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Treatment of Patients With Non-small-cell Lung Cancer With Uncommon *EGFR* Mutations in Clinical Practice

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Abstract. *Background/Aim: To describe real clinical outcomes in patients with non-small cell lung cancer who have uncommon epidermal growth factor receptor (EGFR) mutations. Materials and Methods: We performed a retrospective chart review from 15 medical institutes that cover a population of three million people from April 2008 to March 2019. Results: There were 102 patients with uncommon EGFR mutation. Progression-free survival (PFS) tended to be longer in patients receiving afatinib compared with first-generation EGFR tyrosine kinase inhibitors. PFS in patients treated with afatinib or osimertinib was significantly longer than in patients treated with gefitinib or erlotinib (p=0.030). Multivariate analysis also revealed the contribution of afatinib or osimertinib to increased survival. In patients with exon 20 insertions, chemotherapy was efficacious. Conclusion: In treating patients with uncommon EGFR mutations, our results indicate longer-term survival might be achieved with second-generation or later TKIs and cytotoxic chemotherapeutic drugs.*

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Key Words: Clinical practice, non-small cell lung cancer, uncommon mutation, EGFR, epidermal growth factor receptor.

The treatment of patients with advanced non-small-cell lung cancer (NSCLC) harboring mutant epidermal growth factor receptor (EGFR) has been revolutionized by the development of EGFR tyrosine kinase inhibitors (TKIs) (1-3). The most common types of *EGFR* mutation are exon 19 deletions and

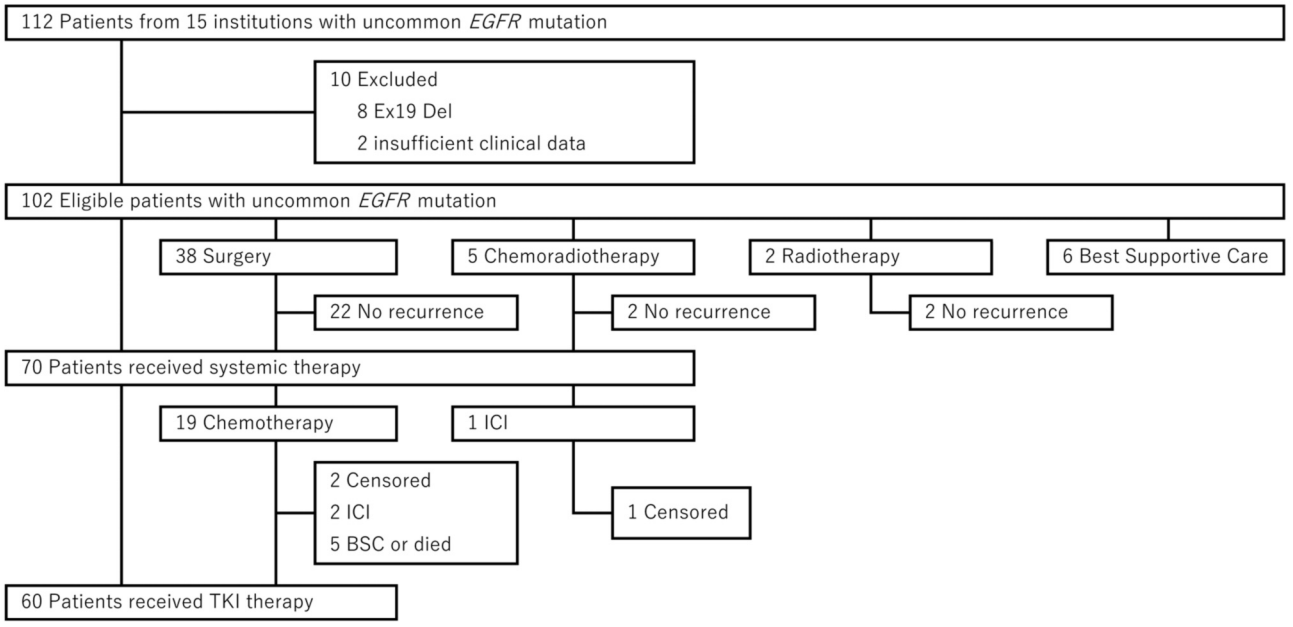

Figure 1. *Study flow chart. EGFR: Epidermal growth factor receptor; Ex19 Del: exon 19 deletion; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor.*

