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Clinical Effects of T790M Mutation in EGFR Tyrosine Kinase Inhibitor Resistant NSCLC Patients

EGFR Tirozin Kinaz İnhibitörlerine Dirençli KHDAK Hastalarında T790M Mutasyonunun Klinik Etkileri

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Abstract

INTRODUCTION: To compare patient characteristics between the T790M-positive and T790M-negative populations, and to analyze the post-progression survival (PPS) after initial tyrosine kinase inhibitor (TKI) failure in order to investigate the prognosis in patients undergoing rebiopsy.
METHODS: We investigated the patient characteristics, including the initial EGFR-TKI response and T790M status at the time of rebiopsy or liquid biopsy, subsequent treatment after resistance to the initial EGFR-TKI (the presence of EGFR-TKI re-challenge), treatment just before biopsy and/or rebiopsy (EGFR-TKIs or chemotherapy), the timing of the rebiopsy (just after the initial EGFR-TKI failure or others).
RESULTS: No difference was found between the two groups with T790M mutation positive and negative in terms of age, gender, and metastasis location. Only patients with positive T790M mutation had higher progression after TKI use compared to negative ones (p: 0.000). The progression-free median survival in patients using TKI was 19.33 months in the group with T790M mutation and 22.25 months in the negative group. Overall survival was found to be 75 months and 27.5 months in the T790M positive and negative group, respectively, and this was statistically significant. (p: 0.009).
DISCUSSION AND CONCLUSION: Overall survival was significantly longer in the T790M positive group than in the T790M negative group. In addition, liquid biopsy can be performed several times for patients with progression after EGFR-TKI use and who do not want to undergo tissue biopsy.

Keywords: liquid bıopsy, lung cancer, survival, T790M mutation, tissue biopsy

Öz

GİRİŞ ve AMAÇ: T790M - pozitif ve T790M - negatif popülasyonlar arasındaki hasta özellikleri karşılaştırıldı ve ilk tirozin kinaz inhibitörü (TKI) başarısızlığından sonra progresyon sonrası sağkalım (PPS) analiz edilerek yeniden biyopsi yapılan hastalarda prognoz araştırıldı.
YÖNTEM ve GEREÇLER: Hastaların karakteristik özellikleri, EGFR-TKI yanıtı, rebiyopsi veya likit biyopsi sırasındaki EGFR durumu, rebiyopsi öncesi uygulanan tedavi (kemoterapi/ EGFR-TKI), ilk EGFR-TKI'a direnç geliştikten sonraki tedavi ve biyopsi zamanı (ilk EGFR-TKI başarısızlığı sonrası) araştırılmıştır.
BULGULAR: T790M mutasyonu pozitif ve negatif olan iki grup arasında yaş, cinsiyet ve metastaz yeri arasında fark saptanmadı. Yalnızca T790M mutasyonu pozitif olan hastalarda TKİ kullanımı sonrası progresyonun negatif olanlara göre daha fazla olduğu görüldü (p: 0.001). TKİ kullanan hastalarda progresyonsuz median sağkalım T790M mutasyonu olan grupta 19,33 ay iken negative olan grupta 22.25 ay olarak saptandı. Genel sağkalım T790M pozitif ve negative olan grupta sırasıyla 75 ay ve 27,5 ay olarak bulundu ve bu istatistiksel olarak anlamlı idi (p: 0.009).
TARTIŞMA ve SONUÇ: Genel sağkalım T790M pozitif grupta,T790M negatif gruba göre istatistiksel olarak anlamlı düzeyde uzun olarak saptandı. Ayrıca EGFR-TKI kullanımı sonrası progresyon olan ve doku biyopsisi yaptırmak istemeyen hastalara likit biyopsisinin birkaç kez yapılabilir.

