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Dose Reduction of *EGFR*-TKIs for *EGFR*-positive Non-small Cell Lung Cancer: A Retrospective Study

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Abstract

Background/Aim: The *epidermal growth factor receptor (EGFR)* gene was the first driver gene discovered in non-small cell lung cancer (NSCLC), and the introduction of tyrosine kinase inhibitors (TKIs) has improved patient prognosis, but often at reduced doses. Conventional dose determination methods for cytotoxic antitumor drugs were not applicable to *EGFR*-TKIs and were determined differently. The purpose of this study was to determine the characteristics of patients undergoing *EGFR*-TKI dose reduction, and the impact of such dose reduction on survival.

Patients and Methods: Patient characteristics, treatment, overall survival, and progression-free survival of patients with *EGFR* mutation-positive NSCLC treated with *EGFR*-TKIs between August 2008 and April 2024 at two hospitals were retrospectively evaluated.

Results: Of 165 patients, 67.3% received TKI dose reduction; patients who received TKI dose reduction had a smaller body surface area (p=0.029), which was more common in patients with better performance status (p=0.026). Side effects, especially diarrhea and rash, were the main reasons for this. Overall survival was significantly longer in the dose reduction group than in the recommended dose group (p=0.011). Multivariate analysis showed that TKI dose reduction was a favorable factor with a hazard ratio of 0.68 (p=0.046).

Conclusion: Reducing TKI dose is an option for patients with *EGFR*-mutated NSCLC, especially in elderly or underweight patients who develop adverse effects, and there is no reason to hesitate to reduce the TKI dose in these patients.

Keywords: Non-small cell lung cancer, *EGFR* mutation, *EGFR*-TKI, osimertinib, dose reduction.

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Introduction

Advances in molecular biology have led to the discovery of numerous driver genes, resulting in great advances in the treatment of advanced non-small cell lung cancer (NSCLC). The epidermal growth factor receptor (*EGFR*) gene was the first driver gene to be discovered, and the introduction of the therapeutic tyrosine kinase inhibitors (TKIs) into clinical practice has led to a significant improvement in patient prognosis (1-4). For conventional cytotoxic antitumor drugs, the antitumor effects are expected to be dose-dependent, thus the most common method has been to determine the maximum tolerated dose by gradually increasing the dose. However, because such a conventional method was unable to determine the maximum tolerated dose of *EGFR*-TKIs, the recommended dose for each TKI was determined using different methods (5-9). Importantly, the phase I trials that determined the recommended dose of *EGFR*-TKIs included many patients who were younger than those seen in actual clinical practice, had good general condition, and did not have any comorbidities (5-9). Furthermore, the number of patients involved in these determinations was not necessarily large (5-9).

It was initially reported that *EGFR* gene-positive lung cancer patients tended to be female, younger, had adenocarcinoma, and were non-smokers (10). Subsequent clinical studies later revealed that *EGFR* gene-positive patients included a fair proportion of elderly patients and patients with smaller body sizes (11). Looking back at the *EGFR*-TKI clinical trials with a focus on dosage, the proportion of patients who received a reduced dose below the recommended dose was not so low as to be negligible (4). More recently, surveys of actual clinical practice have shown that *EGFR*-TKI dose reduction is being carried out in a not-insignificant proportion of patients (12-15).

In light of this, the present study was conducted to clarify the current clinical situation regarding the following two issues: the characteristics of patients undergoing *EGFR*-TKI dose reduction; and whether reducing the dose of *EGFR*-TKI has a detrimental effect on patient survival. Because this was a retrospective study that did not involve a large number of patients, the study does not directly lead to definitive conclusions. However, we believe that the results obtained in this study might provide some suggestions for similar research in the future, and we therefore report them herein.

