC who received osimertinib at Nagoya City University West Medical Center, Nagoya, Japan between January 2010 and December 2020 were examined. Patients who had discontinued osimertinib for > 7 days from the start of treatment or had a reduced initial dose were excluded.

Methods The primary endpoint was to evaluate association between AEs and dose per BCP of Osimertinib. Eligible patients were divided into two groups: those who developed AEs and those who did not, and the differences in dose per BCPs were compared between the two groups. In this study, BW, BSA, Body Mass Index (BMI), and LBM were used as BCPs. Additionally, cutoff values for the dose per BCP associated with the development of AEs were calculated using receiver operating characteristic (ROC) curves.

Clinical characteristics, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), clinical stage, height, BW, BSA, and previous medical treatment history were extracted for each patient. Treatment dose, reason for dose reduction, and treatment period for osimertinib were also investigated. Body surface area was calculated using the Du Bois formula and LBM was calculated using the formula reported by Green *et al*.[22,23]

The medical records of patients were reviewed to investigate the development of AEs during osimertinib treatment. We recorded the most severe grades of hematologic toxicities, hepatic dysfunction, and an increase in serum creatinine during osimertinib treatment. The date of onset and severity of other events (AEs) were evaluated while on osimertinib therapy. The severity of the AEs was assessed using the National Cancer Institute Common Terminology Criteria version 5 grading system.[24] Hepatic impairment was defined as an elevation in either aspartate or alanine aminotransferase levels.

Statistical Analysis The Student's t-test was used to compare the dose per BCP that developed or did not develop AEs, and to compare BCPs between females and males. The Mann–Whitney U test was used to compare age. Fisher's exact test was used to compare sex, prior treatment, and PS. Student's t-test was also used to compare dose per BCP by degree of AEs.

In addition, ROC curves were generated, and the Youden index was used to calculate the cutoff value of the dose per BCP at which the incidence of AEs was high.

Statistical analysis was performed using SPSS version 26.0. p values < 0.05 were considered statistically significant.

Ethics Approval Statement This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subject. This study was approved by the Nagoya City Hospital Clinical Research Review Committee (20-04-383-29).

RESULTS

Forty-seven patients received osimertinib during the study period; one of them patients who received osimertinib for only 4 days, and four who received a reduced dose from the initiation of treatment were excluded. The remaining 42 patients were eligible for inclusion. A summary of the clinical characteristics of the patients is presented in Table 1. The median age (inter quartile range, IQR) was 68.5 (61.8–76.3), and 25 patients (59.5%) were female. Thirty-five patients (83.3%) had an ECOG PS of 0–1. The mean (± standard deviation) of BW and BMI were 53.4 (± 11.8) kg and 21.3 (± 3.8), respectively. These values were within the normal range according to the Japan Society for the Study of Obesity.[25] Female patients had significantly lower BW, BSA, and LBM than male patients (female vs. male, BW: 49.4 ± 10.3 kg vs. 59.2 ± 10.5 kg, BSA: 1.44 ± 0.15 m^2 vs. 1.64 ± 0.15 m^2, LBM: 36.9 ± 5.0 kg vs. 48.3 ± 6.5 kg).

The most common hematological AE was thrombocytopenia (54.8%), followed by neutropenia (38.1%) and leukopenia (28.6%), and the most common non-hematological AE was diarrhea (26.2%) (Table 2A). The severity of thrombocytopenia and neutropenia was mainly grade 1, and that of 8 of the 12 patients who developed leukopenia was grade 2 (Table 2B); no grade 3 cases were recorded.

The differences in the dose per BCP for AEs and no AEs are presented in Table 3. The Dose/BSA and Dose/LBM were significantly higher in patients who developed leukopenia than in those did not (Dose/BSA: 56.7 mg/m^2 vs. 52.0 mg/m^2, Dose/LBM: 2.21 mg/kg vs. 1.91 mg/kg, $p < 0.05$). The dose per BCPs in patients who developed non-hematological AEs was similar to that in patients who did not. Additionally, Dose/BSA and Dose/LBM were significantly higher in patients with leukopenia of grade 2 than in those with leukopenia of grades 0 and 1 (Dose/BSA: 57.6 mg/m^2 vs. 52.3 mg/m^2, Dose/LBM:

