Real-world Outcomes of First-line Afatinib in Patients with Non-small Cell Lung Cancer and Uncommon EGFR Mutations in South Korea

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Abstract

Uncommon epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) are heterogeneous and show variable prevalence and clinical responses to EGFR-tyrosine kinase inhibitors. We investigated the characteristics of uncommon EGFR mutations and the clinical efficacy of afatinib in patients. In this multicenter, retrospective study, we analyzed patients with NSCLC and uncommon EGFR mutations; these were categorized according to their incidence: (1) major uncommon mutations (G719X and L861Q), (2) compound mutations, and (3) minor uncommon mutations (exon 20 insertion, S768I, and de novo T790M). Sixty-four patients (9.1%, 64/703) with uncommon EGFR mutations were identified in 16 South Korean institutes. Afatinib demonstrated activity against major uncommon (median time of treatment [TOT]: 20.3 months, 95% CI: 5.0–27.9; overall survival (OS): 30.6 months, 95% CI: 33.5–34.0) and compound mutations (median TOT: 11.9 months, 95% CI: 3.6–9.6; OS: 29.1 months, 95% CI: 12.1–65.4). Minor uncommon mutations showed unfavorable responses to afatinib (median TOT: 3.8 months, 95% CI: 2.1–4.2; OS: 8.5 months, 95% CI: 4.7–18.2). S768I mutation was present in 14 patients (1.99%, 14/703). Median TOT and OS were not significantly different between S768I and resistant exon 20 mutations. Afatinib is active in patients with NSCLC harboring major uncommon and compound EGFR mutations.

Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are the first-line standard of care for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) harboring EGFR mutations¹. The most common type of EGFR mutation is exon 19 deletions, followed by the L858R point mutation in exon 21, which account for 75–80% of patients with EGFR mutation-positive NSCLC^{2,3}. They are conventionally referred to as common EGFR-TKI sensitive mutations based on numerous clinical trials⁴. However, other uncommon mutations represent a highly heterogeneous group and their clinical significance remains unclear.

Approximately 7–23% of NSCLC tumors harbor uncommon EGFR mutations^{5–12}. The uncommon EGFR mutations include the primary drug resistance mutation T790M, exon 20 insertions, substitution mutations of L861Q, G719X, and S768I, and their coexisting mutations¹³. Double or multiple independent mutations of the EGFR-tyrosine kinase domain, termed compound mutations, account for up to 25% of all uncommon EGFR mutation-positive tumors¹⁴.

The clinical characteristics and most effective treatment strategies for many uncommon EGFR mutations are unclear. This uncertainty reflects the fact that they are rare and have been excluded from most clinical trials. In patients with uncommon EGFR mutations treated with first-generation EGFR-TKIs (gefitinib/erlotinib), the objective response rate (ORR) is approximately 40–50%, and the median progression-free survival (PFS) is approximately 6–7.7 months¹⁵. A few studies have suggested that platinum-based cytotoxic chemotherapy or immunotherapy is preferable to EGFR-TKIs in some patients

^{16–19}. Recently, several studies have demonstrated the activity of a second-generation EGFR-TKI, afatinib, in patients with uncommon EGFR mutations. The Lux-Lung trials showed that the most prevalent uncommon mutations, G719X, L861Q, and S768I, appear to be sensitive to afatinib ¹². Additionally, a well-designed pooled analysis demonstrated the clinical activity of afatinib for the treatment of tumors harboring several uncommon EGFR mutation categories, especially certain exon 20 insertions, that confer resistance to EGFR-TKIs ⁴. However, other studies have shown highly heterogeneous results of EGFR-TKIs against uncommon EGFR mutations.

Therefore, in this study, we aimed to evaluate the clinical characteristics of uncommon EGFR mutations and the real-world efficacy of first-line afatinib in a multicenter dataset of Korean patients with uncommon EGFR-positive advanced-stage NSCLC.

Results

Patients

In total, 703 patients with EGFR-mutated advanced-stage NSCLC were screened, and 64 (9.1%) were analyzed in this study. Patient characteristics were not significantly different between patients with common EGFR mutations and those with uncommon EGFR mutations (data not shown). The characteristics of patients with uncommon EGFR mutations are shown in Table 1. The median age was 64 years (range, 32–84 years), and 28 patients (44%) were men. Thirty-eight patients (59%) were never smokers, and 61 (95%) had adenocarcinomas.

