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Acquired *EGFR* T790M Mutation After Relapse Following EGFR-TKI Therapy: A Population-based Multi-institutional Study

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Abstract. *Aim: To describe the prevalence and determinants of acquired epidermal growth factor receptor (EGFR) T790M gene mutation in a clinical practice setting. Materials and Methods: We performed a retrospective chart review study between January 2013 and November 2017 across multiple institutes, covering a population of 3 million people. Results: We reviewed the charts of 233 patients non-small cell lung cancer with EGFR mutations. Of them, 99 (42.5%) patients had acquired T790M mutations in EGFR. Patients ≥75 years old and patients with an exon 19 deletion had higher rates of acquired T790M mutation than did younger patients and those with an exon 21 L858R mutation. In 75 patients treated with afatinib, 34 (45.3%) patients had acquired T790M mutation. The sensitivity of T790M mutation detection was lower in plasma specimens than in biopsy specimens. Conclusion: This population-based study confirms previous studies and highlights potential determinants of acquired T790M mutation to be considered in clinical practice.*

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Key Words: Acquired *EGFR* T790M gene mutation, epidermal growth factor; receptor-tyrosine kinase inhibitor, EGFR-TKI, population-based study.

Various mechanisms of resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) have been identified, with the most reported mechanism of acquired resistance being secondary T790M mutation in exon 20 of the *EGFR* gene (1, 2). Certain studies have reported acquisition of T790M mutation following EGFR-TKI therapy. These

studies included only patients registered in clinical trials for EGFR-TKI therapy (3-5) and studied only a small number of patients at a single institute (6-10). However, it has not yet been confirmed whether these results reflect the prevalence of acquired T790M mutation in real clinical practice. Therefore, a population-based evaluation of acquired T790M mutation across multiple institutes is needed to provide a more accurate grasp of the situation (11).

Testing for T790M mutation in patients is not often performed in a clinical setting due to the absence of non-invasive, sensitive tests. Re-biopsies performed to examine acquired T790M mutations are associated with risks as well as discomfort and may not provide enough material for genetic analysis in some patients. Circulating tumor DNA has been identified as a specific and sensitive biomarker that can be used for the detection of *EGFR* mutations (12, 13). In addition, liquid biopsy to detect circulating tumor DNA using plasma specimens is a less-invasive means of detecting the T790M mutation (12, 13). However, the sensitivity of the T790M mutation test in plasma specimens is inferior, so further improvement to the test is needed before its utility in a clinical setting can be evaluated.

As for the mechanism of acquired drug resistance after the administration of EGFR-TKI, about half of patients receiving gefitinib and erlotinib are reported to have a T790M mutation. However, a few studies with fewer than 42 patients have found acquired T790M mutations after afatinib treatment (4, 7, 9, 11, 14-16). In order to better understand the current situation of acquired T790M mutation in the clinical practice setting, we performed a retrospective, population-based, multi-institutional study.

Materials and Methods

Patients. This multi-institutional, population-based study included patients with advanced *EGFR*-mutated non-small cell lung cancer (NSCLC) who had a T790M gene mutation test after the administration of one or more TKIs at 15 medical institutes in the Ibaraki prefecture between January 2013 and November 2017. The Ibaraki prefecture in Japan covers an area of 6,095 km^2 and a population of 3 million people. Patients who had a T790M mutation at initial diagnosis were excluded from this study. We investigated the following patient characteristics: age, gender, *EGFR* mutation status, histology of NSCLC, sites where specimens were obtained, specimen used for T790M gene mutation determination, and the presence or absence of a T790M mutation.

Ethics statement. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects in Japan. Informed consent for *EGFR* mutational analysis was obtained from patients, since this analysis was performed under the Japanese insurance system. This study was approved by the Institutional Review Board such as that of the Mito Kyodo General Hospital (no. 17-20) or independent Ethics Committee associated with each study institute.