exon 21 L858R, with all other *EGFR* mutations considered rare and collectively referred to as uncommon types (1-3). Currently, limited prospective information is available regarding the usefulness of EGFR TKIs against uncommon *EGFR* mutations. This is due to most randomized trials including only patients with the two most common mutations, Del19 and L858R (1-3). The lack of clinical information associated with uncommon mutations is becoming increasingly problematic as the improvement of mutation screening techniques identifies more uncommon mutations. There are several uncommon mutations, and some patients have compound mutations, that is, tumors harboring more than one mutation. Uncommon mutations are more prevalent than previously believed, potentially occurring in up to a quarter of patients with *EGFR*-mutant NSCLC (2). To our knowledge, there have been no randomized phase III clinical trials that only included patients with uncommon *EGFR* mutations. There have been two *post-hoc* analyses of clinical trials; a *post-hoc* sub-analysis of the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials (4), and a *post-hoc* analysis of the NEJ-002 trial (5). One phase II clinical trial that only enrolled patients with uncommon *EGFR* mutations has reported (6). Several real-world studies have been reported and some of them comprise 100 or more patients but they include patients treated with first-generation TKIs alone (7-10). Studies treated with first-generation and later TKIs comprise only 50-60 or fewer patients (11-16).

In this study, we collected clinical data on patients with lung cancer treated at multiple medical institutions over an 11-year period, covering a prefecture with a population of 3 million. Given the rarity of NSCLC with uncommon *EGFR* mutation types, this equated to over 100 patients including those treated with first-generation and later TKIs.

Patients and Methods

Patients. Fifteen institutions located in the Ibaraki prefecture (area, 6,097 km^2; population, ~3 million) participated in the present retrospective study. We included patients who were diagnosed as having uncommon *EGFR*-mutated NSCLC between April 2008 and March 2019. All patients demonstrated histological or cytological evidence of NSCLC. Histopathological diagnoses were defined according to the World Health Organization (WHO) classification system (17), and patients staged according to the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system (18). Tumor responses were classified as complete (CR), partial (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE), according to the response evaluation criteria in solid tumors (RECIST, version 1.1) (19). Patient characteristics, efficacy, safety, progression-free survival (PFS) and overall survival (OS) were evaluated using patient data extracted from each institution's database. Patient survival time was calculated from the initiation date of first-line therapeutic drug to the date of death or latest follow-up contact. Serum albumin and C-reactive protein data prior to the initiation of first-line therapeutic drug were collected. The present observational study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan. This study was approved by the Institutional Review Board of the Mito Kyodo General Hospital (no. 18-16) or independent Ethics Committees associated with each study institute.

Measurement of EGFR fusion gene events. *EGFR* mutation analysis was performed by the method normally used by each institution, such as the Cobas® EGFR Mutation Test and allele-specific real-time polymerase chain reaction (PCR), using biopsy specimens and cytology specimens.

Definition of uncommon mutations. Mutation types other than exon 19 deletions and exon 21 L858R are rare and are collectively referred to as uncommon types (1-3). As patients with several exon 19 deletion subtypes other than exon 19 delE746-A750 were reported to be equally sensitive to first-line EGFR-TKIs as patients with exon 19 delE746-A750 (20, 21), we did not include any patients with exon 19 deletion subtypes.

Statistical analysis. Fisher's exact and chi-square tests were used for the comparison of patient characteristics. The survival rate was analyzed by the Kaplan-Meier method and comparisons were performed using the log-rank test. The effects of clinicopathological factors on survival were analyzed using the Cox proportional hazards model. Values of $p<0.05$ were considered to be statistically significant.

