Efficacy and Safety Data of Osimertinib in Elderly Patients with NSCLC Who Harbor the *EGFR* T790M Mutation After Failure of Initial EGFR-TKI Treatment

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Abstract. *Background/Aim:* The aim of this study was to evaluate the safety and efficacy of osimertinib for elderly patients, since the data remain limited. *Patients and Methods:* A total of 77 patients with advanced non-small cell lung cancer (NSCLC) harboring the epidermal growth factor receptor (EGFR) T790M mutation and treated with osimertinib were reviewed. Efficacy and safety indicators, such as EGFR-tyrosine kinase inhibitor (TKI)-related adverse events (AEs) and osimertinib-associated hematotoxicity, were evaluated in elderly patients (elderly group, EG; age, ≥ 75 years) by comparing them with younger patients (non-EG; aged < 75 years). The frequency of AEs associated with osimertinib was compared with the initial EGFR-TKI treatment before osimertinib administration in the same patient cohort. *Results:* Of the total 77 patients, 18 (23%) were assigned to the EG, whereas 59 (77%) were assigned to the non-EG. There were no significant differences in overall response rate and progression-free survival between the two groups. Regarding the safety of osimertinib, the EG had significantly more grade ≥ 2 paronychia than the non-EG (16.6% vs. 1.6%, $p=0.04$). Additionally, the maximum grade of EGFR-TKI-related AEs associated with osimertinib in the EG was significantly lower than that of the initial EGFR-TKI treatment ($p=0.03$). *Conclusion:* Osimertinib is a safe and effective treatment option for elderly patients with advanced NSCLC who harbor the EGFR mutation.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) for advanced *EGFR*-mutant non-small cell lung cancer (NSCLC) have an overall response rate (ORR) of approximately 60-70% (1-3). However, almost all patients ultimately developed disease progression after EGFR-TKIs administration. The *EGFR* T790M point-mutation in exon 20 (T790M), which is an EGFR secondary mutation, has been reported in approximately 50% of tumors at the time of treatment failure with EGFR-TKIs (4, 5). The third-generation EGFR-TKI “osimertinib,” which is an irreversible mutant-selective EGFR-TKI, is potent and effective against *EGFR* mutations, including the T790M mutation (6, 7).

The randomized phase III AURA3 trial assessed the efficacy and safety of osimertinib as a second-line treatment in patients with *EGFR* T790M-positive advanced NSCLC, which progressed following first-line EGFR-TKI therapy. That study demonstrated that compared with the standard platinum-doublet chemotherapy, osimertinib led to significant and meaningful improvements in both progression-free survival (PFS) and ORR (8). Moreover, the pivotal randomized phase III FLAURA trial, which compared osimertinib with standard EGFR-TKIs in patients with previously untreated *EGFR* mutation-positive advanced NSCLC, indicated that patients treated with osimertinib had a significantly longer PFS than those treated with the standard first-generation EGFR-TKIs gefitinib and erlotinib (9).

Two-thirds of all new lung cancer cases are diagnosed in patients aged > 65 years, and this rate is anticipated to increase owing to the growth of the aging population (10, 11). Treatment strategies in elderly patients with lung cancer have received increasing attention. In general, more adverse events (AEs) of first- and second-generation EGFR-TKIs reportedly occur in elderly patients (age, ≥ 75 years) than in younger patients (12, 13). The FLAURA trial included

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Table I. Patient characteristics (N=77).