Table 1. Patient Clinical Variables

Characteristic	Overall (n = 42)	*P* Value*
Age (years),		
median (IQR)	68.5 (61.8–76.3)	
≥ 65, n(%)	30 (71.4)	
≥ 75, n(%)	13 (31.0)	
Sex, n(%)		
Female	25 (59.5)	
Male	17 (40.5)	
ECOG-PS, n(%)		
0–1	35 (83.3)	
2–4	7 (16.7)	
Body constitution parameters, mean ± SD		
Body weight (kg)		
Overall	53.4 ± 11.8	
Female (n=25)	49.4 ± 10.3	0.004**
Male (n=17)	59.2 ± 10.5	
Body surface area (m^2)		
Overall	1.52 ± 0.19	
Female (n=25)	1.44 ± 0.15	<0.001**
Male (n=17)	1.64 ± 0.15	
Body mass index (kg/m^2)		
Overall	21.3 ± 3.78	
Female (n=25)	21.1 ± 3.76	0.542
Male (n=17)	21.7 ± 3.18	
Lean body mass (kg)		
Overall	41.5 ± 7.9	
Female (n=25)	36.9 ± 5.0	<0.001**
Male (n=17)	48.3 ± 6.5	
Previous treatment history, n (%)		
No	16 (38.1)	
Yes	26 (61.5)	
Number of previous treatment regimens, n (%)		
≥2 regimens(cytotoxic agent and EGFR-TKI)	12 (35.7)	
≥2 regimens(anti-PD1 antibody and EGFR-TKI)	3 (7.1)	
1 regimen (EGFR-TKI)	6 (14.3)	
1 regimen (cytotoxic agent)	5 (11.9)	
Dose reduction of osimertinib during treatment, n (%)		
No	28 (66.7)	
Yes	14 (33.3)	

IQR: Inter Quartile Range, SD: Standard Deviation
ECOG-PS: Eastern Cooperative Oncology Group performance status
EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor
PD-1: Programmed Death 1
* * $P < 0.01$: Indicating a statistically significant difference of female vs. male.

2.25 mg/kg vs. 1.93 mg/kg, $p < 0.05$). Similarly, Dose/LBM was significantly higher in patients with neutropenia of grade 2 than in those with neutropenia of grades 0 and 1 (Dose/LBM: 2.32 mg/kg vs. 1.95 mg/kg, $p < 0.05$). In other words, a trend toward a higher dose per BCP was observed in the higher-grade group. (Table 4).

The differences in the incidence of AEs according to each patient's clinical characteristics are shown in Table 5. Patients who developed thrombocytopenia were relatively young and the incidence of leukopenia was higher in females than in males. The incidence of diarrhea was relatively low in patients with a history of treatment.

ROC curves were generated for Dose/BSA and Dose/LBM; they showed significant differences between the groups that developed and did not develop leukopenia (Fig. 1). The AUC for Dose/BSA and Dose/LBM was 0.699 and 0.719, with cut-off, sensitivity, and specificity values of 50.0 mg/m^2, 91.7%, and 53.3% and 1.86 mg/kg, 91.7%, and 46.7%, respectively.

In addition, the incidence of leukopenia and proportion of patients who received a reduced dose of osimertinib during treatment were compared between the groups above and below the cutoff value, which were calculated using the ROC curve (Table 6). The incidence of leukopenia in the above group for Dose/BSA and Dose/LBM cutoff values was significantly higher than that in the below group. From the results, 40.7% (11/27) and 20.0% (3/15) were in the above and below cut off values for Dose/BSA and Dose/LBM, respectively. No significant difference ($p < 0.05$) in the proportion of patients who had a reduced dose of osimertinib was observed between the groups in any BCP, but there was a trend toward a higher proportion of patients who had a reduced dose in the group with above the cutoff value of Dose/BSA or Dose/LBM than below

Table 2. Adverse Events Experienced by Patients Treated with Various Doses of Osimertinib

A. Incidences of adverse events

Types of adverse events	Overall (n = 42)
Hematological events, n(%)	
Thrombocytopenia	23 (54.8)
Neutropenia	16 (38.1)
Leukopenia	12 (28.6)
Non-hematological events, n(%)	
Diarrhea	11 (26.2)
Paronychia	10 (23.8)
Hepatic dysfunction	7 (16.7)
Interstitial pneumonitis	7 (16.7)
Rash	6 (14.3)
Increase serum creatinine	4 (9.5)
Nausea	2 (4.8)
Mucositis	2 (4.8)
Pneumonia	2 (4.8)
Urticaria	2 (4.8)

