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Potential for afatinib as an optimal treatment for advanced non-small cell lung carcinoma in patients with uncommon *EGFR* mutations

Dear Editor,

Uncommon *epidermal growth factor receptor (EGFR)* mutations in non-small cell lung cancer (NSCLC) are a heterogeneous group of genetic alterations that produce variable responses to EGFR-tyrosine kinase inhibitor (TKI) in patients with most of the evidence of the responses to EGFR-TKIs being based on small case studies or single case reports [1–3]. Several studies have demonstrated that patients with uncommon *EGFR* mutations respond poorly to first-generation EGFR-TKIs, such as gefitinib and erlotinib, compared to patients with common *EGFR* mutations [2–5]. Among the rare subtypes, the two highest frequency mutations, G719X in exon18 and L861Q in exon21, have been recognized as being relatively sensitizing mutations; the objective overall response rate and the median progression-free survival (PFS) have been reported to be around 40–70% and 4.0–9.0 months, respectively [1,6,7]. Due to the similar efficiency obtained by platinum-doublet chemotherapy, the therapeutic strategy for advanced NSCLC patients with uncommon *EGFR* mutation has been inconsistent. Recently, a second-generation EGFR-TKI, afatinib, has shown superior efficacy over the first-generation EGFR-TKIs in NSCLC patients with common *EGFR* mutations [8,9]. Furthermore, a post-hoc analysis of the Lux-Lung -2, -3, and -6 trials showed that afatinib was active in NSCLC patients with uncommon *EGFR* mutations, and that the median PFS in the patients with G719X in exon 18 or L861Q in exon 21 were 13.8 months or 8.2 months, respectively [10]. These results indicate that afatinib could be an optimal treatment option for the patients with uncommon *EGFR* mutations. However, there have been no reports that show the superiority of afatinib over the first-generation EGFR-TKIs in a cohort study.

Here, we conducted a retrospective analysis of patients treated with EGFR-TKIs in our cohort and evaluated the efficacy of afatinib with respect to clinical outcomes in advanced NSCLC patients with uncommon *EGFR* mutations and compared it to the efficacy of the first-generation EGFR-TKIs. Clinical data between January 2004 and Jun 2018 were assessed from patients with stage III, IV, or recurrent NSCLC, harboring *EGFR* mutations who received treatment with EGFR-TKIs (N = 177) at Nagoya University hospital. Uncommon *EGFR* mutations were defined as any mutation other than short in-frame deletions of exon 19 and the L858R point mutation in exon 21, and were observed in 18 patients (10.2%). Patient characteristics were not statistically significant differences between the patients with common *EGFR* mutations and those with uncommon *EGFR* mutation (Table 1). The most frequent mutation in the group of uncommon *EGFR* mutations was L861Q in exon 21 (N = 7 [4.0%]) and the second most frequent mutation was G719 A in exon 18 (N = 5 [2.8%]). Among the 18 patients with uncommon *EGFR* mutations, 8 patients had received afatinib and 10 patients had received the first-generation EGFR-TKIs (Table 2). There were no statistically significant differences in the patients' clinical characteristics comparing the two groups. The best overall responses (ORRs) in the afatinib group and the first-generation EGFR-TKIs were 75.0% (N = 6/8) and 40.0% (N = 4/10), respectively

Table 1
Clinical characteristics of 177 lung cancer patients with *EGFR* mutations.

