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ORIGINAL RESEARCH

Clinical Impact of Osimertinib Dose Reduction in the First-Line Setting on EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Retrospective Monocentric Study

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Purpose: Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. In the FLAURA trial, osimertinib demonstrated longer progression-free survival (PFS) and overall survival (OS) compared to gefitinib or erlotinib. In the trial, dose reductions occurred in 5% of patients, primarily due to QT prolongation. However, various adverse events can also lead to dose reductions in clinical practice, and the efficacy of osimertinib after dose reduction remains unclear. The present study was conducted to evaluate the clinical impact of osimertinib dose reduction.

Patients and Methods: This monocentric retrospective study was conducted at Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital. Ninety patients with EGFR mutation-positive non-squamous non-small-cell lung cancer receiving osimertinib as their first-line therapy between August 2018 and December 2021 were included.

Results: Of the cohort, 23 patients had an osimertinib dose reduction during their clinical course. The dose reduction group tended to have a lower median body weight and a higher proportion of elderly patients aged 80 years or older. The median PFS was 21.2 months (95% confidence interval [CI]: 8.22–34.18) in the dose reduction group and 18.6 (95% CI: 13.04–24.23) months in the regular-dose group. The median OS was 29.6 months (95% CI: 17.44–41.70) in the osimertinib dose-reduction group and 37.7 (95% CI: 27.10–48.23) months in the regular-dose group. Dose reduction did not significantly impact the time-dependent hazard ratio (HR) for PFS (HR 1.22 [95% CI: 0.55–1.89]) or OS (HR: 1.24 [95% CI: 0.64–2.42]). The adverse events leading to dose reduction were mainly rash, anorexia, and paronychia, and no fatal adverse events were observed after dose reduction.

Conclusion: The present study suggests that dose reduction may not compromise the efficacy of osimertinib. However, the clinical impact of dose reduction is not fully understood. Physicians should carefully weigh its benefits and risks before implementation.

Keywords: osimertinib, lung cancer, EGFR, dose reduction

Introduction

Mutations of the epidermal growth factor receptor (EGFR) are common oncogenic drivers in non-small cell lung cancer (NSCLC).[1] The frequency of EGFR mutations is as high as 40% in the East Asian population, while it is about 20% among Caucasians.[2–4] In the FLAURA study, osimertinib demonstrated significantly longer progression-free survival (PFS) and overall survival (OS) than first-generation EGFR tyrosine kinase inhibitors (TKIs); gefitinib and erlotinib, while maintaining a similar safety profile.[5,6] Osimertinib also has better efficacy in central nervous system metastases, which are common in EGFR-mutant NSCLC. Osimertinib is currently used as the first-line therapy for EGFR-mutant NSCLC.[5–8]

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Almost half of patients diagnosed with lung cancer are elderly, and patients aged 80 years or older account for 14% of this population.[9,10] Osimertinib demonstrated clinical efficacy in elderly patients and patients with a poor performance status (PS).[11–13] Dose reduction is occasionally required in this population whenever adverse events (AEs) occur. In the FLAURA study, only 5% of patients had dose reduction mainly due to QT prolongation. On the other hand, various adverse events such as skin rash, fatigue, and anorexia led to dose reduction in real-world data.[6,14,15] A Phase 1 study of osimertinib found that the response rate at dosages of 20, 40, and 80 mg/day was similar.[16] However, the long-term efficacy and safety of the drug after its dosage is reduced remain unclear. The present, monocentric, retrospective study was conducted to identify the clinical course, efficacy, and safety of osimertinib dose-reduction.

Methods

Patients and Study Design

Data on patients harboring the common EGFR mutation (Ex19del or L858R) who had received osimertinib as their first-line therapy at Tokyo Metropolitan Cancer and Infectious Diseases Center at Komagome Hospital between August 2018 and December 2021 were collected retrospectively. The patients were divided into a regular-dose group and a dose-reduction group comprising those who had experienced at least one dose reduction in their clinical course (Figure 1). The attending physician determined the dose reduction method, defining cases where osimertinib was given at ≤40 mg daily or 80 mg every other day as dose reduction.

EGFR mutation status was evaluated using the Cobas® EGFR mutation test v2 (Roche, Basel, Switzerland) or next-generation sequencing. This study was approved by the ethics committee of Komagome Hospital (No. 3321) and was conducted in accordance with the 2013 Declaration of Helsinki. Written informed consent was waived because the present study was retrospective. The patient data in the present study was anonymized and maintained with confidentiality.

