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Predictive Factors for Switched EGFR-TKI Retreatment in Patients with EGFR-Mutant Non-Small Cell Lung Cancer

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Background: Third-generation tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) have proved efficacious in treating non-small cell lung cancer (NSCLC) patients with acquired resistance resulting from the T790M mutation. However, since almost 50% patients with the acquired resistance do not harbor the T790M mutation, retreatment with first- or second-generation EGFR-TKIs may be a more viable therapeutic option. Here, we identified positive response predictors to retreatment, in patients who switched to a different EGFR-TKI, following initial treatment failure.

Methods: This study retrospectively reviewed the medical records of 42 NSCLC patients with *EGFR* mutations, whose cancers had progressed following initial treatment with gefitinib or erlotinib, and who had switched to a different first-generation EGFR-TKI during subsequent retreatment. To identify high response rate predictors in the changed EGFR-TKI retreatment, we analyzed the relationship between clinical and demographic parameters, and positive clinical outcomes, following retreatment with EGFR-TKI.

Results: Overall, 30 (71.4%) patients received gefitinib and 12 (28.6%) patients received erlotinib as their first EGFR-TKI treatment. Following retreatment with a different EGFR-TKI, the overall response and disease control rates were 21.4% and 64.3%, respectively. There was no significant association between their overall responses. The median progression-free survival (PFS) after retreatment was 2.0 months. However, PFS was significantly longer in patients whose time to progression was ≥10 months following initial EGFR-TKI treatment, who had a mutation of exon 19, or whose treatment interval was <90 days.

Conclusion: In patients with acquired resistance to initial EGFR-TKI therapy, switched EGFR-TKI retreatment may be a salvage therapy for individuals possessing positive retreatment response predictors.

Keywords: Carcinoma, Non-Small-Cell Lung; Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor; Retreatment; Predictive

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Introduction

Lung cancer is the most common form of cancer and the leading cause of cancer-related mortality worldwide[1]. Because of changing in smoking habits such as cessation of smoking, increase in the number of female smokers, and use of filtered tobacco, the incidence of non-small cell cancer (NSCLC) continues to increase[2,3]. In the early 2000s, platinum-based doublet chemotherapy was the treatment of choice for NSCLC, with the median survival time being less than 8 months[4].

The discovery that mutations in the tyrosine-kinase epidermal growth factor receptor (EGFR) gene were responsible for cell proliferation, cellular escape from apoptosis, and cell migration in NSCLC led to the development of a new class of therapeutic agents, the tyrosine kinase inhibitors (TKIs). Treatment with EGFR-TKI results in significantly prolonged progression-free survival (PFS) than platinum-based doublet therapy, particularly in Asian, female, non-smoking patients[5].

In previous studies, the median PFS following EGFR-TKI treatment ranged from 10 to 14 months[6,7]. However, acquired resistance to EGFR-TKI is unavoidable because of several mechanisms and results in reduced treatment response. In 50%–60% of patients who acquire resistance to first-generation EGFR-TKIs, the mutation T790M is responsible[8]. Resistance can also develop via other mechanisms, such as c-MET amplification, transformation to small cell carcinoma, and AXL activation[8-13]. Although third-generation EGFR-TKIs have proven efficacy in T790M-positive NSCLC patients, there are no effective therapeutic options for patients who acquire resistance by other mechanisms[14,15].

Several clinical trials have been conducted to investigate the efficacy of EGFR-TKI retreatment after first-line EGFR-TKI treatment failure[16-21]. In most of these previous studies, a favorable outcome was achieved in patients who showed a good response to prior EGFR-TKI therapy. However, there are as yet no consistent data on whether factors such as age, sex, smoking history, and subtype of *EGFR* mutation can affect the outcomes of EGFR-TKI retreatment. In 2013, switched EGFR-TKI retreatment was approved in Korea for use in patients who develop acquired resistance to first-line EGFR-TKI. With this as a momentum, we conducted the present study to identify the predictors of improved outcomes following EGFR-TKI retreatment.