Results

Clinicopathological features. During the study period, there were 112 patients with uncommon *EGFR* mutation (Figure 1). Among them, eight patients had exon 19 deletion subtypes other than exon 19 delE746-A750 and were excluded, and two patients were excluded due to insufficient clinical data. This resulted in 102 patients being included and evaluated in this study. Clinicopathological features of the 102 patients are shown in Table I. The median age was 70 years (range=38-92 years) and there were 52 (51.0%) males. Ninety-eight (96.1%) patients had adenocarcinoma. Patients with a smoking history accounted for 52.0%. Table I shows the types of uncommon *EGFR* mutations, comprising single and compound mutations. The most prevalent mutations were exon 18 G719X in 47 (46.1%) patients and exon 21 L861Q in 20 (19.6%) patients. Compound mutations were found in 21 (20.6%) patients.

Table I. *Characteristics of 102 patients with uncommon epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer.*

Characteristic		Value
Age, years	Median (range)	70 (38-92)
Gender, n	Male	52
	Female	50
Histopathological type, n	AD	98
	SQ	3
	LCNEC	1
Performance status, n	0-1	87
	2-4	14
	Unknown	1
Smoking habit, n	Never	45
	Past or current	53
	Unknown	4
Tumor size, n	<30 mm	45
	≥30 mm	55
	Unknown	2
Pleural fluid, n	Absent	84
	Present	18
Stage at the time of initial diagnosis, n	IA-IIB	36
	IIIA-C	17
	IVA-B	49
Surgical resection, n	Present	38
	Absent	64
Albumin, n	<3.5 mg/dl	6
	≥3.5 mg/dl	93
	Unknown	3
C-Reactive protein, n	<1.0 mg/dl	85
	≥1.0 mg/dl	14
	Unknown	3
Uncommon EGFR mutation, n	Single mutation	81
	G719X	47
	Exon 19 insertion	2
	Exon 20 insertion	10
	S768I	2
	L861	20
	Compound	21
	With T790M	7
	Without T790M	14

AD: Adenocarcinoma; SQ: squamous cell lung cancer; LCNEC: large cell neuroendocrine carcinoma.

Patient survival in relation to EGFR mutation type. Seventy out of the 102 patients received systemic therapy for advanced or recurrent disease. Twenty-six patients did not experience recurrence after surgery, chemoradiotherapy or radiotherapy during the follow-up period. Six patients received palliative care alone. Figure 2 shows swimmer plots of 70 patients who received systemic therapy for advanced or recurrent disease. Among these 70 patients, 60 received TKI therapy (30 gefitinib, six erlotinib, 18 afatinib and six osimertinib). The median PFS for the 60 patients treated with TKI therapy was 7.1 months. The median PFS of those with uncommon mutations was 9.1 months for those with exon 18 G719X, and 5.1 months for those with exon 21 L861Q. In five patients with exon 20 insertions, TKIs were administered to only two, resulting in PFS of 0.9 and 5.1 months. The first TKI therapy among these 60 patients achieved PFS of 7.1 months in patients with a single mutation and 11.2 months in those with compound mutation but this difference did not reach statistical significance ($p=0.136$).

The median OS for the 60 patients who received TKI therapy was 30.5 months. Figure 3A shows the survival according to uncommon mutation type. The median OS was 25.3 months for patients with exon 18 G719X, and 9.1 months for those with exon 21 L861Q. For the five patients with exon 20 insertions, the median OS was 39.5 months. The median OS in patients with a single mutation was 21.3 months and

