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Predictors of the acquisition of T790M mutation in EGFR-mutant metastatic lung cancer patients who were treated with EGFR inhibitors

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Abstract:

BACKGROUND AND AIM: The aim of this study was to assess the factors affecting T790M mutation acquisition in epidermal growth factor receptor (EGFR)-mutant metastatic non-small cell lung cancer (mNSCLC) patients.

METHODS: We evaluated the data of EGFR-mutant metastatic lung cancer patients who progressed under tyrosine kinase inhibitors (TKIs) retrospectively. Logistic regression analysis was used to examine the association between the acquisition of the T790M mutation and clinicopathological characteristics.

RESULTS: The study enlisted the participation of 52 patients. Exon 19, Exon 21, and uncommon mutation distributions at diagnosis were 67.3%, 23.1%, and 9.6%, respectively. After the disease progressed under TKIs, the presence of T790M mutation was evaluated with liquid (75%) or tissue biopsies (25%). In 33 (63.5%) patients, T790M mutations were detected. Gender, age, de novo metastatic disease, primary tumor localization (left or right lung), number of metastatic sites, type of TKI, smoking, objective response, and type of biopsy were not statistically significant factors for T790M mutation acquisition in logistic regression analysis. However, progression-free survival (PFS) time (p=0.03) and EGFR inhibitor-related toxicity (p=0.004) were found as predictors of acquisition of T790M mutation.

CONCLUSIONS: Due to the rarity of T790M mutations in EGFR-mutant mNSCLC patients treated with EGFR inhibitors, evidence of their acquisition is limited. In this study, we detected that the presence of EGFR inhibitor-related toxicity and PFS time longer than 12 months were predictors for T790M mutation acquisition.

Keywords:

EGFR mutations, non-small cell lung cancer, T790M mutations, prognosis

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Introduction

Lung cancer is one of the most common malignancies globally, leading to morbidity and death in both males and females. In the treatment of metastatic lung cancer, individual treatments have been applied to the discovery of driver mutations in recent years. Epidermal growth factor receptor (EGFR) mutation is one of the most detected driver mutations seen in lung cancer, and its frequency varies according to ethnicity, gender, age, and smoking history.[1] EGFR mutation is detected in approximately 12%–47% of metastatic non-small cell lung cancer (mNSCLC) patients.[2] In the presence of EGFR mutation, EGFR tyrosine kinase inhibitors (TKIs) are used in the treatment of patients with mNSCLC. In many randomized studies, gefitinib, erlotinib, afatinib, and third-generation osimertinib were found to be superior to cytotoxic chemotherapy in terms of survival outcomes.[3,4]

Many resistance mechanisms have been identified against EGFR inhibitors, such as gatekeeper T790M point mutation on exon 20, histological transformation, activation of parallel signaling pathways, and activation of downstream signaling pathways.[5] The most common resistance mutation to EGFR inhibitors is T790M and is detected in approximately 0.7% of patients with lung cancer at diagnosis.[6] However, with EGFR inhibitor treatment, T790M resistance mutation may develop in 50%–60% of patients, often within the first year.[7] Osimertinib has been shown to provide clinically significant survival results in patients who progress under first-line EGFR TKI and develop T790M mutation.[8] In the literature, the factors or mechanisms that affect the development of T790M mutation under EGFR TKI treatment have not been fully defined. The aim of this study was to evaluate the effect of clinical, pathological, and treatment-related factors on the acquisition of T790M mutation in patients with mNSCLC treated with EGFR TKI.

Materials and Methods

Patients and data collection

Our study was designed retrospectively. Approvals from ethical committees were obtained before the study (Date: June 28, 2021, number: 266738). The study was conducted in accordance with the declaration of Helsinki and good clinical practice guidelines. The patients to be included in the study were determined through the hospital data processing system. Patients who received treatment in the single oncology center outpatient clinic between 2015 and 2020 were included in the study. All patients involved in the study had an EGFR mutation at baseline, were treated with an EGFR inhibitor, and had the T790M mutation studied after progression. Patients who did not have sufficient data for statistical analysis were excluded from the study. The pathological, clinical, radiological, and treatment (surgery, chemotherapy, and radiotherapy) data of the patients were recorded from the patient files. The smoking history of the patients was noted. The tumor stage at diagnosis was performed according to the TNM classification.

TKI types and doses used in the patients were recorded. Treatment-related responses of patients were recorded and classified according to RECIST 1.1 criteria. T790M mutation after progression under EGFR inhibitor treatment was evaluated by taking liquid or tissue samples. Presence of EGFR mutation and T790M mutation after progression was assessed by the real-time PCR method in a standardized laboratory. Univariate and multivariate analyses for parameters affecting the development of T790M mutation in patients were performed.