Patients and Methods

Patients. This was a retrospective study that examined the medical records of all *EGFR* mutation-positive NSCLC patients who received *EGFR*-TKI treatment between August 2008 and April 2024 at two hospitals: Mito Kyodo Hospital, Mito Medical Center, University of Tsukuba, and Ryugasaki Saiseikai Hospital. The pathological diagnosis of NSCLC was based on the World Health Organization classification (16). Before the start of anticancer treatment, all patients with *EGFR*-positive NSCLC were clinically staged according to the TNM classification (17) using head computed tomography (CT) or magnetic resonance imaging, bone scan, 2-deoxy-2-[18F]-fluoro-D-glucose positron emission tomography/CT, ultrasound, and/or abdominal CT. *EGFR* mutation positivity in each patient was confirmed using either the cobas® *EGFR* Mutation Test (Roche Diagnostics, Tokyo, Japan), Oncomine Dx Target Test (Life Technologies Japan, Tokyo, Japan), or Foundation One (Foundation Medicine, Boston, MA, USA). The following clinical information was extracted from medical records: patient age, sex, Eastern Cooperative Oncology Group performance status (PS), histology, and clinical stage at the time of NSCLC diagnosis. Overall survival (OS) of each patient was defined as the time from the start of *EGFR*-TKI treatment to death or last follow-up, and progression-free survival (PFS) was defined as the time from the start of TKI treatment to disease progression or death. In this study, *EGFR*-TKI patients were defined as those receiving any of five TKIs that could be dose-reduced: erlotinib, afatinib, osimertinib, and dacomitinib. Dose reduction of *EGFR*-TKI was defined as any reduction from the recommended dose at least once during the course of treatment. No stratification was performed in this study regarding the amount or duration of dose reduction.

Table I. *Patient characteristics.*

	Overall		Recommended dose		Dose reduction		*p*-Value
Number of patients	165		54		111		
Age [median (range)]	72	(40-92)	72.5	(42-92)	72	(40-92)	0.345
Sex [n (%)]							
Male	68	(41.2)	28	(51.9)	40	(36.0)	0.064
Female	97	(58.8)	26	(48.1)	71	(64.0)	
Height [median (range)]	158	(140-179)	159	(140-178)	155.5	(141-179)	0.131
Weight [median (range)]	51	(32-79)	56.5	(35-78.1)	50	(32-79)	0.016
BSA [median (range)]	1.5	(1.18-1.96)	1.57	(1.2-1.95)	1.47	(1.18-1.96)	0.029
PS [n (%)]							
0~1	138	(83.6)	40	(74.1)	98	(88.3)	0.026
2~3	27	(16.4)	14	(25.9)	13	(11.7)	
Histology [n (%)]							
AD	152	(92.1)	49	(90.7)	103	(92.8)	0.759
NonAD	13	(7.9)	5	(9.3)	8	(7.2)	
EGFR [n (%)]							
Exon 19 deletion	97	(58.8)	32	(59.3)	65	(58.6)	0.078
Exon 21 L858R mutation	54	(32.7)	21	(38.9)	33	(29.7)	
Minor mutation	14	(8.5)	1	(1.9)	13	(11.7)	
Stage [n (%)]							
Other	47	(28.5)	8	(14.8)	39	(35.1)	0.01
4	118	(71.5)	46	(85.2)	72	(64.9)	
TKI name [n (%)]							
Afatinib	46	(27.9)	10	(18.5)	36	(32.4)	0.003
Dacomitinib	4	(2.4)	1	(1.9)	3	(2.7)	
Erlotinib	36	(21.8)	6	(11.1)	30	(27.0)	
Osimertinib	79	(47.9)	37	(68.5)	42	(37.8)	

BSA: Body surface area; PS: performance status; AD: adenocarcinoma; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor.

Statistical analysis. In this study, the chi-squared test, Mann-Whitney *U*-test, and Fisher's exact test were used for statistical comparison between groups. Survival curves were created using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. In addition, the effect of dose reduction on OS and PFS was adjusted using the Cox proportional hazards model. The association between patient characteristics [age, body surface area (BSA), weight, PS, and stage] and survival was also evaluated using multivariate analysis. R version 4.4.1 (2024-06-14, R Foundation, Vienna, Austria) was used for all statistical analyses.

Ethics. This study complied with the "Ethical Guidelines for Clinical Research" of the Ministry of Health, Labor and Welfare of Japan. Comprehensive informed consent was obtained from each patient at the time of consultation. This study was approved by the Ethics Committee of the Mito Medical Center, University of Tsukuba (NO 20-57).

Results

Comparison between the recommended dose group and the dose reduction group. The total number of patients administered *EGFR*-TKI during the study period was 165. Of these, 54 patients never underwent TKI dose reduction during the course of treatment (recommended dose group). On the other hand, 111 of the 165 patients (67.3%) experienced TKI dose reduction (dose reduction group).