Anahtar Kelimeler: akciğer kanseri, doku biyopsi, likit biyopsi, sağkalım, T790M mutasyonu

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INTRODUCTION

In recent years, significant advances have been made to treat patients with advanced lung cancer with targeted therapies and immune targeted therapy approaches. During systemic therapy, almost all tumors develop resistance to treatment due to tumor heterogeneity and clonal change. However, the emergence of the T790M resistance mutation during treatment constitutes most EGFR-TKI drug resistance. EGFR mutations are more frequently detected in never or light smokers, women, and adenocarcinomas. Exon 19 deletions and exon 21 L858R point mutations account for up to 90% of EGFR mutations (1-4).

First-generation EGFR tyrosine kinase inhibitors (TKIs) (i.e. erlotinib and gefitinib) are reversible EGFR inhibitors, whereas second-generation TKIs (i.e. afatinib), are irreversible pan-human epidermal growth factor receptor inhibitors that covalently bind to EGFR. Acquired resistance to EGFR TKIs causes disease progression after 9-15 months of TKI treatment (5-7). Several acquired resistance mechanisms were reported in the literature. The substitution of threonine to methionine at amino acid position 790 (T790M) in exon 20 of the EGFR gene decreases first- and second-generation EGFR TKI binding and enhancing the ATP binding affinity of EGFR-mutant receptor kinase domains in approximately 50% of resistant cases (8,10).

The traditional specimen taken for T790M mutation analysis is a tissue biopsy. However, in cases where the tissue sample can't be reached or can't be obtained due to patient-related reasons (biopsy rejection or unsuitable performance status), the liquid biopsy method is an alternative method that is less invasive and has rapid results. Liquid biopsies are used as to find T790M mutation in patients who have evidence for TKI resistance. However, due to 50% - 90% sensitivity of liquid biopsies depending on mutational analysis methods, when the result is negative, tissue biopsy is preferred (11,12). In addition, liquid biopsy based on the evaluation of genetic markers in blood for early diagnosis and follow-up of the disease is increasingly popular. Liquid biopsies can be helpful in genetic monitoring of the tumor, as the circulating free tumor DNA can represent the tumor genome. Also, liquid biopsy can be carried out many times, allowing molecular changes in tumor cells to be detected dynamically.

Clinical factors affecting acquired resistance mutation prevalence, particularly T790M, are still not clear. The purpose of the present study was to elucidate clinical factors related to the frequency of T790M mutations. We also planned this study for comparing various patient data between the T790M-positive and T790M-negative cases, and to analyze post-progression survival (PPS) after initial TKI failure in order to investigate the prognosis in patients undergoing a rebiopsy.

MATERIALS AND METHOD

Patients

Patients with EGFR-sensitive mutations who underwent a rebiopsy or liquid biopsy between 2015 and 2020 to confirm the emergence of T790M after EGFR-TKI became resistant, were retrospectively analyzed. Patient characteristics investigated included the initial EGFR-TKI response, T790M status during rebiopsy or liquid biopsy, following treatment after resistance to initial EGFR-TKIs (presence of EGFR-TKIs re-challenge), treatment before biopsy and/or rebiopsy (EGFR-TKIs or chemotherapy), and the timing of rebiopsy (following initial EGFR-TKIs failure).

A liquid biopsy was sent from all patients who were resistant to EGFR-TKI drugs. Tissue biopsies were performed from patients with a negative liquid biopsy result (Figure 1).

Here, post-progression survivals (PPS), are identified as the time from progressive disease to death from initial TKI therapy.

EGFR Mutation Analyses

Mutation analysis of exons 18–21 of EGFR was conducted with cycleave PCR (L858R point mutations in exon 21 (L858R) and T790M) and fragment analysis (deletions in exon 19 (Del19)).

Statistical Analysis

Statistical analysis was made through Sigma-Plot software with x2 test to correlate clinical data with T790M status, and Kaplan-Meier Estimator was also used to analyze median PFS and OS.