Assessment and Statistical Analysis

The treatment response and progression of the tumors were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Adverse events (AE) were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Categorical variables in each group were analyzed using Fisher's exact test and Student's *t*-test. Progression-free survival (PFS) and overall survival (OS) were analyzed in each group. PFS was defined as the period from the date of treatment initiation to the date of disease progression or the last follow-up. OS was defined as the period from the date of treatment initiation to the date of death from any cause or the last follow-up. Both OS and PFS were estimated using the Kaplan–Meier method, and differences between the patient groups were compared using the Log rank test. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated using Cox

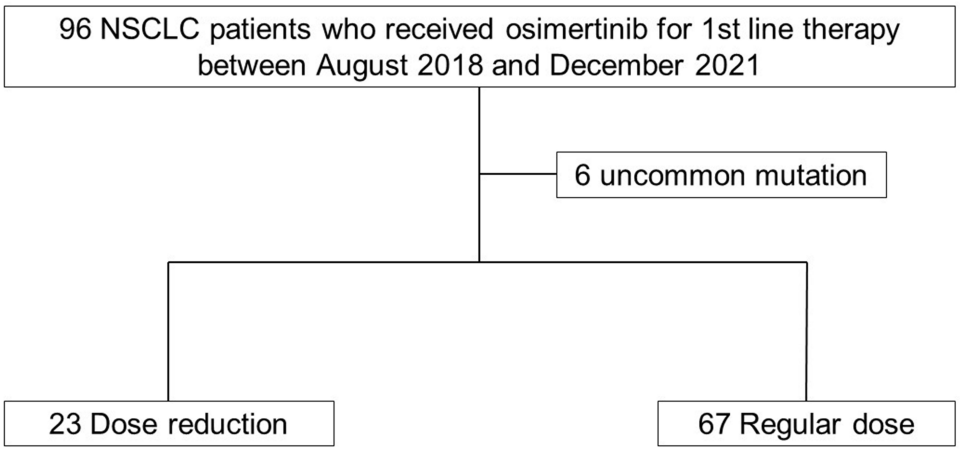

Figure 1 Flowchart of patients receiving osimertinib as their first-line therapy.

proportional hazards regression with time-dependent covariates. The data were analyzed with IBM SPSS Statistics program, version 28.0.1.0 (IBM, Armonk, NY).

Results

Patient Characteristics

In total, 90 patients received osimertinib as their first-line therapy for advanced or recurrent NSCLC at the study center between August 2018 and December 2021. Sixty-seven patients received a regular osimertinib dose (80 mg/day) and had no dose reduction, while 23 patients experienced at least one dose reduction. Table 1 shows the patient characteristics of each group. More elderly patients, ie, those aged 80 years or more, were placed in the dose-reduction group (47.8% vs 20.3%; P = 0.02). The median body weight before treatment was lower in the dose-reduction group (44.9 kg in the dose-reduction group vs 51.5 kg in the regular-dose group; P = 0.03). Dose reduction group had a higher proportion of recurrence cases (43.5% vs 19.4%; P = 0.03). The proportion of female sex, history of smoking, poor PS, histological findings, and baseline CNS metastases were similar between the groups.

Treatment Efficacy

The median follow-up time was 30.9 months (range: 2.3–57.3 months). The median PFS was 21.2 months (95% CI: 8.22–34.18) in the patients with a dose reduction and 18.6 months (95% CI: 13.04–24.23) months in the patients receiving the regular dose (Figure 2A). The median OS was 29.6 months (95% CI: 17.44–41.70) in the dose-reduction group and 37.7 (95% CI: 27.10–48.23) months in the regular-dose group (Figure 2B). Dose reduction did not

Table 1 Patient Characteristics Between the Reduced Dose Group and Regular Dose Group