Characteristics of the patients in these two groups are shown in Table I. The median BSA was 1.57 (range=1.2-1.95) in the recommended dose group but was significantly lower in the dose reduction group (1.47, range=1.18-1.96; p=0.029). The proportion of patients with a PS of 0-1 was

Table II. *Characteristics of patients treated with osimertinib.*

	Overall		Recommended dose		Dose reduction		*p*-Value
Number of patients	79		37		42		
Age [median (range)]	74	(40-92)	74	(42-92)	74	(40-92)	0.64
Sex [n (%)]							
Male	32	(40.5)	18	(48.6)	14	(33.3)	0.178
Female	47	(59.5)	19	(51.4)	28	(66.7)	
Height [median (range)]	155	(140-179)	158	(140-178)	153	(142.4-179)	0.286
Weight [median (range)]	52	(32-79)	54	(36.6-77.7)	49.5	(32-79)	0.115
BSA [median (range)]	1.47	(1.18-1.96)	1.55	(1.27-1.9)	1.435	(1.18-1.96)	0.157
PS [n (%)]							
0~1	67	(84.8)	28	(75.7)	39	(92.9)	0.057
2~3	12	(15.2)	9	(24.3)	3	(7.1)	
Histology [n (%)]							
AD	76	(96.2)	35	(94.6)	41	(97.6)	0.597
NonAD	3	(3.8)	2	(5.4)	1	(2.4)	
EGFR [n (%)]							
Exon 19 deletion	45	(57.0)	21	(56.8)	24	(57.1)	0.259
Exon 21 L858R mutation	28	(35.4)	15	(40.5)	13	(31.0)	
Minor mutation	6	(7.6)	1	(2.7)	5	(11.9)	
Stage [n (%)]							
Other	24	(30.4)	8	(21.6)	16	(38.1)	0.144
4	55	(69.6)	29	(78.4)	26	(61.9)	

BSA: Body surface area; PS: performance status; AD: adenocarcinoma; EGFR: epidermal growth factor receptor.

74.1% in the recommended dose group and in the dose reduction group it was significantly higher at 88.3% (p=0.026). The proportion of patients with a PS of 2-3 was 25.9% in the recommended dose group and 11.7% in the dose reduction group. The proportion of stage IV patients was significantly higher in the recommended dose group (85.2% of patients) than in the dose reduction group (64.9% of patients, p=0.010). The characteristics of the two groups of patients treated with osimertinib are shown in Table II.

Reason for dose reduction of TKI. The most common reason for dose reduction of TKI was side effects, including diarrhea in 22 patients, skin rash in 21 patients, loss of appetite in nine patients, and paronychia in six patients. Other reasons for dose reduction included advanced age in 16 patients, decreased PS in nine patients, and other reasons in 28 patients.

Survival in the two groups. There was no significant difference observed in PFS between the dose reduction and recommended dose groups (median PFS=9 months in the dose reduction group *vs*. median PFS=7 months in the recommended dose group, p=0.0834). On the other hand, OS was significantly longer in the dose reduction group than in the recommended dose group (median OS=20 months in the dose reduction group *vs*. median OS=17 months in the recommended dose group, p=0.011; Figure 1). In the analysis of patients aged 75 years or older with BSA <1.5 m^2, there was no significant difference in PFS or OS between the dose reduction group and the recommended dose group (median PFS, 9 *vs*. 10 months, respectively, p=0.878; median OS, 23 *vs*. 20 months, respectively, p=0.105; Figure 2). PFS was significantly longer in the osimertinib dose reduction group than in the recommended dose group (median PFS, 15 *vs*. 11 months, respectively, p=0.0482). On the other hand, there was no significant difference in OS (median OS, 23 *vs*. 17 months, respectively, p=0.158; Figure 3). A multivariate logistic regression analysis was performed with factors that had values of p<0.05 from the univariate analysis as explanatory