Materials and Methods

1. Study design

The inclusion criteria for this study were patients aged 18 years or older with NSCLC with activating *EGFR* mutations who underwent EGFR-TKI retreatment therapy at the Asan Medical Center between 2005 and 2016. Patients eligible for inclusion in the study were those who received once-daily doses of 250 mg gefitinib or 150 mg erlotinib for at least 1 month prior to disease progression and were then re-treated with a different first-generation EGFR-TKI after stopping the initial therapy. We included patients regardless of whether they were administered conventional chemotherapy between the two EGFR-TKI treatments. Patients must have had at least one measurable lesion and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3. Excluded from the study were patients who switched EGFR-TKI owing to drug toxicity or intolerability, who were treated with second- or third-generation EGFR-TKIs as part of a clinical trial, or whose *EGFR* mutation status was unknown.

2. Treatment response evaluation

Demographic information and clinical data such as vital signs, results of physical examination, and blood test results were extracted from each patient's medical record. Disease progression was assessed by the examination of radiographic data available for each patient, such as chest X-rays and computed tomography scans, which were administered every 1–2 months during treatment. Drug response was assessed via Response Evaluation Criteria In Solid Tumors (RECIST).

Efficacy outcomes including overall response and survival following the second EGFR-TKI treatment were calculated. PFS was defined as the length of time from the start of treatment to the date of disease progression or death. Time to progression (TTP) was defined as the length of time from the start of treatment to the date of disease progression. Overall survival (OS) was defined as the length of time from the start of treatment to the date of all-cause death. Disease control rate (DCR) was defined as the percentage of patients who have achieved complete response (CR), partial response (PR), or stable disease. Response rate (RR) was defined as the percentage of patients who achieved either a CR or PR.

3. *EGFR* mutation analysis

The activating *EGFR* mutation in each enrolled patient was confirmed by nested polymerase chain reaction (PCR).

4. Statistical analysis

DCR and RR were compared using Fisher exact test. TTP,

Table 1. Baseline characteristics

Variable	Initial EGFR-TKI		Total	p-value
	Gefitinib (n=30)	Erlotinib (n=12)		
Age, yr				0.315
<60	14 (46.7)	8 (66.7)	22	
>60	16 (53.3)	4 (33.3)	20	
Sex				0.040
Male	10 (33.3)	0	10	
Female	20 (66.7)	12 (100)	32	
Smoking				0.222
Current*	1 (3.3)	1 (8.3)	2	
Ex-smoker†	6 (20.0)	0	6	
Never smoker‡	23 (76.7)	11 (91.7)	34	
Stage				0.545
IB	3 (10)	0	3	
IIA	2 (6.7)	0	2	
IIIA	1 (3.3)	1 (3.3)	2	
IV	24 (80)	11 (91.7)	35	
EGFR mutation				0.178
Exon 18	1 (3.3)	1 (8.3)	2	
Exon 19	15 (50)	9 (75)	24	
Exon 21	14 (46.7)	2 (16.7)	16	
ECOG PS				0.651
0-1	24 (80)	11 (91.7)	35	
>2	6 (20)	1 (8.3)	7	

Values are presented as number (%).
*Someone who was currently smoking or had stopped smoking less than 1 year ago. †Someone who had stopped smoking 1 year or more ago. ‡Someone who had never smoked cigarettes.
EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Table 2. Response to EGFR-TKI

Variable	Initial EGFR-TKI	Second-line EGFR-TKI
Complete response	0	0
Partial response	31 (73.8)	9 (21.4)
Stable disease	10 (23.8)	18 (42.9)
Progressive disease	1 (2.4)	15 (35.7)
Response rate	31/42 (73.8)	9/42 (21.4)
Disease control rate	41/42 (97.6)	27/42 (64.3)
Response duration, mo	16.0 (1.1–83.3)	3.0 (0.3–11.2)

Values are presented as number (% or range).
Response rate=Complete response+Partial response, Disease control rate=Complete response+Partial response+Stable disease.
EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitor.