	All	Non-Elderly group (non-EG, <75 years) N=59	Elderly group (EG, ≥75 years) N=18	p-Value
Age, median (Range)	66 (36-86)	62 (36-74)	80 (75-86)	
Gender, Female/Male	53/24	39/20	14/4	0.40
Performance status, 0/1/2	44/30/3	33/23/3	11/7/0	0.71
EGFR mutation status				
19 del/L858R/others	44/32/1	35/23/1	9/9/0	0.71
Histology				
Adenocarcinoma/others	75/2	58/1	17/1	0.42
Smoking History				
Yes/No	17/60	14/45	3/15	0.75
Stage at diagnosis				
Postoperative Recurrence/IIIA/IIIB/IV	25/1/4/47	16/1/2/40	9/0/2/7	0.08
Initial EGFR-TKI				
Gefitinib/Erlotinib/Afatinib	52/19/6	38/16/5	14/3/1	0.50

EGFR-TKI: Epidermal growth factor receptor tyrosine kinase inhibitor.

patients of all ages and demonstrated that the safety profile of osimertinib was similar to that of gefitinib and erlotinib (9). Additionally, the frequency of serious AEs was lower in patients treated with osimertinib than in those treated with first-generation EGFR-TKIs. This indicates that osimertinib treatment could be more feasible for elderly patients. However, these data are not sufficient to completely assess the safety and efficacy of osimertinib in elderly patients.

Here, the efficacy and safety of osimertinib was compared between elderly and younger patients. The frequency of AEs associated with osimertinib treatment was also compared with that associated with initial EGFR-TKI treatment before osimertinib treatment in the same patients.

Patients and Methods

Patients. Between July 2014 and June 2017, we reviewed the records of 77 patients with advanced NSCLC at our institute who harbored the T790M mutation and were treated with osimertinib after treatment failure with first- and second-generation EGFR-TKIs (gefitinib, erlotinib, or afatinib). T790M status was confirmed using plasma samples (Roche cobas® EGFR mutation test v2) or tissue samples as previously reported (14, 15). We also evaluated patient characteristics, initial EGFR-TKI- and osimertinib-associated AEs, and clinical outcomes of osimertinib treatment. To evaluate the efficacy and safety of osimertinib in the elderly, the patients were divided into two groups: an elderly group (age, ≥75 years; EG) and a non-elderly group (age, <75 years; non-EG). The objective tumor response to osimertinib was radiographically assessed using the response evaluation criteria in solid tumors (RECIST; version 1.1) (16). The ORR was calculated as the total percentage of patients with a complete response or a partial response. AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). In this study, rash, diarrhea, paronychia, stomatitis, and elevation of aspartate aminotransferase (AST)/alanine

aminotransferase (ALT) were considered EGFR-TKI-related AEs. This retrospective study was approved by the Institutional Review Board of the Aichi Cancer Center, Japan.

Statistical analysis. All statistical analyses were performed using the Graph Pad Prism version 7 for Windows (Graphpad Software Inc., San Diego, CA, USA) or JMP version 9 for Windows statistical software packages (SAS Institute, Cary, NC, USA). Differences in categorical outcomes were evaluated using the χ^2 or the Fisher's exact tests, as appropriate. Changes in the maximum grade of AEs between the initial EGFR-TKI treatment and osimertinib treatment were analyzed using paired *t*-test. PFS was measured from the start of osimertinib administration until the date of RECIST-progression disease. Overall survival (OS) was measured from the start of osimertinib administration to death and was censored at the date of the last visit for patients whose death could not be confirmed. Survival probabilities were estimated using the Kaplan-Meier method wherein differences in the variables were calculated using the log-rank test. All *p*-values were two-sided, and *p*<0.05 was considered statistically significant, unless otherwise stated.

Results

Patient characteristics. Patient characteristics are listed in Table I. The median age of all the patients was 66 years (range=36-86 years). Of the total 77 patients, 59 (77%) were aged <75 years, whereas 18 (23%) were aged ≥75 years. No differences were observed between the two groups regarding patient characteristics (including PS, EGFR mutation status, histology stage at diagnosis, and smoking history). As EGFR-TKIs, gefitinib, erlotinib, and afatinib were administered to 38, 16, and 5 non-EG patients and 14, 3, and 1 EG patients, respectively.

Efficacy and safety of osimertinib. The ORR was 50.8% in the non-EG patients and 61.1% in the EG patients (*p*=0.59; Table

Figure 1. Progression-free survival (A) and overall survival (B) in elderly patients (EG; N=18) and non-EG patients (N=59).