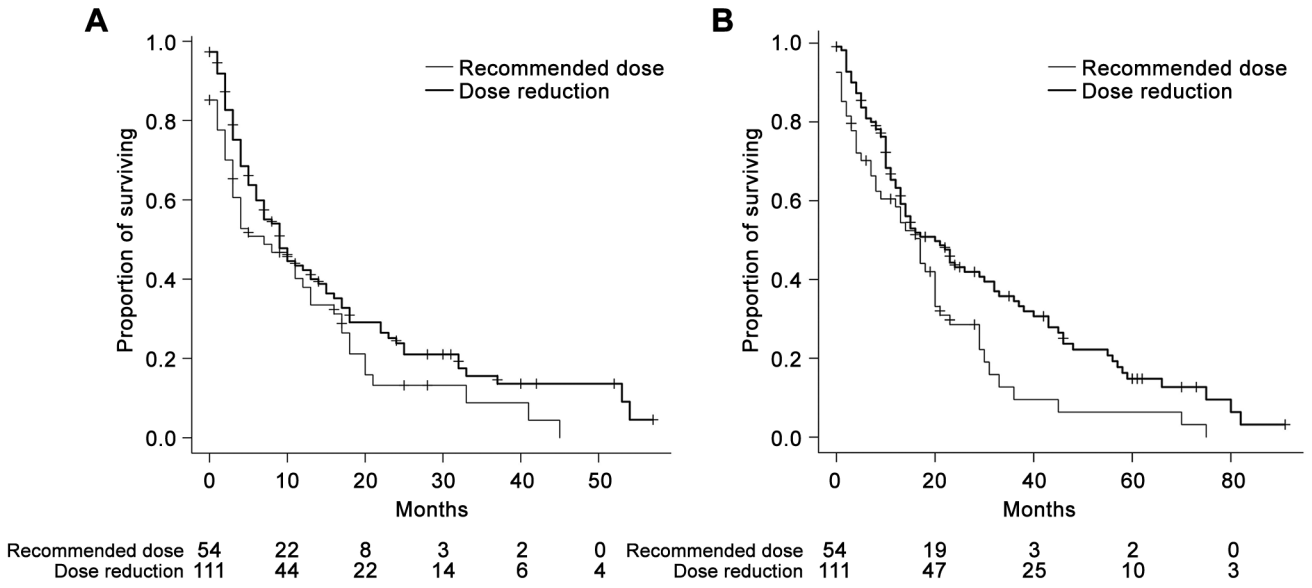

Figure 1. *Kaplan-Meier curves for progression-free survival (A) and overall survival (B) in the dose reduction group (bold) and the recommended dose group (normal).*

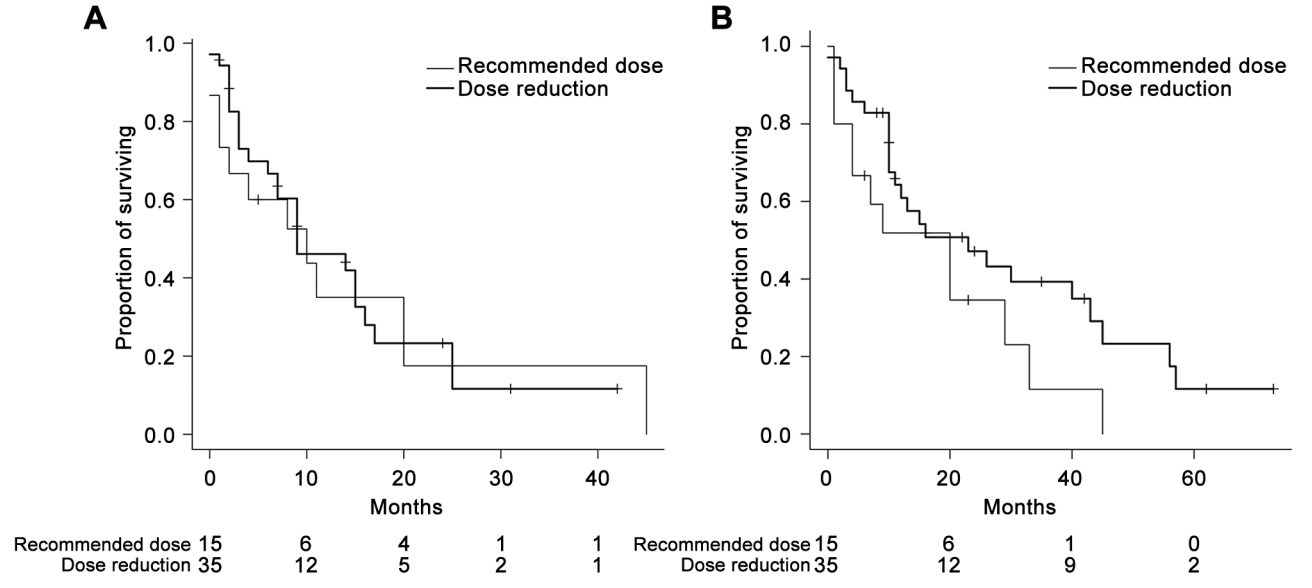

Figure 2. *Kaplan-Meier curves for progression-free survival (A) and overall survival (B) in patients aged 75 years or older with a body surface area <1.5 m^2, comparing the dose reduction group (bold) and the recommended dose group (normal).*

variables and 3-year survival as the objective variable. As a result, TKI dose reduction was extracted as a favorable factor, with an odds ratio of 3.570 (p=0.028; Table III). Cox proportional hazards regression analysis also showed that being Stage IV was a risk factor with a hazard ratio of 1.56 (p=0.037). Whether the TKI dose was reduced or not was a favorable factor with a hazard ratio of 0.68 (p=0.046; Table IV).