Table 3. Univariate and multivariate analysis

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Male	1	0.889	1	0.867
Female	0.95 (0.4–2.1)		1.1 (0.5–2.4)	
ECOG PS				
0-1	1	0.300	1	0.477
2-4	2.2 (1.0–4.8)		1.4 (0.6–3.3)	
Initial TKI TTP, mo				
≥10	1	0.037	1	0.030
<10	2.0 (1.0–3.9)		2.3 (1.1–4.9)	
Subtype of *EGFR* mutation				
Exon 19	1	<0.001	1	0.008
Exon 21	2.4 (1.1–4.9)		1.8 (0.8–3.8)	
Exon 18	3.5 (3.5–143.2)		18.3 (2.7–123.7)	
Interval duration*, day				
<90	1	0.056	1	0.019
≥90	2.14 (1.0–4.8)		2.8 (1.2–6.6)	

*Time interval between first epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and second EGFR-TKI.
HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; PS: performance status; TTP: time to progression.

PFS, and OS were estimated by the Kaplan-Meier method. All analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA).

Results

1. Patient characteristics

A total of 42 patients who received switched EGFR-TKI retreatment between January 2005 and March 2016 were included in the study. Patient baseline characteristics are shown in Table 1. The median age of patients was 64 years (range, 48–86 years), 76.2% of the patients were women, and 95.2% were ex-smokers or had never smoked. The quality of life measured as ECOG PS was 0 or 1 for 35 patients (83.3%).

All patients had histologically-confirmed adenocarcinoma and possessed activating *EGFR* mutations as determined by nested PCR. With regard to *EGFR* genotypes, 24 patients (57.1%) had an exon 19 deletion mutation, 16 (38.1%) had an exon 21 point mutation, and two (4.8%) had an exon 18 point mutation. Stage at initial diagnosis was less than IIIA in seven patients, but their disease advanced to stage IV in 16 months (range, 6.5–37.3 months). Initial EGFR-TKI treatment was gefitinib for 30 patients (71.4%) and erlotinib for 12 patients (28.6%).

2. Efficacy of EGFR treatment and retreatment

RR was 73.8% (31/42) for the first EGFR-TKI treatment and 21.4% (9/42) for retreatment following treatment failure with the first EGFR-TKI. DCR for the first EGFR-TKI treatment was 97.6% (41/42) and 64.3% (27/42) for the second EGFR-TKI (Table 2). There was no significant association between overall RR and DCR of the first and second EGFR-TKI (p=0.676 and p=0.357, respectively).

The time interval between treatment and retreatment ranged from 0 to 34.5 months (median, 7.1 months; 95% confidence interval [CI], 4.6–9.3 months), with 32 of 42 patients receiving systemic chemotherapy prior to the second EGFR-TKI treatment. There was no association between PFS and the number of chemotherapy cycles (p=0.412).

For the first EGFR-TKI treatment, the median PFS was 10.4 months (95% CI, 6.4–13.9) and the median PFS was 2.0 months for the second EGFR-TKI (95% CI, 1.2–2.9). After the second EGFR-TKI, 38/42 patients (90.5%) had experienced a PFS event (disease progression or death).