B. Severities of hematological adverse events according to CTCAE ver5

Adverse events	No. of patients (%) (n = 42)		
	Grade 1	Grade 2	Grade 3
Thrombocytopenia	22 (52.3)	1 (2.3)	0
Neutropenia	11 (26.2)	5 (11.9)	0
Leukopenia	4 (9.5)	8(19.0)	0

CTCAE: Common Terminology Criteria for Adverse Events

the cutoff value Dose/BSA or Dose/LBM cutoff values. Three patients had unscheduled admissions or consultations due to infections, and two had Dose/BSA or Dose/LBM above the cutoff value.

DISCUSSION

To our knowledge, this is the first study to investigate the association between AEs and osimertinib dose on BCPs other than BW, such as BSA, BMI, and LBM. This study revealed a potential adverse interaction between BSA and LBM dose to leukopenia. In addition, the dose threshold for the BCPs at which the incidence of leukopenia increases has also been suggested.

The administration of a high dose generally leads to an increase in blood concentration, and consequently increases the AUC. When both the dose and clearance of drugs are equivalent between patients, the blood concentrations in patients with a small body constitution will be higher than those in patients with a larger body constitution. Therefore, a high dose per BCPs, such as Dose/BW, Dose/BSA, and Dose/LBM, is considered to lead to an increased blood concentration and AUC. In fact, among factors such as BW, age, gender, race, alanine amino transaminase (ALT), creatinine clearance (CrCl), disease state, food state, bilirubin levels, and smok-

Table 3. Difference of Dose per Body Constitution Parameter for Developed or Did not Develop in Each Adverse Events

A. hematological adverse events

Adverse events	Dose/BW (mg/kg)		Dose/BSA (mg/m^2)		Dose/BMI (mg/kg/m^2)		Dose/LBM (mg/kg)	
	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value
Thrombocytopenia								
Yes (n=23)	1.52 ± 0.31	0.335	52.1 ± 6.0	0.183	3.85 ± 0.56	0.968	1.92 ± 0.36	0.179
No (n=19)	1.62 ± 0.37		54.8 ± 6.8		3.84 ± 0.68		2.08 ± 0.39	
Neutropenia								
Yes (n=16)	1.59 ± 0.39	0.683	53.9 ± 7.9	0.673	3.86 ± 0.52	0.923	2.04 ± 0.45	0.590
No (n=26)	1.55 ± 0.31		53.0 ± 5.5		3.84 ± 0.67		1.97 ± 0.33	
Leukopenia								
Yes (n=12)	1.72 ± 0.36	0.058	56.7 ± 7.0	0.031*	4.00 ± 0.53	0.339	2.21 ± 0.37	0.017*
No (n=30)	1.50 ± 0.31		52.0 ± 5.8		3.79 ± 0.64		1.91 ± 0.35	

B. Non-hematological adverse events

Adverse events	Dose/BW (mg/kg)		Dose/BSA (mg/m^2)		Dose/BMI (mg/kg/m^2)		Dose/LBM (mg/kg)	
	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value
Diarrhea								
Yes (n=11)	1.60 ± 0.30	0.675	54.0 ± 5.9	0.693	3.94 ± 0.64	0.547	2.01 ± 0.35	0.902
No (n=31)	1.55 ± 0.35		53.1 ± 6.7		3.81 ± 0.60		1.99 ± 0.39	
Paronychia								
Yes (n=10)	1.65 ± 0.41	0.353	55.0 ± 8.1	0.330	3.93 ± 0.64	0.617	2.12 ± 0.46	0.235
No (n=32)	1.54 ± 0.31		52.8 ± 5.9		3.82 ± 0.61		1.96 ± 0.35	
Hepatic dysfunction								
Yes (n=7)	1.60 ± 0.30	0.754	53.2 ± 6.6	0.950	4.10 ± 0.38	0.250	1.94 ± 0.38	0.676
No (n=35)	1.56 ± 0.35		53.3 ± 6.5		3.80 ± 0.64		2.01 ± 0.38	
Interstitial Pneumonitis								
Yes (n=7)	1.56 ± 0.42	0.955	52.7 ± 8.0	0.772	3.90 ± 0.74	0.802	1.94 ± 0.48	0.694
No (n=35)	1.57 ± 0.32		53.5 ± 6.2		3.84 ± 0.59		2.01 ± 0.36	

Data are shown as mean (standard deviation) for all variables.
Dose/BW: Dose per Body Weight, Dose/BSA: Dose per Body Surface Area, Dose/BMI: Dose per Body Mass Index,
Dose/LBM: Dose per Lean Body Mass
SD: Standard Deviation
* $P < 0.05$: Statistically significant difference in adverse events (yes) vs. adverse events (no).