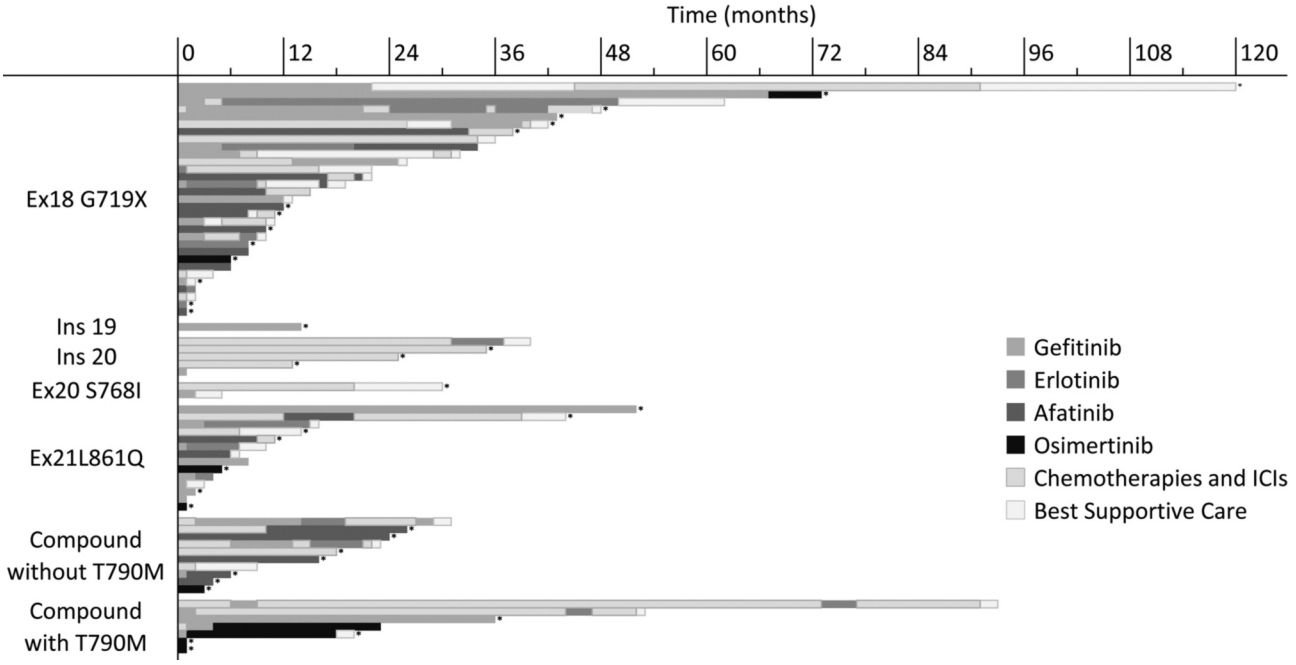

Figure 2. *Swimmer plots of 70 patients who received systemic therapy. Individual swimmer plots display mutation types and duration of treatment methods. Ex: Exon; Ins: insertion; ICI: immune checkpoint inhibitor.*

