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Clinical characteristics of T790M-positive lung adenocarcinoma after resistance to epidermal growth factor receptor-tyrosine kinase inhibitors with an emphasis on brain metastasis and survival

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ABSTRACT

Objectives: We aimed to investigate the clinical characteristics of lung adenocarcinomas with acquired *EGFR* T790M mutation focusing on brain metastasis and survival.

Materials and methods: Our study included patients who had lung adenocarcinoma harboring *EGFR* mutation at 1st biopsy and then underwent 2nd biopsy after resistance to first- or second-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). Statistical analyses were performed to examine the associations between clinicopathologic features of lung adenocarcinoma and presence of acquired T790M mutation.

Results: A total of 111 patients were identified. Of these, 58 patients (52.3%) had acquired T790M mutations. Osimertinib was used in 29 patients (26.1%) after resistance to first- or second-generation TKIs. The T790M mutation was more frequently found in patients with exon 19 deletion than in those with L858R mutations ($p = .026$) and in patients who had longer treatment duration with EGFR-TKI ($p = .0398$). Multivariate analysis revealed that exon 19 deletion ($p = .003$) were independently associated with T790M mutation. Patients with acquired T790M mutation showed a longer progression-free survival. In addition, patients who had T790M mutation or who received osimertinib treatment had a longer overall and post-progression survival than patients who did not. Brain metastasis-free survival was also longer in the T790M-positive group or osimertinib-treated group among patients who had no brain metastasis at the time of diagnosis. Osimertinib treatment was independently associated with longer overall, post-progression, and brain metastasis-free survival.

Conclusion: The status of acquired T790M mutation was correlated with exon 19 deletion and longer progression-free survival to first- or second-generation EGFR-TKIs. A third-generation EGFR-TKI, osimertinib, was strongly associated with brain metastasis-free survival as well as other survival indicators in patients with *EGFR*-mutant lung adenocarcinoma.

1. Introduction

Advanced non-small-cell lung carcinomas (NSCLCs) with activating *EGFR* mutations initially respond to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) [1–3]. However, most patients usually progress after 12 months of treatment [4,5]. Various mechanisms are involved in acquired resistance to EGFR-TKIs, including *EGFR* T790M secondary mutation, *MET* gene amplification, *HER2* gene amplification, and histologic changes such as small-cell lung carcinoma (SCLC) transformation [4–6]. Among these, the most common resistance mechanism is T790M mutation in the *EGFR* gene, which accounts for 50%–60% of EGFR-TKI resistance [4,5,7]. Recently, osimertinib has been approved for the treatment of T790M-positive NSCLCs [8–10]. Thus, evaluating T790M mutation has become important in the treatment of patients with lung cancer harboring *EGFR* mutation. However, detailed analyses on the frequency and clinicopathologic characteristics of T790M mutant lung cancers including survival data are needed.

Furthermore, the association between brain metastasis and T790M mutation or osimertinib has not been well investigated. Previous studies showed that as many as 40% of patients diagnosed with NSCLC will develop brain metastases during the course of their disease, and this risk may be even greater in those who harbor an *EGFR* mutation [11,12]. In addition, patients with *EGFR*-mutant NSCLC may have a high likelihood of being diagnosed with brain metastases because of prolonged survival from targeted agents and the increased quality of

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brain imaging [13]. Thus, clarification on the association between brain metastasis and a resistance mutation to targeted agents may give an insight in the optimal management of patients with *EGFR*-mutant NSCLC.

In this study, we investigated the clinical characteristics of NSCLCs with acquired *EGFR* T790M mutation and their association with survival and brain metastasis in East Asian patients. We also investigated the association between these clinical features and osmertinib therapy after resistance to first- or second-generation EGFR-TKIs.

2. Material and methods

2.1. Patients

The institutional review board approved this retrospective study. Written informed consent from the patients was waived due to the retrospective nature of the study. The inclusion criteria of our study are as follows: lung adenocarcinoma, presence of *EGFR* mutation at 1st biopsy before treatment, treatment with first- or second-generation EGFR-TKIs, and 2nd biopsy after resistance between January 2012 and June 2016. Clinical data including age, sex, smoking history, date of initial diagnosis, date of rebiopsy, rebiopsy site, extrathoracic metastasis, interval between prior EGFR-TKI and rebiopsy, total duration of EGFR-TKI treatment, and survival information were extracted from medical records. Extrathoracic metastasis was defined as metastatic lung tumor that was found in other organs except lung–to-lung metastasis, malignant pleural seeding, and malignant pleural effusion. For brain metastasis, brain magnetic resonance imaging was performed at the time of diagnosis and every 6 months if there was no brain metastasis at the time of initial diagnosis or immediately upon presentation of neurological symptoms.

2.2. EGFR mutation analysis

To determine the *EGFR* mutation status, DNA was extracted using a DNeasy isolation kit (Qiagen, Valencia, CA, USA) from formalin-fixed paraffin-embedded tissues according to the manufacturer's instructions. PNAClamp™ EGFR Mutation Detection Kit (PANAGENE, Daejeon, Korea) was used in all cases.