Table 4. Comparison of Dose per Body Constitution Parameter by Grade of Hematological Adverse Events

	Grade 0 and 1	Grade 2	P value
Thrombocytopenia	n= 41	n= 1	
Dose/BW (mg/kg)	1.56 ± 0.34	1.80	N.D.
Dose/BSA (mg/m^2)	53.2 ± 6.5	58.4	N.D.
Dose/BMI (mg/kg/m^2)	3.84 ± 0.62	3.84	N.D.
Dose/LBM (mg/kg)	1.98 ± 0.38	2.30	N.D.
Neutropenia	n= 37	n = 5	
Dose/BW (mg/kg)	1.53 ± 0.31	1.82 ± 0.42	0.069
Dose/BSA (mg/m^2)	52.6 ± 6.1	58.4 ± 7.5	0.060
Dose/BMI (mg/kg/m^2)	3.80 ± 0.61	4.15 ± 0.58	0.233
Dose/LBM (mg/kg)	1.95 ± 0.36	2.32 ± 0.41	0.039*
Leukopenia	n= 34	n = 8	
Dose/BW (mg/kg)	1.52 ± 0.32	1.77 ± 0.36	0.050
Dose/BSA (mg/m^2)	52.3 ± 6.12	57.6 ± 6.51	0.036*
Dose/BMI (mg/kg/m^2)	3.79 ± 0.63	4.08 ± 0.50	0.224
Dose/LBM (mg/kg)	1.93 ± 0.36	2.25 ± 0.37	0.031*

Data are shown as mean (standard deviation) for all variables.
Dose/BW: Dose per Body Weight, Dose/BSA: Dose per Body Surface Area, Dose/BMI: Dose per Body Mass Index, Dose/LBM: Dose per Lean Body Mass, N.D.: Not Determined
* $P < 0.05$: Statistically significant difference.

Table 5. Comparison of Patient Background Who Developed and Who Did not Develop Adverse Events

A. Hematological adverse events

	Age†		Sex††		Previous treatment history††		Performance Status ††	
Adverse events	year median (IQR)	P value	female/male No.	odds ratio (95% CIs)	Yes/No No.	odds ratio (95% CIs)	2–4/0–1 No.	odds ratio (95% CIs)
Thrombocytopenia								
Yes (n=23)	65.0 (53.0–70.0)	0.012*	12/11	0.50	13/10	0.60	5/18	2.36
No (n=19)	71.0 (67.0–80.0)		13/6	(0.14–1.79)	13/6	(0.17–2.14)	2/17	(0.40–13.84)
Neutropenia								
Yes (n=16)	65.5 (59.5–70.8)	0.082	11/5	1.89	10/6	1.04	2/14	0.60
No (n=26)	69.0 (62.0–77.3)		14/12	(0.51–6.98)	16/10	(0.29–3.76)	5/21	(0.10–3.54)
Leukopenia								
Yes (n=12)	65.5 (53.0–70.8)	0.219	11/1	12.57**	9/3	2.29	1/11	0.36
No (n=30)	69.0 (63.5–78.3)		14/16	(1.44–110.00)	17/13	(0.52–10.21)	6/24	(0.04–3.40)