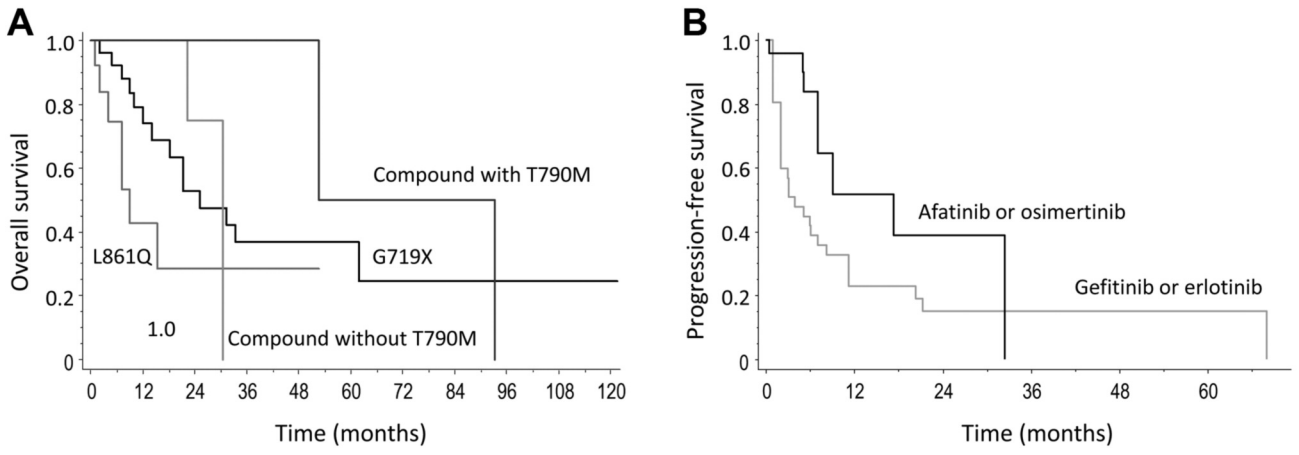

Figure 3. *Kaplan-Meier curves of overall survival according to uncommon epidermal growth factor receptor mutation type (A) and progression-free survival curves of patients according to tyrosine kinase inhibitor (B).*

52.8 months in those with compound mutation but this difference did not reach statistical significance (p=0.087). The median OS for patients with compound mutations accompanying a T790M mutation was 52.8 months, and 30.5 months without an accompanying T790M mutation (p=0.058).

Patient survival in relation to TKIs. In 60 patients who received any TKI treatment for the first time, the median PFS for those treated with gefitinib, erlotinib, afatinib or osimertinib was 3.1, 5.1, 17.3 months, and 'not reached', respectively. Table II shows the characteristics of 36 patients who received first-line TKI treatment with gefitinib or erlotinib and 24 patients who had first-line TKI treatment with afatinib or osimertinib. There was no significant difference in clinicopathological features between the two groups but there was a significant difference in their PFS

Table II. *Comparison of the characteristics of 60 patients with uncommon epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer who received EGFR tyrosine kinase inhibitor.*

Factor	Subgroup	Patients treated with		*p*-Value
		Gefitinib or erlotinib, n	Afatinib or osimertinib, n	
Age	<75 years	28	18	>0.999
	≥75 years	8	6	
Gender	Male	12	13	0.120
	Female	24	11	
Performance status	0-1	30	20	>0.999
	2-4	6	4	
Smoking habit	Never	20	11	0.598
	Past or current	16	13	
Tumor size	<30 mm	16	10	>0.999
	≥30 mm	20	14	
Pleural fluid	Absent	30	16	0.212
	Present	6	8	
Surgical resection	Absent	26	21	0.209
	Present	10	3	
Albumin	<3.5 mg/dl	33	23	0.643
	≥3.5 mg/dl	3	1	
C-Reactive protein	<1.0 mg/dl	31	4	>0.999
	≥1.0 mg/dl	5	20	
Uncommon EGFR mutation	Exon 18-21	30	21	0.499
	Insertion 20	2	0	
	T790M compound	4	3	

Table III. *Uni- and multivariate analyses of prognostic factors in 60 patients with uncommon epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer who received EGFR tyrosine kinase inhibitor (TKI).*

	Univariate analysis (log-rank test)	Multivariate analysis (Cox's proportional hazards model)		
Factor	*p*-Value	HR	95% CI	*p*-Value
Age: <75 years	0.542			
Gender: Female	0.212			
Performance status: 0-1	0.366	0.67	0.27-1.66	0.384
Smoking habit: Absent	0.256			
Tumor size: <30 mm	0.919			
Pleural fluid: Absent	0.665			
Surgical resection: Present	0.247	0.55	0.22-1.34	0.203
Albumin: ≥3.5 mg/dl	**0.042**	0.55	0.19-1.64	0.285
C-Reactive protein: <1.0 mg/dl	0.125			
EGFR mutation: Exon 18-21	0.095			
EGFR-TKI: Afatinib or osimertinib	**0.030**	0.44	0.20-0.94	**0.033**

CI: Confidence interval; HR: hazard ratio. Statistically significant *p*-values are shown in bold.