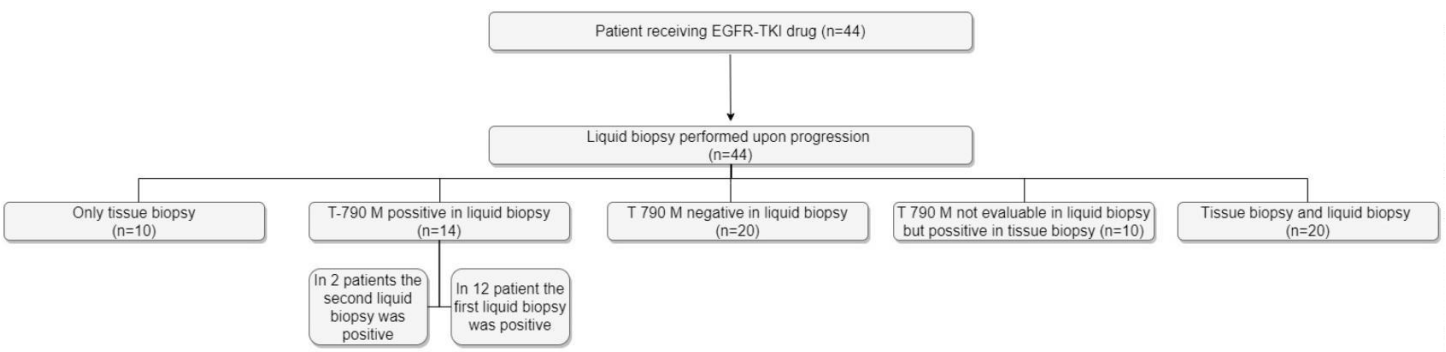

Figure 1: Patient Disposition Chart

Table 1. Characteristics of Patients

	n	%
Gender		
Male	21	47.7
female	23	52.3
Smoking history		
Ex-smoker	9	20.5
Nonsmoker	30	68.2
Smoker	5	11.4
ECOG		
0	17	38.6
1	23	52.3
2	3	6.8
3	1	2.3
Comorbid diseases		
Present	11	25
Absent	33	75
Stage (at diagnosis)		
Stage 1	1	2.3
Stage IIIA	1	2.3
Stage IIIB	4	9.1
Stage IV	38	86.4
Metastasis		
Present	38	86.4
Absent	6	13.6
Response to first line chemotherapy		
Progression	17	38.6
Stable	1	2.3
Partial response	4	9.1
Complete response	4	9.1
EGFR mutation		
Positive	43	97.7
Negative	1	2.3
861Q	1	2.3
858R	14	31.8
EXON20	2	4.5
EXON19	27	61.4
First line TKI		
Afatinib	7	15.9
Gefitinib	6	13.6
Erlotinib	31	70.5
Progression during TKI		
Pulmonary and extrapulmonary	15	34.1
Extrapulmonary	4	9.1
Pulmonary	16	36.4
No progression	9	20.5
T790M		
Positive	24	54.5
Negative	20	45.5

ECOG: Eastern Cooperative Oncology Group
TKI: tyrosine kinase inhibitor
Table 1 is shown in result section.

Table 2. Relationship between Clinical Features According to the T790M Mutation

	T790M positive N:24	T790M Negative N:20	p
Age	62.5±12.7	62.6±11.5	0.944
Male	12 (50%)	9(45%)	0.975
Female	12 (50%)	11 (55 %)	
Comorbid diseases			1.000
Present	6 (25%)	5 (25%)	
absent	18 (75%)	15 (75%)	
Metastasis			
Present	21 (87.5%)	17 (85%)	1.000
absent	3 (12.5%)	3 (15%)	
Progression after TKI use	24 (100%)	11 (55%)	0.000
Present	0	9 (45%)	
absent			
Survival			
Exitus	8 (33.3%)	13 (65%)	0.073
Alive	16 (66.7%)	7 (35%)	

TKI: tyrosine kinase inhibitor
Table 2 is shown in result section.