Characteristic	Total	Common mutation n (%)	Uncommon mutation n (%)	P‡
Total	177	159 (89.8)	18 (10.2)	
Median Age (Range)	66.3	66.3 (35-87)	70.5 (52-87)	0.2406
Gender				
Male	67	62 (92.5)	5 (7.5)	0.4465
Female	110	97 (88.2)	13 (11.8)	
Smoking status*				
Current	19	19 (100.0)	0 (0.0)	0.2586
Former	50	45 (90.0)	5 (10.0)	
Never	104	91 (87.5)	13 (12.5)	
PS				
0	86	75 (87.2)	11 (12.8)	0.4816
1	71	65 (91.5)	6 (8.5)	
≥2	20	19 (95.0)	1 (5.0)	
Stage				
IIIA	4	4 (100.0)	0 (0.0)	0.0008
IIIB	9	5 (55.5)	4 (45.5)	
IV	104	99 (95.2)	5 (4.8)	
Recurrence	60	51 (85.0)	9 (15.0)	
Subtype				
Adenocarcinoma	171	154 (90.1)	17 (9.9)	0.4762
Squamous cell carcinoma	3	3 (100.0)	0 (0.0)	
Adenosquamous cell carcinoma	1	1 (100.0)	0 (0.0)	
NSCLC	2	1 (50.0)	1 (50.0)	

‡ P values were calculated by T-Test, Fisher's exact test or Chi-square test.
* Information was not available for 4 cases.

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Table 2
Clinical characteristics of 18 lung cancer patients with uncommon *EGFR* mutations.

Characteristic	Total	EGFR-TKI		P‡
		Gefitinib/ Erlotinib n (%)	Afatinib, n (%)	
Total	18	10 (55.5)	8 (44.4)	
Median Age (Range)	70.5	70.0 (52-79)	73.0 (61-87)	0.0560
Gender				
Male	5	3 (60.0)	2 (40.0)	0.8139
Female	13	7 (53.8)	6 (46.2)	
Smoking status				
Former	5	2 (40.0)	3 (60.0)	0.4101
Never	13	8 (61.5)	5 (38.5)	
PS				
0	11	5 (45.5)	6 (54.5)	0.4597
1	6	4 (66.7)	2 (33.3)	
≥2	1	1 (100.0)	0 (0.0)	
Stage				
IIIB	4	3 (75.0)	1 (25.0)	0.1634
IV	5	1 (20.0)	4 (80.0)	
Recurrence	9	6 (66.7)	3 (33.3)	
Subtype				
Adenocarcinoma	17	9 (52.9)	8 (47.1)	0.3574
NSCLC	1	1 (100.0)	0 (0.0)	
EGFR mutation status				
Ex18:G719A	5	2 (40.0)	3 (60.0)	
Ex18:G719C	1	0 (0.0)	1 (100.0)	
Ex19:K574E	1	1 (100.0)	0 (0.0)	
Ex19:L747-S752del	1	1 (100.0)	0 (0.0)	
Ex19:L746-E749delA750VT751S	1	1 (100.0)	0 (0.0)	
Ex21:L861Q	7	4 (57.1)	3 (42.9)	
Ex21:L858R + T790M	1	1 (100.0)	0 (0.0)	
Ex18:G719 A and Ex21:L861Q	1	0 (0.0)	1 (100.0)	

‡ P values were calculated by *T*-Test, Fisher's exact test or Chi-square test.