(4.0 *vs*. 17.3 months, p=0.030; Figure 3B). Table III shows the results of uni- and multivariate analyses of prognostic factors for these patients; only 'first-line TKI treatment with afatinib or osimertinib' was a significant favorable factor.

Discussion

In many previous reports of real clinical practice, uncommon *EGFR* mutations accounted for a small percentage of all patients with NSCLC with *EGFR* mutations (13, 22-24). The most frequently detected single mutations among uncommon *EGFR* mutations were G719X, L861Q, S768I, exon 20 insertions, but their frequency varied between reports (13, 22-24). Compound mutations were found in anywhere from a few percent to half of all patients with uncommon *EGFR* mutations (7, 13, 14, 22). In our cohort of 102 patients with NSCLC, G719X and L861Q were the two the most frequent single uncommon mutations, and 20.6% of patients had compound mutations. The higher proportion of females and non-smokers in patients with common *EGFR* mutation in NSCLC has been widely accepted, and previous reports have indicated uncommon mutations were more frequent in males and smokers (7, 9). In our cohort, men accounted for half and smokers were more than half of all patients.

In patients with common *EGFR*-mutated NSCLC, long-term survival can be achieved with TKI treatment. In those with uncommon *EGFR* mutations, however, it is still to be determined which, if any, TKIs will provide long-term therapeutic benefit. A general consensus is that first-generation TKIs would not contribute to long-term survival in patients with uncommon *EGFR* mutations. In practice, patients with uncommon *EGFR* mutations treated with first-generation TKIs had a median PFS and OS of 2.2-7.7 months and 11.9-19.0 months, respectively (8, 9, 25). Regarding patients with specific uncommon *EGFR* mutations treated with first-generation TKIs, the median PFS in those with G719X and L861Q mutations was 1.8-11.6 months and 3.0-8.9 months, respectively, while the median OS was 19.8-25.2 months and 22.0 months, respectively (2, 7-10, 26). Longer survival has been reported when patients were treated with later-generation TKIs, which led to median PFS and OS of 6.4-10.2 months and 20.2-23.6 months, respectively (11, 13, 14). In our study including patients treated with first-generation and later TKIs, median PFS and OS in patients first treated with TKIs was 7.1 months and 30.5 months, respectively. The median PFS in patients with G719X and L861Q was 9.1 months and 5.1months, respectively, while the median OS was 25.3 months and 9.1 months, respectively. Our results are comparable with previous reports.

Analysis of the LUX-Lung trials indicated afatinib, a second-generation EGFR-TKI, had clinical activity against

uncommon point mutations or duplications in exons 18-21, including G719X, S768I and L861Q, but had limited activity against exon 20 insertions or *de novo* T790M mutations (4). Median PFS and OS of patients harboring uncommon *EGFR* mutation in exons 18-21 in the LUX-Lung trails was 10.7 months and 19.4 months, respectively. Following this analysis, there was increased interest in treating patients with uncommon *EGFR* mutations with afatinib. In a pooled analysis assessing the activity of afatinib in 315 EGFR TKI-naïve patients with uncommon *EGFR* mutations treated in randomized clinical trials, afatinib demonstrated activity against G719X, L861Q and S768I mutations (27). Some real-world observations are consistent with these clinical trial data, and support its superiority to first-generation TKIs in patients with uncommon *EGFR* mutations (12, 15, 16, 28). For example, in a real-world study of 51 patients with uncommon mutations not including patients with exon 20 insertions, afatinib conferred significantly longer PFS than first-generation EGFR TKIs (median of 11.0 *versus* 3.6 months) (12). In our patients with uncommon mutation, PFS was longer in those receiving afatinib than those treated with gefitinib or erlotinib (median of 17.3 *versus* 4.0 months) but this did not reach significance owing to the small sample size.