Characteristics	Subtypes	Dose Reduction (n=23)	Regular Dose (n=67)	P-value
Age, median (range) years		72 (51–87)	71 (35–86)	0.09
	Age ≥ 80 years, n (%)	11 (47.8)	14 (20.9)	0.02
Sex, n (%)	Male	6 (26.1)	25 (37.3)	0.45
	Female	17 (73.9)	42 (62.7)	-
Body weight (kg, range)	Recorded	44.9 (36.6–57.4)	51.5 (29.8–99.9)	0.03
	Not recorded	8	11	-
Smoking history, n (%)	Ever	10 (43.5)	33 (49.3)	0.63
	Never	13 (56.5)	34 (50.7)	-
PS, n (%)	0–1	19 (82.6)	50 (74.6)	0.57
	≥2	4 (17.4)	17 (25.4)	-
Stage, n (%)	IV	13 (56.5)	54 (80.6)	0.03
	Recurrence	10 (43.5)	13 (19.4)	-
Histology, n (%)	Adenocarcinoma	23 (100)	64 (95.5)	0.57
	Other	0	3 (4.5)	-
EGFR mutation, n (%)	Exon 19 del	9 (39.1)	31 (46.3)	0.63
	Exon 21 L858R	14 (60.9)	36 (53.7)	-
CNS metastasis, n (%)	Yes	7 (30.4)	26 (38.8)	0.62
	No	16 (69.6)	41 61.2)	-

Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor, PS; performance status.

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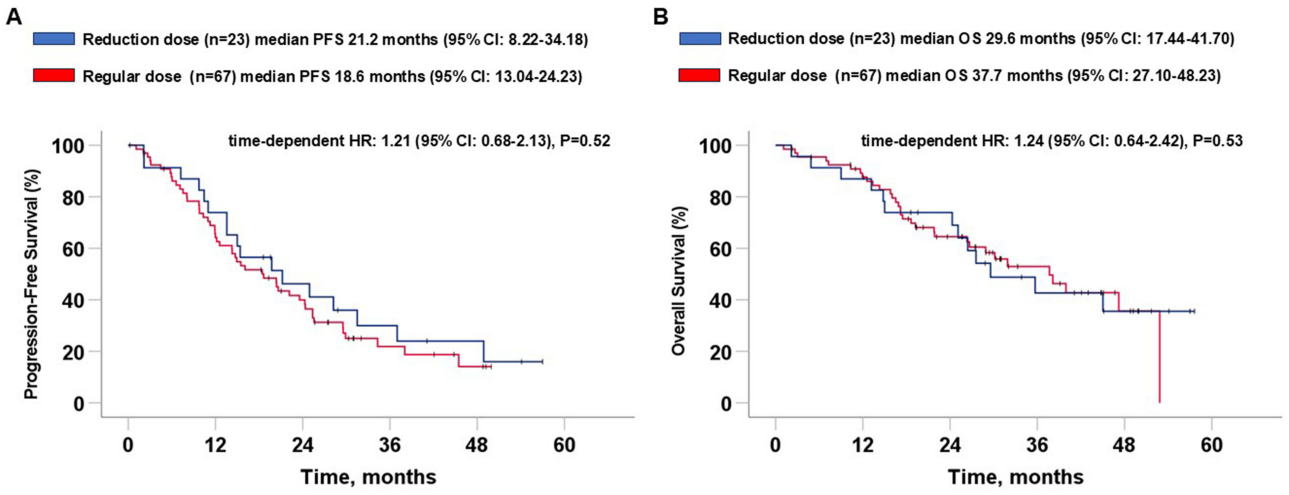

Figure 2 Progression-free survival (PFS) and overall survival (OS) in the dose-reduction and regular-dose groups. (**A**) PFS and (**B**) OS of each group.

significantly impact the time-dependent hazard ratio for PFS (HR 1.21 [95% CI: 0.68–2.13], P = 0.52) or OS (HR: 1.24 [95% CI: 0.64–2.42], P = 0.53). CNS disease progression during osimertinib therapy was 8.7% (n = 2) in the dose-reduction group and 11.9% (n = 8) in the regular-dose group (P = 1.00). Table 2 shows the response rate of the groups. The objective response rate did not differ significantly between the dose-reduction and regular-dose groups (65.6% vs 77.6%; P = 0.27).

The swimmer plot shows the duration of osimertinib therapy and adverse events in the dose-reduction group (Figure 3). The median time to the first dose reduction was 89 days (range: 14–632 days). The initial dose reduction was to 40 mg/day in 21 out of 23 patients, while the remaining 2 patients were reduced to 80 mg every other day. Two patients had dose reduction for reasons other than adverse events. At the data cutoff date, six patients were receiving ongoing treatment. Six patients had received subsequent treatment, although no patient aged ≥80 years was among these. Twelve patients had systemic progression, and 2 patients had CNS progression. Five patients experienced an adverse event associated with osimertinib 40 mg/day or 80 mg every other day and required further dose reduction.