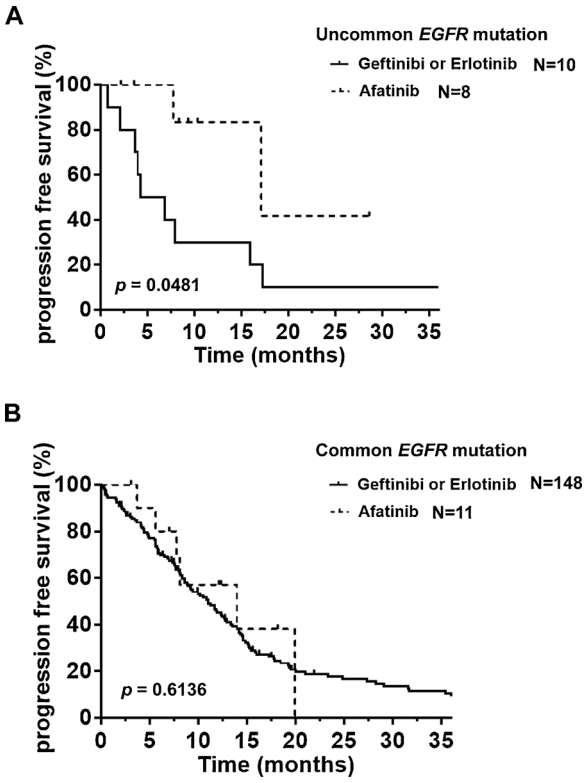

Fig. 1. Kaplan-Meier plot of progression-free survival (PFS) in the patients with uncommon *EGFR* mutations (A) and common *EGFR* mutations (B). PFS was defined as the time from the start of first-line TKI treatment to disease progression or death, whichever was earlier, and data were censored at the last follow-up date. The log-rank test was implemented to analyze the differences between the patient groups.

(Table 3). The PFS in the afatinib group were significantly longer than those in the first-generation EGFR-TKIs group (P = 0.0481; Fig. 1, A), with median PFS of 17.1 and 5.5 months, respectively. To evaluate the efficacy of afatinib in patients with *EGFR* mutations, we also analyzed 159 patients with common *EGFR* mutations in this cohort. Among them, 11 patients had received afatinib. The patient characteristics were not statistically different between the afatinib and first-generation EGFR-TKIs groups (data not shown). The ORRs in the afatinib group and the first-generation EGFR-TKIs group were 63.6% (7/11) and 47.1% (66/138), respectively (Table 3). The median PFS (14.0 vs 11.0 months) was also longer in the afatinib group than in the first-generation *EGFR*-TKIs group; however, these differences did not reach statistical significance (P = 0.6136; Fig. 1B).

In this retrospective analysis, the ORR and PFS found in the first-generation *EGFR*-TKIs group were consistent with previous reports, and the efficacy of afatinib showed a statistically significant superiority over the first-generation *EGFR*-TKIs in patients with uncommon *EGFR* mutations. The ORR of the 8 patients treated with afatinib was 75.0%, which is similar to the result of the post-hoc analysis in the Lux-Lung trails which showed that the ORR of patients with the G719X mutations in exon 18 or L861Q in exon 21 were 77.8% and 56.3%, respectively [10]. However, the median PFS in our cohort was somewhat longer than one seen from the post-hoc analysis of the Lux-Lung trails [10]. This difference might be due to the limitations of a small case study, racial differences, and the various follow-up terms used to evaluate the

Table 3
Response to EGFR-TKIs in patients with uncommon *EGFR* mutations.

	Common mutation				Uncommon mutation			
	Gefitinib or Erlotinib‡		Afatinib		Gefitinib or Erlotinib		Afatinib	
	N = 138	%	N = 11	%	N = 10	%	N = 8	%
Best response								
PR	65	47.1	7	63.6	4	40.0	6	75.0
SD	45	32.9	3	27.3	4	40.0	2	25.0
PD	28	20.0	1	9.1	2	20.0	0	0.0
ORRs	66	47.1	7	63.6	4	40.0	6	75.0
DCRs	112	80.0	10	90.9	8	80.0	8	100.0

PR; partial response, SD; stable disease, PD; progression disease.
ORR; overall response rate, DCR; disease control rate.
‡ 10 patients were not evaluated.

responses in a retrospective analysis. The successful establishment of a therapeutic strategy for uncommon *EGFR* mutations is limited by the low frequency and the heterogeneity of the various alterations. Furthermore, patients with low frequency *EGFR* mutations have not been included in the majority of pivotal clinical trials for *EGFR*-TKI treatment. These limitations make it hard to accumulate any reliable evidence; therefore, sharing information from even single case report or small case studies, is crucial for patients with uncommon *EGFR* mutations. Our results suggest that afatinib is an optimal treatment for patients with advanced NSCLC who harbor uncommon *EGFR* mutations. Further large-scale studies are urgently needed to address this issue.

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