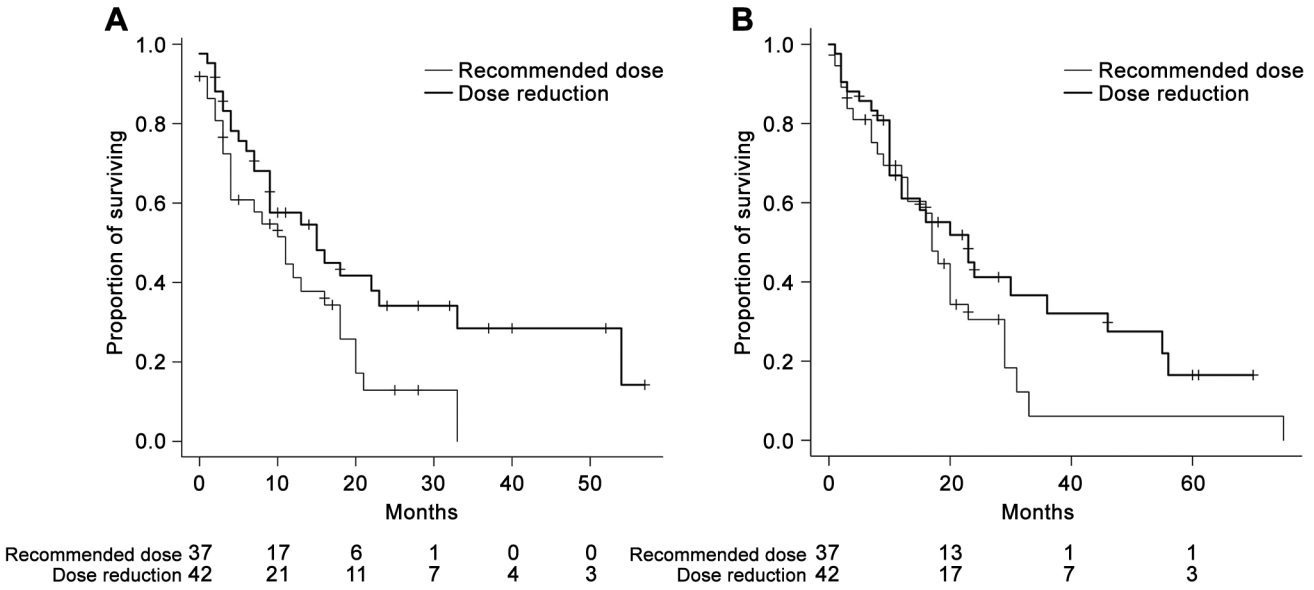

Figure 3. *Kaplan-Meier curves of progression-free survival (A) and overall survival (B) in patients treated with osimertinib in the dose reduction group (bold) and the recommended dose group (normal).*

Discussion

This study revealed the following four points: 1) In the five types of *EGFR*-TKIs currently available, dose reduction was performed in 67.3% of the 165 TKI-administered patients researched; 2) In particular, dose reduction was performed in 40% of patients with the third-generation TKI, osimertinib; 3) The most common reasons for reducing the dose of TKI were side effects, low body weight, and old age. However, poor PS was not the reason for dose reduction; and 4) When comparing PFS and OS between patients who underwent dose reduction and those who did not, reducing the dose of TKI did not result in a disadvantage to survival. Furthermore, the OS was significantly longer in patients who underwent dose reduction than in those who did not.

Dose-finding studies of many antitumor drugs have not necessarily investigated large numbers of patients (18). The same was true for the clinical trials used to set the recommended doses of *EGFR*-TKIs, which were determined based on the results of 50-60 patients (5, 8). Unlike conventional antitumor drugs, side effects of the most *EGFR*-TKIs are not dose-dependent (19). Therefore, except for the maximum tolerated dose determined for skin toxicity caused by erlotinib, the maximum tolerated dose has not been determined, and the recommended dose has been determined taking into account efficacy and side effects (7-9). *EGFR*-positive patients are evaluated to be predominantly younger women, and the median age of the *EGFR*-positive patients in most clinical trials was in the 50s (5-7). There have been attempts to improve the response rate of gefitinib, a first-generation TKI, by combining it with other antitumor drugs and taking into

Table III. *Logistic regression analysis in all the 165 TKI-treated patients with overall survival ≥3 years or <3 years.*

Factor	*p*-Value	Odds ratio	95%CI
Body surface area >1.5 or not	0.941	0.97	0.43-2.18
PS: 0-1 or not	0.589	1.44	0.38-5.42
Stage: IV or not	0.153	0.54	0.24-1.25
Dose reduction of TKI or not	0.028	3.57	1.15-11.10

CI: Confidence interval; PS: performance status; TKI: tyrosine kinase inhibitor.