Multivariate analysis for PFS and OS (Table 3) showed that poor performance status (PS ≥ 2) and age ≥80 years were independent predictive factors for both poor PFS and OS. PS ≥ 2 was significantly associated with worse PFS (HR: 2.41, 95% CI: 1.32–4.41, P = 0.004) and OS (HR: 4.54, 95% CI: 2.26–9.11, P < 0.01). Similarly, age ≥80 years was an independent predictor of worse PFS (HR: 1.87, 95% CI: 1.01–3.47, P = 0.048) and OS (HR: 3.03, 95% CI: 1.45–6.36, P < 0.01). Dose reduction did not emerge as an independent prognostic factor for either PFS (HR: 1.07, 95% CI: 0.57–2.03, P = 0.83) or OS (HR: 1.02, 95% CI: 0.47–2.22, P = 0.95).

Table 2 Objective Response Rate of Each Group

	Dose Reduction n, %	Regular Dose n, %	P-value
CR	0	0	-
PR	16 (63.6)	52 (77.6)	-
SD	6 (27.3)	11 (16.4)	-
PD	0	1 (1.5)	-
NE	1 (9.1)	3 (4.5)	-
ORR	65.2	77.6	0.27

Abbreviations: CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

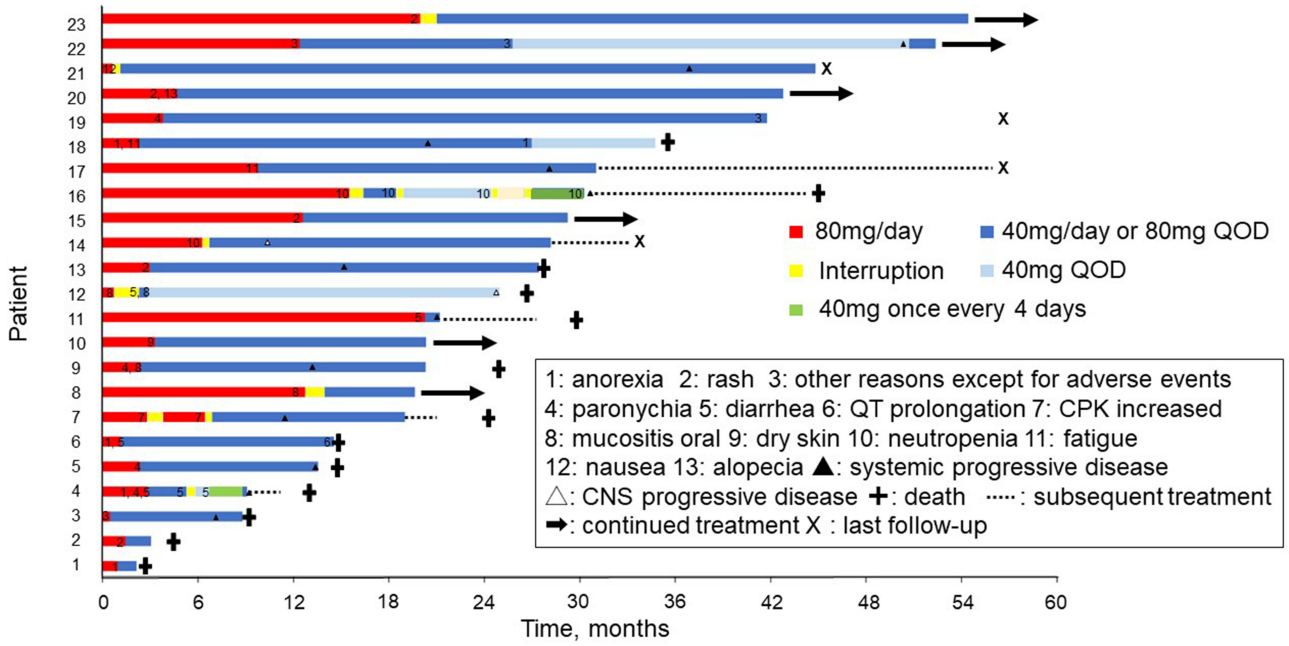

Figure 3 Clinical course of dose reduction group.