B. Non-hematological adverse events

	Age†		Sex††		Previous treatment history††		Performance Status ††	
Adverse events	year median (IQR)	P value	female/male No.	odds ratio (95% CIs)	Yes/No No.	odds ratio (95% CIs)	2–4/0–1 No.	odds ratio (95% CIs)
Diarrhea								
Yes (n=11)	77.0 (65.0–79.0)	0.163	5/6	0.46	3/8	0.13**	4/7	5.33
No (n=31)	68.0 (59.0–71.0)		20/11	(0.11–1.85)	23/8	(0.03–0.62)	3/28	(0.96–29.51)
Paronychia								
Yes (n=10)	67.5 (64.0–70.0)	0.406	8/2	3.53	7/3	1.60	0/10	N.D.
No (n=32)	69.0 (59.8–77.8)		17/15	(0.65–19.28)	19/13	(0.35–7.34)	7/25	
Hepatic dysfunction								
Yes (n=7)	68.0 (65.0–75.0)	0.974	2/5	0.21	2/5	0.18	2/5	2.40
No (n=35)	69.0 (61.0–77.0)		23/12	(0.04–1.24)	24/11	(0.03–1.10)	5/30	(0.36–15.94)
Interstitial Pneumonitis								
Yes (n=7)	67.0 (53.0–75.0)	0.716	3/4	0.44	4/3	0.79	2/5	2.40
No (n=35)	69.0 (62.0–77.0)		22/13	(0.09–2.30)	22/13	(0.15–4.09)	5/30	(0.36–15.94)

† Mann-Whitney U-test, ††Fisher's Exact test
* $P < 0.05$, * * $P < 0.01$: Statistically significant difference.
IQR: Inter Quartile Range, CIs: Confidence Intervals, N.D.: Not Determined

ing status, expected to affect pharmacokinetics, BW has been found to have the largest effect on clearance of osimertinib in population pharmacokinetic models based on data for phase I and phase II clinical trials constituting 780 patients. Within the range of 43–90 kg of BW, osimertinib AUC at steady state ranged from -20 to +30% compared to the median BW of 62 kg.[14] Therefore, AUC may change in relation to BW. However, osimertinib is predominantly metabolized in the liver by cytochrome CYP 3A4/5 and is a substrate of ABCB1 and ABCG2.[15,16,26] Although the hepatic function may affect the blood concentration and AUC of osimertinib, mild or moderate hepatic impairment had no effect on the apparent plasma clearance of osimertinib.[27] Another study on the clearance of osimertinib in patients with severe renal impairment reported that there was no correlation between AUC and creatinine clearance.[28] Furthermore, genetic polymorphisms in CYP3A4/5, ABCB1, and ABCG2 may also affect the AUC of osimertinib. However, in Japanese patients with NSCLC, genetic polymorphisms in CYP3A4/5, ABCB1, ABCG2 did not affect the AUC of Osimertinib.[17,29] In other words, BCPs, such as BW,

Table 6. Incidence of Leukopenia, Proportion of Patients Who Reduced Dose of Osimertinib during Treatment, and Number of Patients Who Had Unscheduled Admissions or Consultations Due to Infectious Events According to Dose per BSA or Dose per LBM

	Dose/BSA (mg/m^2)			Dose/LBM (mg/kg)		
	> 50.0 (n = 27)	≤ 50.0 (n = 15)	odds ratio (95% CIs)	> 1.86 (n = 25)	≤ 1.86 (n = 17)	odds ratio (95% CIs)
Leukopenia						
Yes	11	1	9.63* (1.10–84.23)	11	1	12.57** (1.44–110.00)
No	16	14		14	16	
Incidence rate, %	40.7	6.7		44.0	5.9	
Osimertinib dose reduction during treatment						
Yes	11	3	2.75 (0.63–12.08)	10	4	2.17 (0.55–8.59)
No	16	12		15	13	
Proportion of patients who reduced dose, %	40.7	20.0		40.0	23.5	
Unscheduled admissions or consultations due to infectious events						
Yes	2	1		2	1	

* $P < 0.05$, * * $P < 0.01$: Statistically significant difference.
BSA: Body Surface Area, LBM: Lean Body Mass, CIs: Confidence Intervals
Fisher's exact test was performed.