Table IV. *Cox proportional hazards regression analysis in all the 165 TKI-treated patients with overall survival.*

Factor	*p*-Value	Hazard ratio	95%CI
Body surface area >1.5 or not	0.963	0.99	0.70-1.41
PS: 0-1 or not	0.156	0.71	0.44-1.14
Stage: IV or not	0.037	1.56	1.03-2.36
Dose reduction of TKI or not	0.046	0.68	0.46-1.00

CI: Confidence interval; PS: performance status; TKI: tyrosine kinase inhibitor.

account gene polymorphisms (20, 21). However, since gefitinib could only be administered in one dosage form, 250 mg tablet, it was not possible to reduce the dose during treatment. For second- and third-generation TKIs, a dose finding study have been attempted taking into account the site of metastasis (22). Subsequent studies in actual clinical practice have reported that *EGFR*-positive patients included elderly and underweight patients (11). Patients with these characteristics have rarely been included in clinical trials, and reducing the dose of TKIs in these patients seemed not to be anticipated. However, a closer look at the clinical trials of *EGFR*-TKIs reveal that dose reduction of TKIs occurs in 20%-30% of patients (4), and furthermore, in clinical practice, dose reduction occurs in 30%-40% of patients. In addition, this latter study found that appropriate dose reduction was not associated with poorer outcomes. Considering these results, there seems little need to hesitate to reduce the dose of TKIs when side effects occur, out of concern that it may shorten survival. Adherence to the recommended doses of TKIs might not be necessary, especially in elderly and underweight patients. Actually, since it is currently impossible to measure TKI blood concentrations in clinical practice, the appearance of a facial rash might also be used as a reference in clinical practice, as it is considered evidence that the TKI blood concentration is within the appropriate range. Also, in analyzing the difference in survival rates between all TKI treatments and osimertinib specifically, two factors stand out: osimertinib has been shown to provide a longer PFS than second-generation TKIs, and immune checkpoint inhibitor treatment has become available since osimertinib was introduced. Based on this, our considerations were as follows: Unlike second-generation TKIs, dose reduction of osimertinib due to side effects did not impair the duration of response, and if the dose reduction was appropriate, it might contribute to extending PFS. On the other hand, regarding OS, many *EGFR*-positive patients respond to immune checkpoint inhibitors after TKIs (23), and we speculated that this effect outweighed that of reducing the dose of TKIs.

Although this study was able to provide new findings as described above, it had several limitations: The first was that this was a retrospective study. It is desirable to investigate as many patients as possible, but even in this regard, caution is required. The next limitation to note is that the comparison of survival times was not performed using propensity matching to match patient backgrounds. It was determined that if this comparison had been performed, the study would have been able to come closer to more convincing evidence. However, we were able to show that there was no worsening of prognosis in the group that included a greater number of patients with poorer clinical conditions, such as older age or low body weight, and we evaluated that our initial objective was achieved. Although phase II trials have been conducted using TKI doses lower than the recommended levels for elderly patients (24), it is unlikely that phase I trials to establish the recommended dose of *EGFR*-TKIs, which have already been in clinical use for some time, will be conducted in the future. In that sense, it is important to conduct real-world clinical investigations including as many patients as possible. We believe that our results provide considerable insight into the future clinical application of *EGFR*-TKIs.

Conclusion

When side effects occur in patients with *EGFR* gene-mutated NSCLC in clinical practice, particularly in elderly or underweight patients, reducing the dose of TKI is a suitable option, with no cause for hesitation.

Funding

No funding was received.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

AM, YM, KM, and HS designed this study. AM, HM, YM, SO, GO, SS, KM, TK, and HS collected data. AM, YM, KM, and HS analyzed the data. AM and HS prepared the manuscript. TS, YY, HS, and NH supervised this study. All Authors have approved the final version of the manuscript for submission.

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