The time from EGFR inhibitor onset to progression was defined as progression-free survival (PFS). The death status of the patients was checked through the death notification system of the Ministry of Health. The time from the onset of metastasis to death was defined as overall survival (OS). Univariate and multivariate analyses were performed for factors affecting OS.

Statistical analysis

All statistics were performed with SPSS 25 (IBM Corp., Armonk, NY, USA). Continuous variables were indicated by the median values (minimum–maximum), and categorical variables were shown by numbers and percentages. Survival analyses and curves were performed using the Kaplan–Meier method. To predict the emergence of the T790M mutation, we used both univariate and multivariate logistic regression analyses. Also, variables that were found to be significant in other studies on the subject in the literature were included in the analyses. Overlapping variables were not used. For model fit, the Hosmer-Lemeshow test was used. A type-1 error level of less than 5% was defined as statistically significant.

Results

Patient characteristics

Fifty-nine patients whose T790M mutation status was evaluated were identified. However, seven patients were excluded, and an analysis was performed with the data of 52 patients. The median age was 58 (33–78) years. The most common primary tumor location was the right lung (59.6%). The primary histopathological subtype was adenocarcinoma (98.1%). The most common EGFR mutations detected at the time of diagnosis were exon 19 (67.3%) and exon 21 (23.1%), respectively. Of the total patients, 45 (86.5%) patients presented with de novo metastatic at the time of diagnosis. Bone (63.5%), brain (28.8%), and liver (13.5%) were the most common extrapulmonary metastatic sites. The clinical and pathological features of the patients are shown in Table 1.

Treatment approaches and survival outcomes

Primary lung surgery was performed on 4 (7.7%) patients. Palliative chemotherapy was applied to 15 (28.8%) patients before EGFR TKI, and 22 (42.3%) patients received palliative radiotherapy (Table 1). As EGFR TKI, 44 (84.6%) patients used erlotinib, 4 (7.7%) patients used gefitinib, and 4 (7.7%) patients used afatinib. The objective response rate to EGFR inhibitors was found to be 86.5%. EGFR TKI-related toxicity was observed to be grade 1–2 in 30.8% and grade 3–4 in 9.6% of patients. The hematologic toxicity rate was 7.7%, and the most common nonhematologic toxicity was dermatitis (26.9%). T790M mutation development in patients was evaluated by using liquid (75%) or tissue biopsy (25%). T790M mutation was detected in 33 (63.5%) patients. Thirty (90.9%) patients with T790M mutation continued treatment with osimertinib. Clinical and pathological factors predicting the development of T790M mutation were evaluated; EGFR TKI-related toxicity (p=0.004) and PFS time (p=0.03) were found to be statistically significant factors in multivariate analysis (Table 2). The median follow-up time was 32 months. At the time of analysis, 30 (57.7%) patients had died. In all patients, the median OS time was 44.8 months (95% CI, 27.5–62.0) [Fig. 1]. The five-year survival rate was detected as 31.4%. The median survival time was found to be 50.8 months (95% CI, 40.7–60.9) in patients with T790M mutation and 32.8 months (22.7–42.8) in patients without T790M mutation [Fig. 2]. This situation remained within the statistical significance limit for OS in multivariate analysis (p=0.07).

Table 1: Clinicopathological and treatment characteristics of the patients

Characteristics	n (n=52)	%
Age at diagnosis		
<60	31	59.6
≥60	21	40.4
Gender		
Male	24	46.2
Female	28	53.8
Smoking		
Yes	15	28.8
No	29	55.8
Unknown	8	15.4
Primary tumor location		
Right	31	59.6
Left	20	38.5
Bilateral	1	1.9
Type of mutation		
Exon 19	35	67.3
Exon 21	12	23.1
Others	5	9.6
Stage at diagnosis		
Stage 1	2	3.8
Stage 2	2	3.8
Stage 3	3	5.8
Stage 4	45	86.6
Metastatic locations		
Bone	33	63.5
Brain	15	28.8
Liver	7	13.5
Number of metastatic sites		
1–2	34	65.4
>2	17	32.7
Unknown	1	1.9
Prior treatments before EGFR TKI		
Primary surgery	4	7.7
Palliative chemotherapy	15	28.8
Palliative radiotherapy	22	42.3
Type of EGFR TKI		
Erlotinib	44	84.6
Gefitinib	4	7.7
Afatinib	4	7.7
Objective response to EGFR TKI		
Yes	45	86.5
No	7	13.5
PFS time		
<12 month	13	25
≥12 month	39	75
EGFR TKI-related toxicity		
Yes	20	38.5
No	32	61.5
Biopsy type		
Liquid	39	75
Tissue	13	25
Acquisition of T790M mutation		
Yes	33	63.5
No	19	36.5