Adverse Events Leading to Osimertinib Dose Reduction

Table 4 shows that grade 2 and 3 adverse events (AEs) led to a reduction in the osimertinib dosage. The AEs leading most often to a dose reduction were rash (21.7%), anorexia (17.4%), and paronychia (13.0%). No cases of drug-induced interstitial lung disease were observed in the dose-reduction group. Table 5 shows other adverse events after the dose reduction, and the swimmer plots (Figure 3) show the timing of the onset of each AE. The AEs occurring after dose reduction were mainly cutaneous, subcutaneous, and gastrointestinal disorders. One patient had grade 3 QT interval prolongation, and another patient had grade 3 neutropenia.

Table 3 Univariate and Multivariate Analyses for PFS and OS

Variable	Univariate of PFS			Multivariate of PFS			Univariate of OS			Multivariate of OS		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Male	1.66	1.00–2.74	0.049	1.30	0.74–2.28	0.83	1.26	0.68–2.37	0.47	0.92	0.46–1.87	0.83
Age ≥80 years	2.04	1.20–3.47	<0.01	1.87	1.01–3.47	0.048	2.74	1.46–5.15	<0.01	3.03	1.45–6.36	<0.01
Stage IV	1.47	0.83–2.62	0.20	-	-	-	1.26	0.64–2.52	0.49	-	-	-
PS ≥2	2.76	1.57–4.87	<0.01	2.41	1.32–4.41	0.004	4.43	2.27–8.66	<0.01	4.54	2.26–9.11	<0.01
EGFR del 19	0.66	0.40–1.08	0.10	-	-	-	0.77	0.43–1.40	0.40	-	-	-
Dose Reduction	1.21	0.68–2.13	0.52	1.07	0.57–2.03	0.83	1.24	0.64–2.42	0.53	1.02	0.47–2.22	0.95
CNS metastases	1.77	1.09–2.97	0.02	1.42	0.84–2.39	0.21	1.51	0.82–2.77	0.18	1.27	0.67–2.36	0.44

Abbreviations: CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression free survival; PS, performance status.

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Table 4 Adverse Events Leading to the Initial Osimertinib Dose Reduction

Adverse Events, n, (%)	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Anorexia	0	2 (8.7)	2 (8.7)	0	4 (17.4)
Diarrhea	0	2 (8.7)	1 (4.3)	0	3 (13.0)
Nausea	0	0	1 (4.3)	0	1 (4.3)
Rash	0	3 (13.0)	2 (8.7)	0	5 (21.7)
Paronychia	0	2 (8.7)	1 (4.3)	0	3 (13.0)
Mucositis oral	0	1 (4.3)	2 (8.7)	0	3 (13.0)
Dry skin	0	1 (4.3)	0	0	1 (4.3)
Alopecia	0	1 (4.3)	0	0	1 (4.3)
Fatigue	0	2 (8.7)	0	0	2 (8.7)
Neutropenia	0	0	2 (8.7)	0	2 (8.7)
CPK increased	0	0	1 (4.3)	0	1 (4.3)

Abbreviation: CPK, Creatine phosphokinase.

Table 5 Adverse Events After Osimertinib Dose Reduction

Adverse Events, n, (%)	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Anorexia	0	1 (4.3)	0	0	1 (4.3)
Diarrhea	1 (4.3)	0	1 (4.3)	0	2 (8.7)
Mucositis oral	1 (4.3)	0	0	0	1 (4.3)
Neutropenia	0	0	1 (4.3)	0	1 (4.3)
QT prolongation	0	0	1 (4.3)	0	1 (4.3)

Discussion

Few studies have evaluated the treatment efficacy and safety of osimertinib after dose reduction. To the best of our knowledge, the present study is the first to evaluate the impact of osimertinib dose reduction using the time-dependent hazard ratio. Adverse events, including cutaneous and gastrointestinal disorders, were the main reasons for dose reduction. Patients who underwent dose reduction tended to have a lower median body weight and a higher proportion of individuals aged 80 years or older compared to those who received the regular dose. The results demonstrated no impact of dose reduction on either time-dependent hazard ratio of PFS or OS. No cases of drug-induced interstitial lung disease or fatal adverse events were observed following a dose reduction. The present study suggests that long-term efficacy and safety may be maintained with a reduced dose of osimertinib.

Of the entire cohort, 23 patients (25.6%) received a reduced osimertinib dosage. The incidence of osimertinib dose reduction was higher than the figure of 5% reported in the FLAURA trial.[6] However, dose reduction was required in 20–40% of patients according to real-world data, and the frequency in the present study was equivalent to those reported previously.[12–15]

Adverse events reportedly occurred more frequently in patients with a low body weight and the elderly.[15,17] The patient background in the osimertinib dose reduction group tended to have a lower median body weight and a higher proportion of patients aged ≥ 80 years.