Table 1

Clinical characteristics of non-small cell lung cancer patients with uncommon EGFR mutations. Values are presented as numbers (percentages), unless otherwise stated. ^aChi-square test: ECOG PS, Eastern Cooperative Oncology Group performance status.

Characteristics	Total (n = 64)	Major (n = 33)	Compound (n = 23)	Minor (n = 8)	<i>p</i> value ^a
Age (median, range)	66 (32–83)	63 (34–83)	67 (32–81)	77 (53–81)	0.156
Male	28 (44)	14 (42)	12 (52)	2 (25)	0.401
Smoking	38 (59)	20 (61)	12 (52)	6 (75)	0.516
Never	26 (41)	13 (39)	11 (48)	2 (25)	
Ever					
ECOG PS	58 (92)	29 (88)	22 (96)	7 (100)	0.407
0 and 1	5 (8)	4 (12)	1 (4)	0 (0)	
≥2					
Stage	35 (55)	17 (52)	16 (70)	2 (25)	0.081
3	29 (45)	16 (48)	7 (30)	6 (75)	
4					
Subtypes	61 (95)	32 (97)	22 (96)	7 (88)	0.522
Adenocarcinoma	3 (5)	1 (3)	1 (4)	1 (12)	
Others					
Median number of metastasis sites (range)	1.5 (0–5)	2 (0–5)	1 (0–3)	2 (1–5)	0.066

The uncommon EGFR mutation categories are listed in Table 2. Overall, 33 patients (51%) included in the analysis had a major uncommon mutation (G719X and L861Q), 23 (36%) had a compound mutation, 4 (6%) had an exon 20 insertion, 3 (5%) had an S768I mutation, and 1 patient (2%) had a T790M mutation.

Table 2
EGFR mutation status of non-small cell lung cancer patients with uncommon EGFR mutations. Values are presented as numbers (percentages). ^asensitive mutations included EGFR 19 deletion and L858R mutation.

Mutation category	N (%)
Major uncommon mutation	33 (51)
G719X	19 (30)
L861Q	14 (21)
Compound	23 (36)
G719X + S768I	11 (17)
G719X + L861Q	4 (6)
T790M + sensitive mutations ^a	4 (6)
T790M + G719X	2 (3)
19deletion + 20insertion	1 (2)
19deletion + L861Q	1 (2)
Exon 20 insertion	4 (6)
S768I	3 (5)
T790M	1 (2)

Efficacy to afatinib in patients with uncommon EGFR mutations

After receiving afatinib, patients with uncommon mutations exhibited a significantly inferior ORR (48.4% vs. 67.1%; $p = 0.003$), time of treatment (TOT) (median: 16.0 months vs. 24.3 months; $p = 0.051$), and overall survival (OS) (median: 30.9 months vs. 50.9 months; $p = 0.011$) than patients with common mutations.

Table 3 lists the ORRs of patients with the uncommon EGFR mutation subtype. The ORR was higher in patients with compound mutations (ORR = 56.5%) and major uncommon mutations (ORR = 46.9%) than in those with minor uncommon mutations (ORR = 16.7%).

Table 3

Tumor response to afatinib in non-small cell lung cancer patients with uncommon EGFR mutations. Values are presented as numbers and percentages. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not-available; ORR, objective response rate; DCR, disease control rate.

Mutation category	Objective response					ORR,%	DCR,%
	CR, n	PR, n	SD, n	PD, n	NA, n		
Major uncommon mutations	0	15	13	4	1	46.9	87.5
G719X		9	8	2	0	47.3	
L861Q		6	5	2	1	46.1	
Compound mutations	0	13	7	3	1	56.5	87.0
Minor uncommon mutations	0	1	3	2	2	16.7	66.7
S768I		1	0	1	1		
Exon 20 insertion		0	3	1	0		
de novo T790M		0	0	0	1		

The median TOT of all patients with uncommon mutations was 16.0 months (95% confidence interval [CI]: 6.2–15.3). The major uncommon mutation group showed the longest TOT (median: 20.3 months, 95% CI: 5.0–27.9), followed by compound mutation (12.3 months, 95% CI: 3.9–9.9) and minor uncommon mutation (3.8 months, 95% CI: 2.1–4.2) groups (Fig. 1).

OS differed significantly between patients within uncommon mutation categories. Patients with the major uncommon mutation and compound mutation showed significantly longer OS than those in the minor uncommon mutation group (median: 30.6 months, 95% CI: 33.5–34.0 and 29.1 months, 95% CI: 12.1–65.4 vs 8.5 months, 95% CI: 4.7–18.2; $p = 0.036$) (Fig. 2).