Results of univariate and multivariate analysis of potential predictors of treatment response are shown in Table 3. The analysis showed that longer PFS following switching was significantly associated with *EGFR* mutation subtype (p<0.001) and with a TTP longer than 10 months (p=0.037). No significant association was found between PFS and the in-

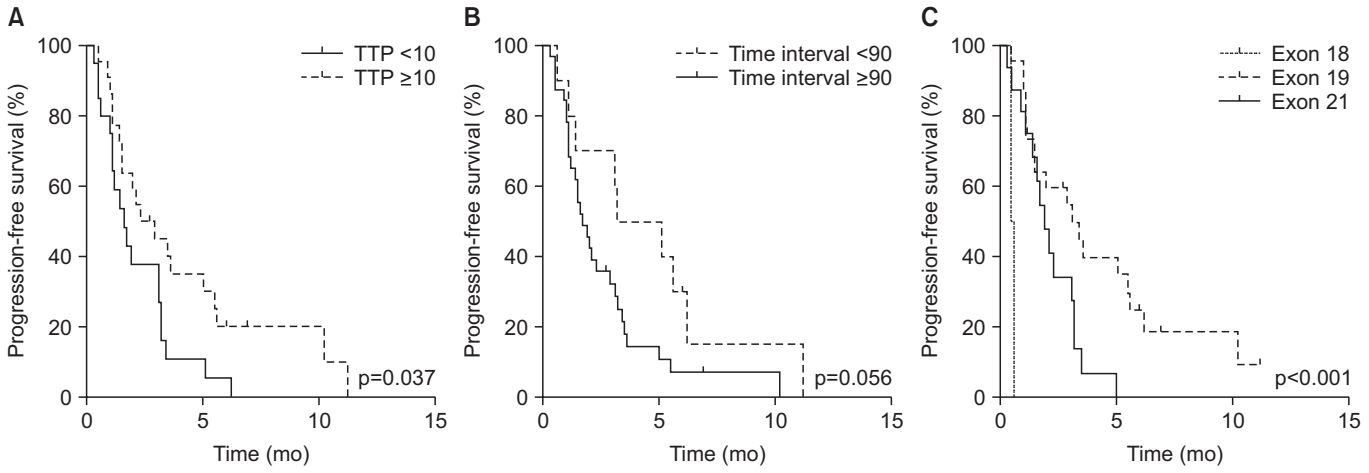

Figure 1. (A) Progression-free survival of second epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) by time to progression (TTP). (B) Progression-free survival of second EGFR-TKI by interval duration. (C) Progression-free survival of second EGFR-TKI by *EGFR* mutation subtype.

terval of time elapsed between the two EGFR-TKI treatments (p=0.056). There was no association between PFS and ECOG score (p=0.300), smoking history (p=0.089), or site of metastasis (p=0.594). In particular, no significant differences were noted in the PFS of patients having bone or brain metastases. Thirty-six patients had experienced an OS event, and median OS for EGFR-TKIs was 26.6 months (95% CI, 21.5–31.8 months).

After adjusting for sex, age, ECOG, PS, and response to EGFR-TKI, multivariate analysis showed that PFS was significantly longer in patients who had a TTP greater than 10 months following the first EGFR-TKI treatment (p=0.030) and for patients with an exon 19 mutation (p=0.008). Additionally, having a time interval between treatments of less than 90 days showed significantly longer PFS (p=0.019) (Figure 1).

The order of administration of gefitinib and erlotinib had no effect on the outcome. The median PFS was 2.3 months for patients treated with erlotinib after gefitinib failure, whereas the median PFS was 1.2 months for patients treated with gefitinib after erlotinib failure. The difference in median PFS did not achieve statistical significance (p=0.851).

Discussion

A number of mechanisms leading to EGFR-TKI resistance have been identified[12,14,15,22-24], and treatment options for patients with EGFR-TKI resistance are still being investigated. The T790M mutation, c-MET amplification, AXL activation, transformation to mesenchymal cells, and tumor heterogeneity are all possible mechanisms leading to resistance to first-generation EGFR-TKI[12-14]. At present, there are no proven treatment options for patients with acquired resistance except for those with the T790M mutation.