PFS and OS was 18.9 months and 38.6 months, respectively, in the FLAURA study, and 19.1 months and 39.3 months, respectively, in the Japanese subset.[5,6,18,19] The duration of PFS and OS in the regular-dose group were consistent with these findings. The efficacy of osimertinib therapy in the regular-dose group did not differ significantly from the findings of previous reports; therefore, the regular-dose group was considered appropriate for comparison with the dose-reduction group. In the dose-reduction group, more patients aged ≥80 years were included. The efficacy of osimertinib in patients aged ≥75 years was reportedly associated with a median PFS and OS ranging from 15.9 to 22.1 months and 30.0 months, respectively.[12,13,15,20] PFS and OS of the dose-reduction group were consistent with these real-world studies. The present study showed that the time-dependent hazard ratio of PFS and OS in the dose-reduction group did not differ significantly from that of the regular-dose group. This study suggests that long-term efficacy may be maintained regardless of osimertinib dose reduction. Dose-reduction in the second-line setting exhibited comparable ORR and PFS to the regular dose.[21] These findings support the results of our study.

On the other hand, early osimertinib dose reduction is reportedly a risk factor for the deterioration of brain metastases and an insufficient inhibitory concentration against cancer cells in the central nerve system (CNS).[14] In the present study, two cases of CNS progression were observed during osimertinib administration in the dose-reduction group. No differences were observed in the incidence of progression of brain metastases during treatment. However, the diagnosis of brain metastases based on imaging studies and follow-up intervals were decided at the attending physician's discretion. Furthermore, in the early stages of osimertinib therapy, the patients had a higher tumor burden than at a later stage of treatment. High tumor burden, defined as multiple metastases and rapidly progressive disease, may be a risk factor for poor EGFR-TKI efficacy;[22–24] thus, physicians should carefully consider the timing of dose reduction.

The main reasons for dose reduction in the present study were cutaneous, subcutaneous, and gastrointestinal disorders. After dose reduction, no cases of drug-induced interstitial lung disease, one of the reasons for treatment discontinuation, were observed.[15,25] Adverse events leading to death were also not observed. Adverse events were managed by reducing the drug dosage; some patients received less than 50% of the standard dose for long-term therapy. Dose reduction may help to control adverse events, potentially allowing osimertinib therapy to be extended. Therefore, it may be a reasonable option for patients who are unable to tolerate adverse events.

The present study had several limitations. First, it was monocentric and retrospective and had a relatively small sample size. The patients were divided into two groups, thereby limiting the interpretability of the data on the efficacy and safety of osimertinib dose reduction. Second, the decision and method of dose reduction varied among attending physicians, which could have potentially influenced the results. However, few studies have examined this topic; thus, the findings of the present study are worth reporting. Prospective research into optimizing the osimertinib dosage for elderly patients with a low body weight, which is currently underway, is likely to shed light on these and other questions.[26]

Conclusion

The present study suggests that dose reduction may not compromise the efficacy of osimertinib. Adverse events, particularly cutaneous and gastrointestinal disorders, were the main reasons for dose reduction. Adverse events leading to death or drug-induced interstitial lung disease were not observed after dose reduction Patients who underwent dose reduction tended to have a lower median body weight and a higher proportion of individuals aged 80 years or older. Given its efficacy and safety, dose reduction may help prolong osimertinib therapy in these populations. However, its clinical impact remains unclear. Therefore, physicians should carefully weigh the benefits and risks before implementing dose reduction.

Disclosure

Makiko Yomota received honoraria from AstraZeneca, Takeda, MSD, Chugai Pharmaceutical, Ono Pharmaceutical, and Bristol-Myers Squibb. Shoko Kawai received honoraria from AstraZeneca, and Chugai Pharmaceutical. Masahiro Seike had grants or contracts from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Nippon Kayaku, and Kyowa Hakko Kirin, honoraria from AstraZeneca, MSD, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Pfizer, Novartis, Takeda Pharmaceutical, Kyowa Hakko Kirin, Nippon Kayaku, Daiichi-Sankyo Company, Merck Biopharma, and Amgen Inc. Yukio Hosomi received honoraria from

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