Table I. *Characteristics of 233 patients with epidermal growth factor (EGFR)-mutated non-small cell lung cancer.*

Characteristic	Value
Age, years	
Median (range)	70 (32-93)
≥75	72 (30.9%)
<75	161 (69.1%)
Gender, n (%)	
Male	89 (38.2%)
Female	144 (61.8%)
Histology, n (%)	
Adenocarcinoma	226 (97.0%)
Squamous cell carcinoma	4 (1.7%)
Adenosquamous cell carcinoma	2 (0.9%)
Other	1 (0.4%)
Pathological stage, n (%)	
IIIA-B	54 (23.2%)
IVA-B	179 (76.8%)
EGFR mutation, n (%)	
Exon 19 deletion	122 (52.4%)
Exon 21 L858R	103 (44.2%)
Other	8 (3.4%)
Specimen type obtained, n (%)*	
Biopsy	99 (42.5%)
Cytology	41 (17.6%)
Plasma	127 (54.5%)

*Thirty-four patients had T790M mutation tests using both plasma and biopsy or cytology specimens.

T790M mutation analysis. Specimens were obtained from each patient who experienced relapse after the administration of one or more EGFR-TKIs. T790M mutation analysis was performed by the assay 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, cytology specimens, and plasma specimens. In some patients, T790M genetic tests were performed using biopsy/cytology and plasma specimens.

Statistical analysis. Differences in proportions between the two independent groups were compared by the chi-square test. A value of $p<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Two hundred and thirty-three patients with NSCLC harboring *EGFR* mutations who had undergone a T790M mutation test after acquired resistance to EGFR-TKI in 15 institutes in a prefecture of Japan, covering a population of 3 million, were included in this study. Patient characteristics are shown in Table I. The median age was 70 (range=32-93) years. One hundred and forty-four (61.8%) patients were female. Two hundred and twenty-six (97.0%) patients had been diagnosed with lung adenocarcinoma with activating *EGFR* mutations at initial

Table II. *Rate of epidermal growth factor (EGFR)-T790M mutation according to patient characteristics.*

	EGFR-T790M mutation		
	Positive	Negative	*p*-Value
Age			
≥75 years	40 (55.6%)	32 (46.4%)	
<75 years	59 (36.6%)	102 (63.4%)	0.0096
Gender			
Male	40 (44.9%)	49 (55.1%)	
Female	59 (41.0%)	85 (59.0%)	0.5868
Female, ≥75 years	27 (50.9%)	26 (49.1%)	
Patients other than above	72 (40.0%)	108 (60.0%)	0.2057
Female, ≥65 years	42 (38.9%)	66 (61.1%)	
Patients other than above	57 (45.6%)	68 (54.4%)	0.3525
Histology			
Adenocarcinoma	95 (42.0%)	131 (58.0%)	
Non-adenocarcinoma	4 (57.1%)	3 (42.9%)	0.4620
EGFR mutation#			
Exon19 deletion	66 (54.1%)	56 (45.9%)	
Exon 21 L858R	33 (32.0%)	70 (68.0%)	0.0012
Specimen type			
Biopsy only, 71 patients	45 (63.4%)	26 (36.6%)	–
Cytology only*, 35 patients	17 (48.6%)	18 (51.4%)	–
Plasma only**, 93 patients	27 (29.0%)	66 (71.0%)	–
Biopsy/cytology & plasma, 34 patients	15 (44.1%)	19 (55.9%)	–

#EGFR mutation: 122 patients had Exon 19 deletion, 103 patients had Exon 21 L858R, and 8 patients had other mutations. Significantly different at *p=0.2083 *vs*. biopsy; **p=0.0001 *vs*. biopsy, p=0.0591 *vs*. cytology.

diagnosis. One hundred and twenty-two (52.4%), 103 (44.2%) and eight (3.4%) patients had an exon 19 deletion, an exon 21 L858R mutation or other mutations before the initial EGFR-TKI treatment, respectively. Of 233 patients, 99, 41 and 127 patients underwent a T790M mutation test using biopsy, cytology and plasma specimens, respectively; 34 patients had T790M mutation tests performed both on biopsy/cytology and plasma specimens. Ninety-nine (42.5%) out of 233 patients had a T790M mutation either in biopsy/cytology specimens or in plasma specimens, or in both.

Table II shows the patient characteristics and the rate of T790M mutation. The rate of the T790M mutation was significantly higher in patients ≥75 years old than in those younger (p=0.0096). Sixty-six (54.1%) out of the 122 patients with an exon 19 deletion and 33 (32.0%) out of the 103 patients with exon 21 L858R had acquired a T790M mutation. There was a significant difference in the prevalence of T790M mutations between the two major EGFR mutations (p=0.0012).