Patients with minor uncommon mutations and any other mutation showed significantly longer survival than those with single minor mutations (median TOT: 10.6 months vs. 3.8 months; $p = 0.014$ and median OS 28.8 months vs. 8.5 months; $p = 0.065$) (Fig. 3).

Outcomes in patients with tumors harboring minor uncommon mutations

We categorized exon 20 insertions and S768I and T790M mutations as minor uncommon mutations according to their incidence rates. Among these, the S768I mutation was present in 14 patients (1.99%, 14/703). Only three patients had an isolated S768I mutation, and 11 had a concurrent G719X mutation. The ORR and disease control rate (DCR) were 58.3% and 83.3% for patients with the S768I mutation, respectively. The median TOT for patients with the S768I mutation was 8.2 months (95% CI: 5.3–7.3), which was not significantly different to that for patients with primary resistance mutations (exon 20

insertions and T790M substitution) (8.7: months, 95% CI: 0.2–7.4; $p = 0.804$). Moreover, the median OS was not significantly different between patients with S768I mutations and those with primary resistance mutations (22.9 months vs. 26.9 months; $p = 0.728$).

Discussion

This study showed the mutation patterns of NSCLC harboring uncommon EGFR mutations and the real-world efficacy of afatinib in Korean patients. Among 703 patients with advanced-stage NSCLC, we identified 64 cases of uncommon mutations, corresponding to a prevalence of 9.1%. To the best of our knowledge, the current multicenter registry constitutes the largest study from Korea to report the clinical outcomes of patients with NSCLC and uncommon mutations using first-line afatinib. The most frequent uncommon mutations observed in our cohort were compound mutations (36%), followed by G719X (30%), L861Q (21%), exon 20 mutations (12%, exon 20 insertion [6%], S768I [5%], and de novo T790M [2%]). The incidence rates of uncommon EGFR mutations vary significantly among ethnicities and countries. The incidence rate of exon 20 mutations in our study was lower than that reported in other studies. For example in a German cohort study, 4% (23/573) had uncommon EGFR mutations, among which exon 20 mutations were the most frequent (55%)²⁰. Additionally, in an Indian cohort study, 6.58% (83/1260) had uncommon mutations, among which exon 20 mutations were also the most common (exon 20 insertion, 19.3%; T790M, 12%; and S768I, 3.6%)²¹.

The overall median TOT and OS of our cohort of patients treated with first-line afatinib were 16.0 months (95% CI: 6.2-15.3) and 30.9 months (95% CI: 22.3-45.2), respectively. Favorable efficacy of afatinib was observed in patients with major uncommon mutations (G719X and L861Q) and compound mutations. The median TOT and OS of patients using afatinib therapy for a major uncommon mutation were 20.3 months (95% CI: 5.0-27.9) and 30.6 months (95% CI: 33.5-34.0), respectively. Preclinical studies have shown that uncommon EGFR mutations, such as G719X and L861Q, are sensitive to first- and second-generation EGFR-TKIs²²⁻²⁴, and several clinical studies have reported that the median PFS can reach 7.7 months in patients with advanced NSCLC and uncommon EGFR mutations receiving EGFR-TKIs alone as first-line therapy^{15,25,26}. These results are also comparable with the recently published data for afatinib. For instance, Yang et al. reported the efficacy of 315 patients with uncommon mutations who received first-line afatinib. In this analysis, the median time to treatment failure (TTF) of patients with major uncommon mutations was 10.8 months, suggesting a favorable outcome⁴. A major difference between our study and that by Yang et al. is that S768I was categorized as major uncommon mutation in Yang et al.

Compound EGFR mutations are present in up to a quarter of NSCLC tumors and are associated with poor prognosis^{3,27}. However, the current study demonstrates that afatinib is active in most compound mutations, even in those with known resistance mutations, such as T790M and exon 20 insertion mutations. Median TOT (12.3 months) and OS (29.1 months) in patients with compound mutations were comparable with those in patients with major uncommon mutations.