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor, PFS: Progression-free survival

Table 2: Univariate and multivariate logistic regression analyses for T790M acquisition in the EGFR-mutant patients

Patient characteristics	Univariate analysis		Multivariate analysis	
	p	OR (95% CI)	p	OR (95% CI)
Age (<60 vs. ≥60)	0.43	0.63 (0.20–1.99)		
Gender (male vs female)	0.79	1.08 (0.34–3.34)		
Smoking (yes vs no)	0.43	0.60 (0.16–2.14)		
Primary tumor location (left vs right)	0.39	1.68 (0.51–5.55)		
De novo metastatic disease (yes vs no)	0.23	2.26 (0.52–13.47)		
Number of metastatic sites (1–2 vs >2)	0.41	1.68 (0.48–5.84)		
Liver metastasis (yes vs no)	0.61	1.57 (0.27–9.04		
Brain metastasis (yes vs no)	0.70	1.27 (0.35–4.51)		
EGFR mutation type (other vs exon 19)	0.20	2.18 (0.64–7.33)	0.68	1.45 (0.23–9.01)
Type of EGFR TKI (erlotinib vs other)	0.95	0.95 (0.20–4.52)		
Objective response to EGFR TKI (no vs yes)	0.64	1.51 (0.26–8.70)	0.97	0.95 (0.45–20.24)
PFS time (<12 months vs ≥12 months)	**0.03**	10.28 (1.21–86.98)	**0.035**	13.08 (1.19–143.07)
EGFR TKI-related toxicity (no vs yes)	**0.001**	8.04 (2.24–28.87)	**0.004**	10.19 (2.10–49.32)
Biopsy type (liquid vs tissue)	0.51	1.62 (0.37–7.07)	0.32	2.54 (0.40–16.18)

Hosmer-Lemeshow test p-value=0.79. EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor, PFS: Progression-free survival, OR: Odds ratio, CI: Confidence interval

Discussion

In this study, we determined the frequency of acquisition of T790M mutation after disease progression under EGFR inhibitors in patients with EGFR-mutant mNSCLC. We detected that the presence of EGFR TKI-related toxicity and long PFS duration predicted T790M acquisition. In a study published by Matsumoto et al.,[9] the presence of T790M mutation before EGFR TKI treatment was associated with short PFS, and the development of T790M mutation after progression under EGFR TKI was found at a rate of 50%–60%. After the development of EGFR TKI resistance, T790M mutation can be detected up to 68% ratio by taking sufficient tissue samples and rebiopsy.[10]

After EGFR TKI resistance, patients with T790M mutation detected using liquid biopsy had a worse PFS than those detected using tissue biopsy, and therefore T790M mutation assessment should be performed using tissue biopsy.[11] The factors affecting the development of T790M resistance mutation after progression with EGFR TKI therapy are not fully known. In a study published by Kawamura et al.,[12] the development of T790M mutation was found to be statistically significantly higher in patients without de novo metastatic disease who had undergone primary lung surgery and in patients with an EGFR TKI using more than 1 year. Due to the high rate of de novo metastatic disease in our study, the history of surgery was not analyzed. In a study published by Chai et al.,[13] the acquisition of T790M mutation was found to be statistically significantly higher in patients with partial response to EGFR TKI. In another study conducted by Huang et al.,[14] which evaluated the acquisition of T790M mutation, it was shown that the probability of detecting T790M mutation was statistically significantly increased in cases of exon 19 deletion, PFS for longer than 11 months, and rebiopsy from metastasis region. In another study conducted by Ouyang et al.,[15] it was found that low body mass index, high neuron-specific enolase level before EGFR TKI, and the presence of retroperitoneal lymph node metastasis were associated with the development of T790M mutation. The studies in the literature were generally designed retrospectively, and different factors were found to predict the acquisition of T790M mutation in different studies.

We found that patients who developed T790M mutations tended to have better survival than patients who did not develop T790M mutation although it was not statistically significant. This can be explained by the use of osimertinib, which is effective in this resistance mutation after the T790M mutation develops. In real-life data published by Auliac et al.,[16] osimertinib treatment provided a PFS of 12.4 months and an OS of 20.5 months in the acquired T790M mutant mNSCLC patients who were previously treated with EGFR TKI. In addition, another study observed longer OS with the presence of the exon 19 mutation compared with the