II). The median PFS was 10.5 months (95%CI=7.8-15.8) in the non-EG patients and 17.7 months in the EG patients (95%CI=8.4-not reached [NR]) ($p=0.11$; Figure 1A). Although PFS associated with the EG was longer, there were no significant differences between the EG and non-EG. Additionally, there were no significant differences in OS (EG=38.6 months; 95%CI=14.3-52.8 vs. non-EG, NR; 95%CI=15.5-NR) ($p=0.20$; Figure 1B). The frequencies of EGFR-TKI-related AEs and the hematotoxicity associated with osimertinib in the EG and non-EG patients are presented in Figure 2. In both groups, thrombocytopenia was the most common AE associated with osimertinib. There were no significant differences in the frequency of all-grades of EGFR-TKI-related AEs and the hematotoxicity between the EG and non-EG, although the frequency of hematotoxicity was higher in the EG. However, the EG had significantly more instances of grade ≥ 2 paronychia (16.6% vs. 1.6%, $p=0.04$). In contrast, there were no significant differences in the frequencies of dose reduction or treatment discontinuation between the EG and non-EG (Table III). Among the 7 EG patients who underwent dose reduction from 80 mg to 40 mg, 1 had elevated creatinine levels (grade 2), 1 had fatigue (grade 2), 2 had paronychia (grade 2), 1 had stomatitis (grade 2) and 2 had appetite loss (grade 1). One patient in each group discontinued treatment owing to interstitial lung disease.

Inter-comparison of EGFR-TKI-related AEs between initial EGFR-TKI treatment and osimertinib in EG. To evaluate the differences in AEs between the initial EGFR-TKI and osimertinib treatments, the frequency of EGFR-TKI-specific AEs and hematotoxicity associated with osimertinib were compared to those of initial EGFR-TKI treatments before

Table II. Overall Response to osimertinib (N=77).

Response	Non-EG (N=59)	EG (N=18)	<i>p</i> -Value
Partial response	30	11	0.59
Stable disease	14	4	
Progressive disease	8	2	
Not evaluable	7	1	
Overall response rate	50.8%	61.1%	

osimertinib therapy in the same patients. The maximum grade of EGFR-TKI-related AEs associated with osimertinib was significantly lower than that associated with initial EGFR-TKI treatment ($p=0.03$, Figure 3A), although two patients had higher-grade EGFR-TKI-related AEs associated with osimertinib than their AEs after initial EGFR-TKI treatment. In contrast, the maximum grade of hematotoxicity in patients treated with osimertinib was significantly higher than of patients treated with initial EGFR-TKI treatment ($p<0.01$, Figure 3B); however, not all hematotoxicities led to dose modification.

Discussion

Our study indicated no significant differences in the frequency of dose reduction or treatment discontinuation between EG and non-EG, although the EG demonstrated a significantly higher frequency of grade ≥ 2 severity paronychia than the non-EG. Additionally, the maximum grade of the EGFR-TKI-related AEs associated with

Figure 2. Frequency of all-grade and Grade ≥ 2 EGFR-TKI-related AEs (A and C) and hematotoxicity (B and D) of osimertinib in the elderly patients (EG; N=18) and non-EG patients (N=59).

osimertinib in EG was significantly lower than that associated with initial EGFR-TKI treatment ($p=0.03$). However, the maximum grade of hematotoxicity in patients treated with osimertinib (not leading to dose modification) was significantly higher than in those treated with initial EGFR-TKI treatment ($p<0.01$). Therefore, osimertinib may be a more feasible treatment option in elderly patients with EGFR-positive NSCLC.