RESULTS

Gefitinib (N: 6; 13.6%), erlotinib (N: 31; 70.5%) or afatinib (N: 7; 15.9%) were used for forty-four patients as first-line treatment. Liquid biopsies were sent from all patients. Tissue biopsies were performed from those whose liquid biopsy result was negative. Both tissue and liquid biopsies were sent from 30 patients. For 10 patients, the tissue biopsy was positive as well as the liquid biopsy being negative. In 20 patients, both tissue and liquid biopsy were negative. The liquid biopsies of 14 patients were found to be positive. The characteristics of patients are shown in Table 1.

No difference was found between the two groups with positive and negative T790M mutations in terms of age, gender and metastasis location (Table 2).

Only patients with a positive T790M mutation had higher progression after TKI use compared to patients with a negative mutation (p: 0.000). The progression-free median survival in patients using TKI was 19.33 months in the group with a T790M mutation, and 22.25 months in the negative group (Figure 2). Overall survival was 75 months and 27.5 months, respectively, in the T790M positive and negative group and this was statistically significant (p: 0.009) (Figure 3).

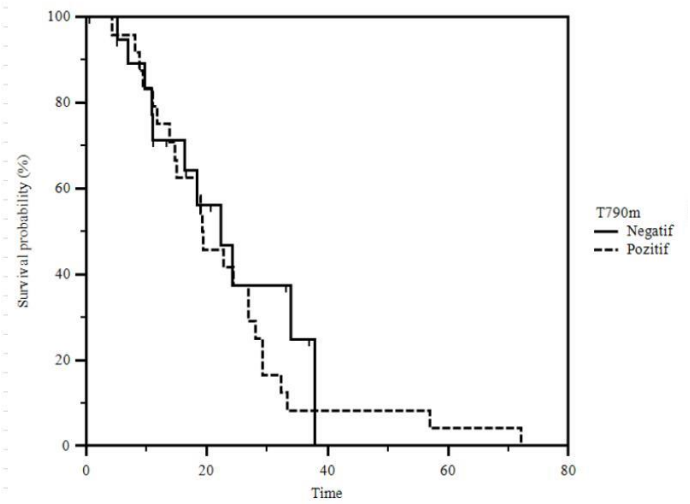

Figure 2: Survival in T790M Mutation Positive and Negative Patients with Progression Free Survival after TKI use

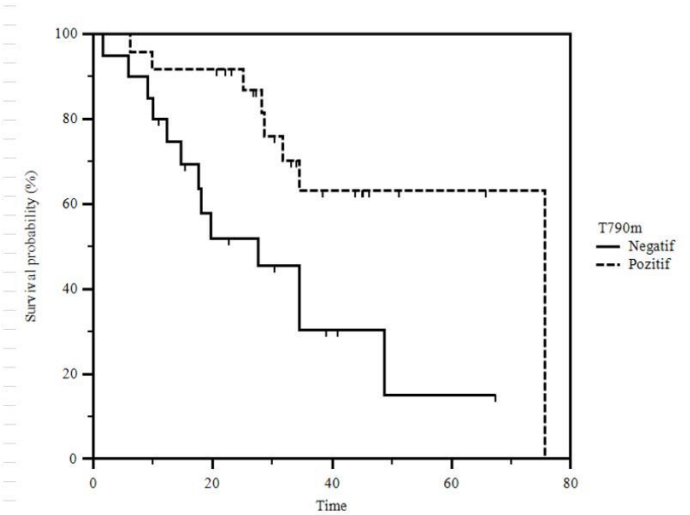

Figure 3: Overall Survival in T790M Mutation Positive and Negative Patients

DISCUSSION

Evidence on clinical characteristics of cases who have EGFR mutations potentially estimating the acquisition of T790M mutation is currently limited, and is conducted only with Asian cases (13-20). In our study, no difference was found between the two groups of T790M mutation positive and negative, in terms of clinical features. Previous studies examined age as a clinical factor correlated with T790M mutation, but without any important results in most patients (15). However, a Japanese case series reported positive correlations in cases that were older than 75 years, but the median age was older than our series (19). In another study cases younger than 65 with exon 19 deletion as baseline sensitizing mutation were found to be correlated with acquired T790M mutation at disease progression (20). The low number of patients in our study and the low number of patients over the age of 65 may be the reason why no difference was found.