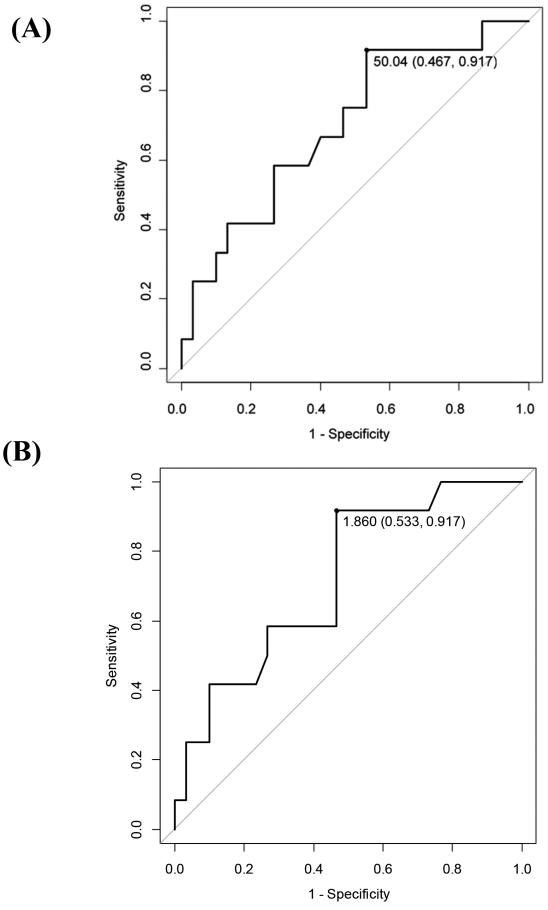

Fig. 1. ROC Curve Analysis of Dose per Body Surface Area and Dose per Lean Body Mass for Leukopenia

(A) Dose per body surface area, AUC value: 0.699 Cutoff value: 50.0 mg/m^2
(B) Dose per lean body mass, AUC value: 0.719, Cutoff value: 1.86 mg/kg.

BSA, or, LBM, may be related to blood concentration or AUC of osimertinib in clinical practice.

Researchers have suggested an association between AUC of osimertinib and AEs. The probability of developing rash or diarrhea increased with increasing AUC. However, the study of Japanese patients did not show an association between AUC and diarrhea or skin disorders. These reports are controversial.[17] In a previous assessment of the relationship between trough concentration of osimertinib and AEs, patients with neutropenia or leukopenia tended to have high trough concentrations.[30] This report suggested that patients with hematological toxicity of osimertinib tended to have high trough concentration.

Following these reports, our results suggest that Dose/BCPs, such as BW, BSA, or, LBM, may be related to blood concentration or AUC of osimertinib, and may also be associated with the incidence of AEs in clinical practice.

A tendency of increased incidence of diarrhea or rash has been reported in patients with a high AUC of osimertinib.[14] However, there are no reports on the effect of dose per BCP on the AEs of osimertinib. In contrast, a real-world clinical study on the treatment with osimertinib reported that the incidence of AEs in patients weighing < 45 kg was higher than that in patients weighing > 45 kg,[31] although prior clinical trials of osimertinib reported no association between BW and the incidence of AEs.[12,13] In the present study, there were no cases of severe liver or renal dysfunction, which indicated low drug clearance. Therefore, the results of this study, which showed a higher incidence of leukopenia in patients receiving a high Dose/BSA or Dose/LBM of osimertinib, suggest that high doses per BCP can be a risk factor for leukopenia.

A previous observational study reported that elderly patients treated with osimertinib had a higher incidence of hematological AEs.[32] Although other risk factors for hematological toxicity of EGFR-TKIs have not been reported, a previous treatment history of chemotherapy and ECOG-PS are risk factors for febrile neutropenia in patients treated with cytotoxic anticancer agents.[33] However, this study indicated that incidence of leukopenia was not associated with age, prior treatment, or PS. Female patients treated with osimertinib had a significantly higher ($p > 0.05$) incidence of leukopenia than male patients, indicating that sex is associated with a higher incidence of leukopenia and this could be attributed the lower BSA and LBM of females than that of males. Furthermore, the Dose/BSA or Dose/LBM in females was higher than that in males. Therefore, this study found no differences in the backgrounds of patients that could be risk factors for leukopenia, except for BCPs and sex.

When Dose/BCPs were compared according to the severity of hematological AEs, the Dose/BSA, or Dose/LBM were sig-