Specimen types, sites where specimens were obtained, and prevalence of T790M mutation. Table II depicts specimen types and the rate of T790M mutation. Seventy-one, 35, and 93 patients had biopsy, cytology, and plasma specimens, respectively, confirming acquisition of T790M mutation in 63.4%, 48.6% and 25.8%, respectively. There was no difference in the rate of T790M mutation between the biopsy specimens and the cytology specimens (p=0.2083), but the rate of acquired T790M mutation in the biopsy specimens was higher than that in the plasma specimens (p=0.0001). Table III shows details of the sites where specimens were obtained and the rate of T790M mutation.

Concordance and discordance between biopsy/cytology specimens and plasma specimens. Thirty-four patients had a T790M mutation test using both plasma and biopsy or cytology specimens. Thirteen (43.3%) out of the 34 patients were found to have acquired a T790M mutation by one or both specimens. Of these, tests in 21 were both negative and in three patients were both positive for T790M mutation. Biopsy/cytology specimens were positive for T790M mutation in eight patients but were negative in the plasma specimens; in two patients, testing was negative for T790M mutation in biopsy/cytology specimens but was positive in plasma specimens. Rate of concordance was 70.6%.

Acquired resistance of T790M following TKI therapy. Fifty-seven (42.9%) out of 133 patients and 34 (45.7%) out of 105 patients who were treated with gefitinib and erlotinib,

respectively, had subsequently acquired a T790M mutation. Out of 75 patients treated with afatinib, 34 (45.3%) had acquired a T790M mutation (Table IV).

Table IV also shows the acquired resistance of a T790M mutation in patients treated with two and three TKIs. There was no significant difference in induction of T790M mutation between patients treated with two TKIs and those treated with three (p=0.3282).

Discussion

Among the mechanisms of acquired resistance to first-generation EGFR-TKIs, acquired T790M mutation is the most common mechanism. Some recent reviews have reported that an acquired T790M mutation was found in approximately 50-60% of patients with EGFR-TKI resistant disease (1, 2, 17). These results were based on studies on patients registered in clinical trials for EGFR-TKI therapy (3-5) and on small numbers of patients within a single institute (6-10). The present population-based study reviewed patient records from real clinical practice, revealing that acquired T790M mutation was present in 42.5% of patients with acquired resistance to EGFR-TKIs. These results are similar to those of the previous studies (3-10). With the exception of Ko *et al*. (6), previous studies have found that the prevalence of the T790M mutation is significantly higher in NSCLCs with an exon 19 deletion than in those with exon 21 L858R mutations (9, 11, 14, 16), and our results are consistent with those. Interestingly, we found that the rate of acquired T790M mutation was significantly higher in patients ≥75 years old than in younger ones. In previous reports on T790M mutation, the median age of patients with *EGFR* mutation was 63-65 years (4, 7, 14, 15), whereas in our study it was 70 years. It is still not understood why the elderly patients in this study had a higher rate of T790M mutation than younger patients. The difference in rates of T790M mutation between elderly and young patients might be due to difference in their background. To clarify why this would lead to differences in prevalence, investigation of more detailed clinical information would be required.

There was no difference in the rate of T790M mutations between the biopsy specimens and the cytology specimens, but there was a significant difference in the those between the biopsy and the plasma specimens. Thress *et al*. reported the positivity rate of simultaneous measurements of tissue specimens and plasma specimens as 81% and 58%, respectively (3). Other researchers have found that the positive rate of acquired T790M mutations in plasma specimens was around 40% (12, 13). Jenkins *et al*. reported that plasma testing did not detect the T790M mutation in plasma-circulating tumor DNA of approximately 40% of patients with a T790M-positive tissue test result (5). In our results, the prevalence of an acquired T790M mutation was 22.8%, which is lower than previous reports (3, 12, 13). Our result was probably influenced by the high proportion of measurement in patients with a negative test for acquired T790M mutation in biopsy specimens and by those who had difficulty in taking tissue specimens.

In this study, the prevalence of acquired T790M mutations was evaluated simultaneously in 34 patients with biopsy/cytology specimens and plasma specimens. It is interesting that there were two patients who were negative for acquired T790M mutation in biopsy/cytology specimens but positive in their plasma specimens. It is desirable to develop methods that can accurately evaluate specimens obtained by less invasive techniques.