In this study, we showed that minor uncommon mutations, including exon 20 insertions, exon 20 S768I, and exon 20 T790M, were associated with an unfavorable response to afatinib. The median TOT and OS of patients using afatinib for these minor uncommon mutations were 3.8 months (95% CI: 2.1-4.2) and 8.5 months (95% CI: 4.7-18.2), respectively. These results are in line with those of Yang et al., who reported the TTF (median: 4.2 months) and ORR (24.3%) in patients with an exon 20 insertion⁴, and suggest that afatinib shows inferior efficacy to that expected in patients treated with conventional platinum-based chemotherapy. Large-scale prospective clinical trials, such as IPASS, NEJ002, and WJTOG3405, showed consistent results that the median PFS of patients using conventional platinum-based chemotherapy is 5 to 6 months²⁸⁻³⁰. Additionally, several studies have claimed that EGFR-TKIs can be used as a subsequent therapy for patients with uncommon mutations, whereas platinum-based chemotherapy should be administered as a first-line treatment^{12,31,32}. This supports our view that first-line platinum-based chemotherapy confers clinical benefits in patients with single exon 20 mutations. Recently, several agents targeting exon 20 insertions have been actively investigated. For example, a phase III study of mobocertinib (TAK-788), a novel, irreversible, small-molecule EGFR inhibitor specifically designed to target exon 20 insertion mutants, has been conducted in patients with advanced NSCLC harboring these mutations³³. Preclinical data and phase I/II studies have reported that mobocertinib demonstrates antitumor activity with manageable toxicity in patients with advanced EGFR exon 20 insertion mutations^{33,34}. Furthermore, the phase 1 CHRYSALIS trial (NCT02609776) showed that amivantamab, a bispecific antibody directed against EGF and MET receptors, induces an objective response in 40% of patients with previously treated NSCLC harboring EGFR exon 20 insertion mutations, with 47% maintaining their response for at least 6 months and 47% remaining on therapy after a median follow-up of over 9 months³⁵. It was approved by the FDA in May 2021 as the first agent for adult patients with advanced NSCLC and EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy³⁶.

We observed that first-line afatinib showed more favorable efficacy in patients harboring minor uncommon mutations with other mutations than in those harboring single minor uncommon mutations (median TOT: 10.6 months vs. 3.8 months; $p = 0.014$ and median OS: 28.8 months vs. 8.5 months; $p = 0.065$). This is consistent with studies from Taiwan (median PFS: 11.9 vs. 6.5 months; $p = 0.010$)¹⁵ and China (median PFS: 9.3 vs 7.0 months; $p = 0.4495$)¹⁷, in which the uncommon compound mutation group showed a relatively good response to EGFR-TKIs compared with the uncommon single-mutant group. Therefore, although single minor uncommon mutations do not necessarily confer sensitivity to afatinib, minor uncommon mutations with other EGFR mutations do not limit the efficacy of afatinib.

S768I mutations in EGFR exon 20 are rare (1.99%, 14/703 in our study) and are typically observed in combination with other EGFR mutations³⁷. This mutation accounts for approximately 1% of all EGFR mutations³⁸ and is usually categorized as a major uncommon mutation. Patients with this mutation reportedly have a favorable response to EGFR-TKIs³⁹. However, in our study, we observed that patients with the S768I mutation showed a relatively unfavorable response to afatinib. Russo reported the case of an S768I mutation with a poor outcome after afatinib treatment. The rapid development of the T790M

secondary mutation may be responsible for the low response to afatinib ⁴⁰. Unfortunately, we identified only three patients who underwent re-biopsy after progression to afatinib, and T790M development was not observed among these patients. As our sample size was small, the use of afatinib against S768I mutations requires confirmation in a larger scale study.

This study had several limitations. First, it was a retrospective study with an inevitable bias. Second, the detection rate of exon 20 mutations was very low; therefore, we could not conduct a subgroup analysis of each type of exon 20 mutation. We used the PNAClampTM EGFR Mutation Detection kit (PANAGENE, Inc., Daejeon, Korea) to detect EGFR mutations using real-time polymerase chain reaction (PCR). This technique is a highly sensitive method for detecting EGFR mutations but is restricted to several targetable mutations ⁴¹. We believe that this might have contributed to the low incidence of exon 20 mutations. Byeon et al. reported that 27 of 1,419 patients with advanced NSCLC had an exon 20 insertion in Korea ⁴². They used various techniques to detect EGFR mutations, including next-generation sequencing (NGS), which indicates that highly sensitive NGS techniques can expand the detection of targetable somatic mutations in EGFR. Third, TOT and OS might have been overestimated in the study owing to the small sample size. Despite these limitations, this study is the first multicenter study in South Korea to report the clinical outcomes of patients with NSCLC and uncommon mutations with using first-line afatinib based on real-world experience, and its applicability to real clinical practice, especially for Asian populations, could allow better patient management and improved survival outcomes in patients with uncommon EGFR mutations.