Elderly patients generally have more comorbidities and a more compromised organ function than younger patients. Some studies have evaluated the efficacy and feasibility of first-line EGFR-TKIs, such as gefitinib and erlotinib, in elderly patients with NSCLC who harbor an *EGFR* mutation (12, 17, 18). These studies reported that EGFR-TKIs were highly effective with acceptable toxicity incidence in elderly

patients with advanced NSCLC who harbored *EGFR* mutations. Conversely, Rossi *et al.* reported that elderly patients (age, >70 years) experienced more toxicities and were more likely to have grade ≥ 3 rash, fatigue, and diarrhea (19). A greater number of elderly than younger patients require discontinuation or reduction of their EGFR-TKI dosage. Recently, Tanaka *et al.* conducted a phase I study of afatinib in patients aged ≥ 75 years with advanced NSCLC who harbored *EGFR* mutations; they reported that the recommended dose for elderly patients was 30 mg/day, which is 10 mg less than the starting dose of afatinib in younger patients (20).

In contrast, the FLAURA trial demonstrated that the safety profile of osimertinib was similar to that of gefitinib and erlotinib (9). Additionally, the frequency of serious

Table III. *Details of dose reduction and discontinuation.*

	Non-EG (N=59)	EG (N=18)	<i>p</i> -Value
Dose reduction	N=10	N=7	0.18
	Bradycardia (grade 2; N=1)	Appetite loss (grade 1; N=2)	
	Paronychia (grade 2; N=1)	Stomatitis (grade 2; N=1)	
	Stomatitis (grade 2; N=2)	Paronychia (grade 2; N=2)	
	AST/ALT elevation (grade 2/3; N=1/1)	Cre elevation (grade 2; N=1)	
	Fatigue (grade 2; N=1)	Fatigue (grade 2; N=1)	
	DVT (grade 2; N=1)		
	Diarrhea (grade 2/3; N=1/1)		
Treatment Discontinuation	N=1	N=1	0.43
	ILD (grade 1; N=1)	ILD (grade 3; N=1)	

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; ILD: interstitial lung disease; DVT: deep vein thrombosis; Cre: creatinine.

AEs was lower in patients treated with osimertinib than in those treated with first-generation EGFR-TKIs. This indicates that osimertinib treatment could be more feasible for elderly patients. In fact, our study showed no significant differences in EGFR-TKI-related AEs and dose reduction or treatment discontinuation of osimertinib between the EG and non-EG. However, the frequency of hematotoxicities associated with osimertinib treatment, which did not lead to dose reduction or treatment discontinuation, was significantly greater than the frequency associated with initial EGFR-TKI treatment. An inter-comparison analysis of EG patients revealed that the maximum grade of EGFR-TKI-related AEs associated with

osimertinib was significantly lower than that associated with initial EGFR-TKI treatment. Furthermore, regarding the efficacy of osimertinib, no significant differences were observed between the EG and non-EG.

This study has several limitations. First, it was a retrospective study with a small sample size. Second, AEs associated with osimertinib can include bias when compared to prior EGFR-TKIs because patients treated with osimertinib might be accustomed to the management of EGFR-TKI-induced AEs following prior EGFR-TKI treatment. Further investigation regarding the efficacy and safety of osimertinib in elderly patients might be necessary.

In conclusion, this study presented the safety and efficacy

data regarding the use of osimertinib in elderly patients in comparison to younger patients and initial TKIs. Osimertinib is a feasible treatment for elderly patients with advanced *EGFR*-mutant NSCLC, in the context of both the efficacy and safety of *EGFR*-TKIs.

Conflicts of Interest

Dr. Hida received research grants from Ono Pharmaceutical, Novartis Pharma, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, Bristol-Meyers Squibb, Clovis Oncology, Eisai, Takeda Bio, Dainippon Sumitomo Pharma, Abbvie, MSD, Merck Serono, Kyowa Hakko Kirin, Daiichi Sankyo, Servier, Kissei, Ignyta, and Astellas. He also received personal fees from Ono Pharmaceutical, Novartis Pharma, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, MSD, Kissei, Clovis Oncology, and Bristol-Meyers Squibb. The other Authors have no conflicts of interest to declare.

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