Although no prospective, randomized controlled trials have been conducted examining retreatment efficacy, there is some evidence that retreatment is effective in some patients. While the median PFS of first-line EGFR-TKI treatment was 10–14 months[6,7], PFS following EGFR-TKI re-administration was 2–13.8 months[18,25-28]. The greater variability in PFS following EGFR-TKI retreatment compared to that of first-line therapy might be attributable to differences in the study populations and small sample sizes. However, it suggests that we should search for factors predicting favorable outcome and narrow down the indication of EGFR-TKI retreatment according to those factors.

In our study, RR for EGFR-TKI retreatment was 21.4% and DCR was 64.3%. Previous studies have reported RR percentages ranging from 9.5% to 27.3% and DCR percentages ranging from 28.6% to 77.3%[17,18,21,25]. Our results showed that the RR for EGFR-TKI retreatment was not correlated with the RR for first-line EGFR-TKI, while longer PFS for second-line EGFR-TKI was related to longer TTP for first-line EGFR-TKI. These data suggest that a favorable outcome from first-line EGFR-TKI should be considered when selecting patients as candidates for retreatment.

The type of retreatment protocol to use is another consideration. Retreating with the same EGFR-TKI[20,21,25,29,30], switching to another EGFR-TKI[17,18,26-28], and using EGFR-TKI therapy in combination with standard chemotherapy[31] have all been attempted. Tang et al.[32] conducted a prospective study in which patients who showed a response to gefitinib therapy were enrolled and divided into two categories based on whether the retreatment was with gefitinib or erlotinib. There was no significant difference in the outcome between the two groups. In general, efficacy does not seem to be associated with the

kind of EGFR-TKI used for retreatment[20,32] but is associated with the response to prior EGFR-TKI treatment[19,21,28,33].

The time interval between the two EGFR-TKI treatments also should be scrutinized. There have only been a few studies reporting effects of the time interval between the first and second EGFR-TKI treatment[32-34]. These studies found that more favorable outcomes were associated with a time interval of more than 3 months. Longer intervals could provide more time for EGFR-TKI–sensitive cells to regrow and respond to the second EGFR-TKI treatment. However, the effect of the time interval should be evaluated in the context of any conventional chemotherapy administered during the interval period. Chemotherapy can alter both EGFR phosphorylation and the proportion of EGFR-TKI sensitive and resistant tumor cells and can therefore have an impact on the effect of the second EGFR-TKI treatment. Chin et al.[35] showed that lung cancer cells exposed to cisplatin exhibited reduced sensitivity to erlotinib through down-regulation of PTEN.

In our study, chemotherapy during the EGFR-TKI–free interval was not related to PFS, but interval durations of less than 90 days were associated with longer PFS. Current National Comprehensive Cancer Network guidelines recommend continuation of EGFR-TKI in asymptomatic progression[36], but the Korean regulations currently do not permit continued treatment. In the case of asymptomatic progression, continuation of EGFR-TKI might be helpful because the drug can still inhibit EGFR-TKI–sensitive clones having rapid growth potential regardless of the presence of slower-growing, resistant cancer cells[14]. Hence, our results may reflect the difference in growth rate between EGFR-TKI–sensitive and –resistant clones because the shorter time interval can be considered similar to continued treatment. However, the real effect of the time interval in retreatment should be further investigated.

Our study was retrospective and had a small sample size; therefore, it is not possible to draw any definitive conclusions regarding positive predictors of retreatment outcomes. However, our findings suggest that TTP longer than 10 months after first-line EGFR-TKI therapy, an EGFR-TKI–free interval less than 90 days, and having an exon 19 deletion mutation are predictors of a favorable response to retreatment.

Identification of positive retreatment outcome predictors may help guide selection of patients who are more likely to benefit from EGFR-TKI retreatment. Appropriate retreatment candidate selection also would reduce unnecessary medical costs and undesirable toxicity. Therefore, along with continuing efforts to elucidate the precise mechanisms of resistance in patients with mutations other than T790M, studies should also be conducted to identify the positive predictors of EGFR-TKI retreatment response.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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