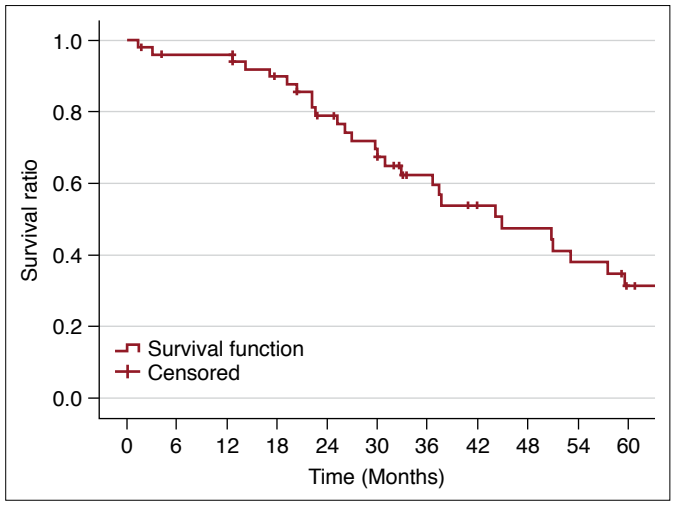

Figure 1: The Kaplan-Meier curve for OS in EGFR-mutant mNSCLC patients
OS: Overall survial, EGFR: Epidermal growth factor receptor, mNSCLC: mutant metastatic non-small cell lung cancer

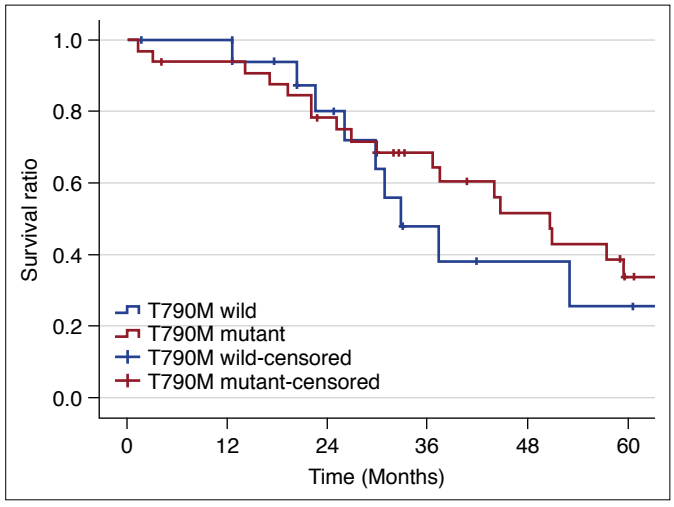

Figure 2: The Kaplan-Meier curve for OS by T790M acquisition status in mNSCLC patients
OS: Overall survial, mNSCLC: mutant metastatic non-small cell lung cancer

exon 21 mutation in patients using osimertinib with an acquired T790M mutation.[17] Osimertinib unresponsiveness after EGFR TKI resistance is explained by loss of T790M mutation and newly developed EGFR mutations (C797S, L718Q, and G724S) and bypass of pathway activation with other mutations (MET, HER2, KRSA, and BRAF).[18] If T790M mutation is acquired after progression with EGFR TKI, more effective treatment can be planned with concurrent inhibition therapy in the presence of other concomitant mutations such as MET amplification.[19] However, in a study published by Akamatsu et al.,[20] the addition of bevacizumab to osimertinib did not provide additional benefit in patients with a T790M mutation who had previously used EGFR TKIs.

Our study had some limitations as it was of a retrospective nature. The number of patients was limited due to a rare tumor, and the patient population was heterogeneous. Some data were missing.

Conclusion

In our study, we evaluated the T790M mutation development status after progression under EGFR TKI in EGFR-mutant mNSCLC patients. We found that the presence of the EGFR inhibitor-related toxicity and longer PFS than 12 months were predictors for T790M mutation acquisition. In addition, a better trend was detected in terms of OS in patients with T790M mutation due to the use of new generation EGFR inhibitors. This study is one of the rare studies in the literature evaluating patients with EGFR mutation and subsequent treatment-related T790M mutation in mNSCLC. Multicenter studies involving large numbers of patients are needed to determine the factors affecting the development of de novo or treatment-associated resistance mutations in lung cancer. Also, understanding the mechanisms of treatment-associated resistance mutation development at the molecular level will provide better management of the treatment process.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the Istanbul University Faculty of Medicine Ethics Committee (No: 266748, Date: 28/06/2021).

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Externally peer-reviewed.

Authorship Contributions
Concept – İ.D., N.P., N.K., S.V., P.S., A.A.; Design – İ.D., N.P., N.K.; Supervision – S.V., P.S., A.A.; Funding – İ.D., N.P., N.K.; Materials – İ.D., N.P., N.K.; Data collection &/or processing – İ.D., N.P., N.K.; Analysis and/or interpretation – İ.D., N.P., N.K.; Literature search – İ.D., N.P., N.K.; Writing – İ.D., N.P., N.K., S.V., P.S., A.A.; Critical review – S.V., P.S., A.A.

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