In conclusion, this study demonstrated the efficacy of first-line afatinib for the treatment of tumors harboring uncommon EGFR mutations, especially G719X, L816Q, and compound mutations. Although the incidence of S768I, exon 20 insertion, and de novo T790M mutations was low, patients with these mutations showed unfavorable responses to first-line afatinib and poor survival outcomes.

Methods

Study design and participants

Details of patients with tumors harboring uncommon mutations treated with first-line afatinib in the Real-world Experience of SEquential Treatment of afatinib followed by osimertinib (RESET) study, a retrospective multicenter observational study across 16 medical centers in South Korea, were collected. Briefly, eligible patients were aged 19 years or older with treatment-naïve, histologically or cytologically documented NSCLC that was American Joint Committee on Cancer (8th edition) stage 3B, 3C, 4A, or 4B. Key exclusion criteria were patients who were not treated with afatinib as first-line therapy. Electronic medical records from October 2014 to October 2019 were reviewed. The peptide nucleic acid-mediated real-time PCR clamping method was used to detect *EGFR* mutations in all medical centers.

Uncommon mutations were categorized into three groups according to their incidence rate: (1) major uncommon mutations (G719X and L861Q), (2) compound mutations, and (3) minor uncommon

mutations (exon 20 insertion, S768I, and de novo T790M). One unusual case and cases with both 19 deletions and L858R mutations were excluded from the analysis.

Clinical data collection and efficacy evaluations

Baseline demographic characteristics (age, sex, and Eastern Cooperative Oncology Group performance status) were collected. Smoking status was categorized into never, former, and current smokers according to the classification of the National Health Interview Survey. The date of diagnosis, initiation of first-line afatinib, information on EGFR mutation (i.e., presence/absence and profile), number of metastatic organs, existence of specific organ metastasis, and dose modification of afatinib were recorded.

Efficacy outcomes included ORR, DCR, TOT, and OS. Tumor response was assessed using computed tomography scans, but decisions concerning the follow-up intervals or radiologic tools were entirely at the discretion of the physician. Response to afatinib was calculated according to Response Evaluation Criteria in Solid Tumors 1.1. TOT was defined as the time from the start of therapy to treatment discontinuation for any reason or death. This was chosen as a pragmatic endpoint suited to real-world studies⁴. OS was calculated from the date of therapy initiation to the date of death.

Statistical analysis

The patients' baseline characteristics are shown as descriptive data. Chi-squared and Fisher's exact tests were used to compare differences between categorical variables. TOT and OS were estimated using the Kaplan-Meier method, and differences in time distributions were compared using the log-rank test. The estimated median time (months) and 95% CI are presented. All p-values were two-sided, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

Ethics approval

The study and protocol were approved by the Institutional Review Board (IRB) of Kosin University Gospel Hospital (IRB no. 2021-06-22) and Pusan National University Hospital (IRB no. 2107-001-104) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived by the IRB of Kosin University Gospel Hospital (IRB no. 2021-06-22) and Pusan National University Hospital (IRB no. 2107-001-104) because of the retrospective nature of the study and the analysis used anonymous clinical data.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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Author contributions

Study concept and design: K.M., and J.TW. Acquisition of data: K.M., C.CM., L.SY., P.CK., C.YS., L.KY., K.SJ., L.JE., L.SY., P.CK., L.SH., J.SH., Y.SH., and J.TW. Analysis and interpretation of data: K.M., C.CM. and J.TW., Drafting of manuscript: K.M., and J.TW. Critical revision: C.CM., L.SY., P.CK., C.YS., L.KY., K.SJ., L.JE., L.SY., P.CK., L.SH., J.SH., Y.SH., and J.TW. All authors contributed to the approval of the submitted and final versions.

Competing Interests Statement:

The author(s) declare no competing interests.

Additional information

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Figures

Figure 1

Time of treatment in patients with non-small cell lung cancer tumors harboring uncommon EGFR mutations ($p < 0.001$ by log-rank test)

Figure 2

Overall survival in patients with non-small cell lung cancer tumors harboring uncommon EGFR mutations (p = 0.001 by log-rank test)

Figure 3

Time of treatment (a) and overall survival (b) in patients with minor uncommon EGFR mutations