Osimertinib, a third-generation EGFR-TKI, is expected to have clinical activity against uncommon *EGFR* mutations. In a recent phase II study of osimertinib as a first-line therapy for patients with NSCLC with uncommon *EGFR* mutations, the objective response rate was 50%, median PFS was 8.2 months, and median OS was not reached (6). They demonstrated favorable activity with manageable toxicity in patients with NSCLC harboring uncommon *EGFR* mutations (6). The outcomes of osimertinib therapy in patients with uncommon *EGFR* mutations in real clinical practice are yet to be reported. In this study, due to the small number of patients receiving this TKI, it was not possible to determine the outcome of osimertinib therapy alone, and no comparison could be made between osimertinib and afatinib treatments. However, by comparing the survival outcomes of patients treated with gefitinib or erlotinib with those treated with afatinib or osimertinib, we were able to show in a multivariate analysis that treatment with afatinib or osimertinib was a favorable prognostic factor.

There are many reports that PFS and OS for patients with a compound mutation are longer than for those with single uncommon mutation (7, 9, 10, 11, 14, 29). Our results are consistent with these previous reports, but the difference did not reach statistical significance. Interestingly, our study showed OS of patients with compound mutation accompanying T790M mutation tended to be longer than those without T790M mutation. Previous studies reported both first- and second-generation TKIs did not have activity for patients with a compound mutation accompanying T790M mutation. In the sub-analysis of three LUX-Lung studies, the median OS for patients harboring *de novo* T790M mutation alone or in combination with another mutation was 14.9 months, which is shorter than the median OS of patients harboring exon18-21 mutation (4). In real-world observations, median OS for patients with compound mutations with an accompanying a T790M mutation was 2.4-16.9 months, and was 21.6-27.7 months in those without (7, 8). Administration of osimertinib, the third-generation TKI, would contribute to this favorable survival.

Exon 20 insertion mutations are known to have little therapeutic effect on EGFR-TKI and usefulness of chemotherapeutic drugs. In the sub-analysis of three LUX-Lung studies, median PFS and OS of patients with exon 20 insertions was 2.7 months and 9.2 months, respectively (4). In practice, patients harboring exon 20 insertions treated with first-generation TKIs had a median PFS and OS of 2.0-3.0 and 9.7-16.7 months, respectively (7, 8, 11). In our five patients with exon 20 insertions, OS was 39.5 months, which was mainly achieved by cytotoxic drugs. TKIs were administered only to two out of the five patients and were not effective (median PFS of 0.9 months). The results from previous studies and ours suggest that chemotherapy should be applied instead of TKIs in patients with exon 20 insertion mutations.

This population-based, multi-institute study covering a single prefecture has several limitations. It was a retrospective study with a small number of patients from varied backgrounds. As several treatments were administered for a small number of patients with several mutation types, detailed comparisons by treatment line were not possible. Moreover, detailed consideration of adverse events was lacking. However, this study has clinical significance as it reflects real practice without selection bias. As such, our results should be used to complement clinical trial results when patients are collected with a selection bias. The increasing use of next-generation sequencing technology will significantly expand our knowledge of uncommon *EGFR* mutations, in which case, the present study will provide key indicative information.

In conclusion, personalized treatment needs to evolve for NSCLC with different types of uncommon *EGFR* mutation. Afatinib and osimertinib show therapeutic promise but it is important that the optimal treatment fully exploits the characteristics of the drug and provides significant benefits to patients. As such, it is important to share not only the results of clinical trials but also valuable experience gained in daily practice and to make use of them in clinical care.

Conflicts of Interest

No Authors have any conflict of interest to disclose regarding this study.

Authors' Contributions

YY, TT, TK, HN, KF, HS and NH designed the study. YY, TT, YY, HI, KH, TS, HY, TE,YI, RN, YI, HS, KI, KS, MI, NK, KK, HI, MS, TS, IS, YS, YF, KM, TK, SH, AN, TY, HO, SH, MK and TK collected the data. YY, TT and HS analyzed the data and prepared the article. All Authors approved the final version of the article.

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