nificantly higher in group with high leukopenia severity than in group with low leukopenia severity. Similarly, Dose/LBM was significantly higher in the high severity neutropenia group than in the low severity neutropenia group, leading to bias toward high Doses/BCPs in groups with high leukopenia and neutropenia severity. Hence, high Doses/BCPs may be related to the severity of leukopenia and neutropenia. However, no significant difference was observed in Dose/BCPs between the groups with any severity of thrombocytopenia. In a previous study, although patients with neutropenia or leukopenia tended to have high trough concentrations, thrombocytopenia was not associated with trough concentration.[30] Our results were consistent with those of this previous study. The patients with high Dose/BCPs are expected to have higher AUC and trough concentration of osimertinib. Therefore, in this study, leukopenia and neutropenia may have been associated with high Dose/BCPs, but thrombocytopenia was not associated with Dose/BCPs. Moreover, the proportion of patients with a reduced dose of osimertinib during the treatment period was compared between patients with Dose/BSA or Dose/LBM above and below the cutoff value to assess the influence of these BCP on the treatment intensity of osimertinib. The proportion of patients who had reduced dose in the group above the cut-off value was approximately 40%, which was higher than the 20% in the group below the cut-off value, although there were no significant differences ($p < 0.05$). The results of the phase I and subsequent clinical trials of osimertinib have reported that the proportion of patients who needed to reduce the dose or discontinue treatment due to AEs was less than 10%.[12, 34–37] Therefore, these previous reports indicate that osimertinib is more tolerable than first- or second-generation EGFR-TKIs. However, the proportion of patients who received a reduced dose of osimertinib in this study was higher than that in previous reports, and patients who received a reduced dose had a higher dose per BCP. These results suggest that a high dose per BCP may not only cause a high incidence of AEs, such as leukopenia, but also a high severity of AEs in a dose-dependent manner. This may consequently affect treatment outcomes, because a high risk of dose reduction may lead to low treatment intensity.

In general, infections are more often complicated in cancer patients.[38] Moreover, patients with cancer have higher rates of severe sepsis and higher mortality rates than patients without cancer.[39,40] In lung cancer patients, infections can affect survival and lead to fatal outcomes.[41,42] In addition, a previous study has reported that EGFR-TKIs increase the risk of infection, and thus, their use requires caution.[6] Therefore, infection control is extremely important in patients treated with cytotoxic agents and EGFR-TKIs. The results of this study suggest that a higher dose of Osimertinib per BCP may increase the incidence and severity of hematological toxicity, which may also increase the risk of infection. From the results of this study, two out of the three patients who had unscheduled admissions or consultations were due to infectious events. Furthermore, these patients received a high dose per BCP, indicating that dose per BCP may be an indicator for risk of infection. Most oral molecular targeting agents, including osimertinib, are now approved for a fixed dose independent of BCPs. However, frail patients with low BSA or LBA were included in clinical trials in fewer cases. In clinical practices, frail patients can also receive these medications. Therefore, although the sample size is small, the results of this study may indicate the potential risk due to adverse events with the fixed dose. A previous study reported that the AUC of osimertinib is related to the incidence of AEs.[14] However, AUC measurements are complicated and expensive in routine clinical practices. Alternatively, dose per BCPs can be easily and noninvasively attained from routine clinical practices; therefore, it may be a useful surrogate tool for assessing the risk of AEs.

This study has a few limitations. First, this was a single-center study and the number of patients was limited. The detection power of this study may not have been sufficient based on the sample size. Second, because this was a retrospective and observational study, the causal relationship between osimertinib and AEs may not have been evaluated. In addition, the incidence of non-hematological AEs was underestimated because they may not have been documented in the medical records. The incidence of hematologic toxicities was higher in this study than in previous large clinical trials,[13,34] which may be due to a higher proportion of patients with history of cytotoxic-agents. Third, the Dose/LBM ratio may have been overestimated because the LBM was calculated using the formula reported by Green *et al*.[23] The LBM based on this formula tends to yield a low estimated value in patients with a high BMI. However, in this study, obese patients had a BMI ≥ 30 was one. Fourth, the incidence of unscheduled admissions or consultations due to infectious events might not have been sufficiently evaluated because consultations by the patients themselves with other institutions could not be followed. However, this study revealed that some patients with a high dose per BCP required unplanned hospitalization owing to infection. Therefore, further studies with larger sample sizes are needed.

In conclusion, this study suggests an association between Dose/BSA or Dose/LBM of osimertinib and the development or severity of leukopenia, especially sex related associations. The threshold Dose/BSA or Dose/LBM ratio, and the one at which leukopenia incidence increased were also suggested. As Dose/BSA or Dose/LBM can be obtained easily and noninvasively from routine clinical practice and do not require complicated blood concentration or AUC measurements, which involves costs for blood concentration measurement, they may serve as useful tools for assessing the risk of leukopenia induced by osimertinib.

Conflict of interest The authors declare no conflict of interest.

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