Regarding the mechanism of acquired drug resistance after administration of EGFR-TKIs, about half of the patients treated with gefitinib and erlotinib were reported to have an acquired T790M mutation. For the second-generation TKI, afatinib, acquired T790M mutation as a resistance mechanism has not

Table III. *Rate of epidermal growth factor (EGFR)-T790M mutation according to site of specimen analyzed.*

Specimen	Site	T790M mutation rate, n (%)
Biopsy	Liver	6/8 (75.0%)
	Pleura	0/2 (0%)
	Bone	0/2 (0%)
	Lung (trans-bronchial)	27/56 (48.2%)
	Sub cutaneous tissue	0/1 (0%)
	Brain	0/1 (0%)
	Lymph nodes	7/9 (77.8%)
	Not specified	14/19 (73.7%)
Cytology	Pleural fluid	12/27 (44.4%)
	Pericardial fluid	1/3 (33.3%)
	Cerebrospinal fluid	1/5 (25.0%)
	Ascites	1/2 (50.0%)
	Not specified	3/3 (100%)

Table IV. *Acquired resistance of T790M mutation in patients treated with two and three tyrosine kinase inhibitors (TKIs).*

TKI treatment history	T790M mutation rate, n (%)
Gefitinib	57/133 (42.9%)
Erlotinib	48/105 (45.7%)
Afatinib	34/75 (45.3%)
First-generation TKI and afatinib[#]	19/34 (55.9%)
Gefitinib and afatinib	7/11 (63.6%)
Gefitinib and erlotinib	8/16 (50.0%)
Erlotinib and afatinib	4/7 (57.1%)
Three TKIs*	1/4 (25.0%)

[#]The order of administration of these two TKIs was not specified. *The order of administration of three TKIs was not specified.

been fully studied. Some previous studies have reported a rate of 25.0%-47.6% for acquired T790M mutation after upon recurrence after the administration of afatinib treatment in patients with *EGFR* mutation (4, 7, 9, 11, 14-16). However, only 3-42 patients were treated with afatinib, with many results coming from a single institute (4, 7, 9, 14-16). One study from Kyushu University reported the results of 37 patients across 13 institutes, and acquired T790M mutations upon recurrence after the administration of afatinib were found in 43.2% of patients with *EGFR* mutation (11). In the present study, the corresponding number was 34 (45.3%) out of 75 such patients. At the present time, this is the largest scale study evaluating acquired T790M mutations in recurrence after afatinib therapy. Recently, Wu *et al*. reported that 20 out of 42 patients had acquired a T790M mutation after afatinib administration and found that there was no difference in the rate of acquired T790M mutation between those treated with first-generation EGFR-TKI and naive patients treated with first-generation EGFR-TKI (46.4% and 47.6%, respectively) (14). In our patients, the rate of acquired T790M mutations was similar in any combination of EGFR-TKI (gefitinib and erlotinib, 50%; gefitinib and afatinib, 63.6%; erlotinib and afatinib, 57.1%). Only four patients were examined for T790M gene mutation after the administration of three TKIs, and only one of these patients acquired a T790M mutation. Although this is an interesting research question, we could not draw any conclusions from this result due to the small number of patients.

This population-based, multi-institutional study covering a single prefecture has several limitations. Firstly, it was a retrospective study with patients from miscellaneous backgrounds. The specimens evaluated, the methods of obtaining specimens, and the methods for examining T790M were not unified. The limited number of patients and the short period of investigation were also limitations. In addition, there was no information on the therapeutic effects and the survival times. However, this study reflected real practice without selection bias, and our results might be used to complement clinical trial results for patients collected by selection bias. Therefore, it is considered to have clinical significance.

In conclusion, we studied the rate of acquired T790M gene mutations in biopsy/cytology specimens and plasma specimens in patients experiencing recurrence following TKI therapy. The rate of acquired T790M mutation after afatinib administration was also evaluated in this population-based, multi-institutional study. We believe that it is important to understand, not only the results of patients undergoing clinical trials, but also the patients in current clinical practice in order to fully comprehend drug resistance due to acquired *EGFR* T790M gene mutation.

Conflicts of Interest

None declared.

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