2.3. Statistical analysis

Relationships between clinicopathologic parameters and T790M status were evaluated using the Chi-square test (Table 1). When an expected frequency is less than 5, the Fisher's exact test was used. Multivariate logistic regression analysis was performed to examine independent factors predicting T790M status among significantly correlated variables. Progression-free survival, overall survival, post-progression survival, and brain metastasis-free survival were evaluated among patients according to T790M mutation status or osimertinib therapy status using the Kaplan–Meier method, and statistical differences in survival times were determined using the log-rank test. Post-progression survival was defined as overall survival minus progression-free survival for first- or second-generation EGFR-TKIs. The Cox proportional hazards model was applied for multivariate survival analysis. A p value of < 0.05 was considered to indicate a significant difference. All statistical analyses were conducted using IBM SPSS Statistics v.20 (IBM, Armonk, New York, USA).

3. Results

3.1. Patient characteristics

A total of 111 patients comprising 45 men (40.5%) and 66 women (59.5%) were identified during the study period. The mean age was 59.4 years (range, 25–80 years). There were 77 non-smokers (69.4%) and 34 smokers (30.6%). The clinicopathologic characteristics of the patients are summarized in Table 1. *EGFR* mutation status in the first biopsy showed Exon 19 deletion in 54 patients (48.6%), L858R substitution in 51 (45.9%), and other mutations in 6 (5.4%). Gefitinib was used as first-line EGFR-TKI in 80 patients (72.1%), erlotinib in 27 (24.3%), and afatinib in 4 (3.6%). The mean total duration of first- or second-generation EGFR-TKI treatment was 14.2 months (range, 1–45 months). Osimertinib was used in 29 patients (26.1%) after resistance to first- or second-generation TKIs. Of them, 24 (82.8%) harbored T790M mutation and 5 (17.2%) did not.

Table 1
Patient characteristics according to T790M mutation status.

Variables	All, n (%)	T790 M positive, n (%)	T790 M negative, n (%)	p-value
Number of cases	111 (100.0)	58 (52.3)	53 (47.7)	
Age, mean (range)	59.4 (25–80)	59.5 (25–80)	59.4 (31–79)	0.948
< 60 years	52 (46.8)	27 (46.6)	25 (47.2)	
≥60 years	59 (53.2)	31 (53.4)	28 (52.8)	
Sex				0.174
Male	45 (40.5)	20 (34.5)	25 (47.2)	
Female	66 (59.5)	38 (65.5)	28 (52.8)	
Smoking history				0.467
Non-smoker	77 (69.4)	42 (72.4)	35 (66.0)	
Smoker	34 (30.6)	16 (27.6)	18 (34.0)	
EGFR mutation type at 1st biopsy				0.017
Exon 19 deletion	54 (48.6)	35 (60.3)	19 (35.8)	
L858R	51 (45.9)	22 (37.9)	29 (54.7)	
Others	6 (5.4)	1 (1.7)	5 (9.4)	
Extrathoracic metastasis				0.476
Present	98 (88.3)	50 (86.2)	48 (90.6)	
Absent	13 (11.7)	8 (13.8)	5 (9.4)	
EGFR-TKI				0.924
Gefitinib	80 (72.1)	41 (70.7)	39 (73.6)	
Erlotinib	27 (24.3)	15 (25.9)	12 (22.6)	
Afatinib	4 (3.6)	2 (3.4)	2 (1.8)	
Line of initial EGFR-TKI				0.471
First	71 (64.0)	34 (58.6)	37 (69.8)	
Second	35 (31.5)	21 (36.2)	14 (26.4)	
Third	5 (4.5)	3 (5.2)	2 (3.8)	
Interval between prior EGFR-TKI and rebiopsy				0.036
< 12 months	24 (21.6)	8 (13.8)	16 (30.2)	
≥12 months	87 (78.4)	50 (86.2)	37 (69.8)	
Total duration of EGFR-TKI treatment				0.015
< 14 months	60 (54.1)	25 (43.1)	35 (66.0)	
≥14 months	51 (45.9)	33 (56.9)	18 (34.0)	
SCLC transformation				0.008
Present	6 (5.4)	0 (0.0)	6 (11.3)	
Absent	105 (94.6)	58 (100.0)	47 (88.7)	
Survival				0.030
Alive	58 (52.3)	36 (62.1)	22 (41.5)	
Dead	53 (47.7)	22 (37.9)	31 (58.5)	

Secondary T790M mutation analysis was done using samples from the lungs (n = 48, 43.2%), lymph node (n = 29, 26.1%), liver (n = 15, 13.5%), fluid cell block (n = 9, 8.1%), bone and soft tissue (n = 5, 4.5%), and other sites (n = 5, 4.5%) (Table 2). SCLC transformation was observed in 6 patients (5.4%).

3.2. Characteristics of the patients with T790M mutation

There were 58 patients with secondary T790M mutation (52.3%). The characteristics of these 58 patients are outlined in Table 1. No associations between T790M mutation status and age, sex, smoking history, extrathoracic metastases, EGFR-TKI agents, and line of initial