In this study, the prevalence of acquired T790M mutations was evaluated simultaneously in 44 patients with biopsy and plasma specimens. Both tissue and liquid biopsies were collected from 30 patients. Tissue biopsies of 10 patients were positive whereas their liquid biopsies were negative. In 20 patients, both tissue and liquid biopsy were negative. Liquid biopsies of 14 patients were found to be positive. Since liquid biopsies were noninvasive, tissue biopsies were performed on those whose liquid biopsy results were negative. Positive results in 14 of the 44 patients indicated a high rate. For this reason, it would be more appropriate to conduct and evaluate liquid biopsies first, which is a less invasive method. Thress *et al.* reported the positivity rate of simultaneous measurements of tissue specimens and plasma specimens as 81% and 58%, respectively (21). Other researchers have found that the positivity rate of acquired T790M mutations in plasma specimens was approximately 40% (22, 23). Jenkins *et al*. reported that plasma testing did not detect the T790M mutation in plasma-circulating tumor DNA of ca. 40% of patients who had T790M-positive tissue testing results (24). Even in two patients, it was seen that the first liquid biopsy was negative, and then the second liquid biopsy sent 3 months later was positive. Of course, patients cannot wait for the second liquid biopsy and it will be more accurate to send tissue biopsies during this period. However, it may be appropriate to send a liquid biopsy from time-to-time in patients who are also negative in tissue biopsies, because tissue biopsies are an invasive method. Alternatively, if the patient does not want to have a tissue biopsy with an invasive method again, we think that several liquid biopsies can be sent from the patient.

The T790M mutation was detected in our study after afatinib, erlotinib and gefitinib treatment. After erlotinib treatment, the T790M mutation was detected in 16 patients and it was found in four patients who received afatinib and gefitinib treatment. One study from Kyushu University reported the results of 37 patients across 13 institutes who acquired T790M mutations upon recurrence after the administration of afatinib were found in 43.2% of patients with *EGFR* mutations (25). In another study, the rate of acquired T790M mutations was similar in any combination of EGFR-TKI (19).

In our study, patients with a positive T790M mutation had higher progression after TKI use compared to patients with a negative mutation. While progression was observed in all patients with positive T790m mutation in patients using TKI, progression was observed in 11 (55%) of the patients without T790M mutation, which was statistically significant. It was argued in a trend that was not statistically significant that there was a higher prevalence of T790M mutation in patients with better and longer response to previous EGFR TKIs, which is in agreement with the data reported for a smaller Japanese series (17).

It is recommended in European Guidelines that tissue or liquid biopsies are performed for disease progression (26); however, the accurate time for cf-DNA analysis and liquid rebiopsy for initial negativity was not elucidated.

However, previous data of a Caucasian cohort revealed that T790M was more prevalent in lung/pleura tissue, and lymph node

biopsies compared to more distant areas (48). A likely explanation argues that tumor heterogeneity of metastatic areas affects tissue biopsy when compared with liquid biopsy. They also conducted liquid/tissue biopsy according to instructions for clinical practice, and not for prospective rebiopsy protocol, in which the time point of specimen collection was pre-defined (27). In our study, although progression was detected less in extrapulmonary organs, it was generally preferred to take a tissue biopsy from the lung, where it is more common.

Finally, we also analyzed the survival data of the patients and found that the progression-free median survival in patients using TKI was 19.33 months in the group with T790M mutation and 22.25 months in the negative group. Overall survival was 75 months and 27.5 months, respectively, in the T790M positive and negative groups, which was statistically significant. In another study, it was reported that there was a median OS of 52.8 months in T790M patients (vs. 25 months in without T790M patients); all of whom received second-line osimertinib treatment; this might explain survival benefits (20). In another study (17), the PPS and OS in patients with EGFR T790M positive (N = 21) who received osimertinib were longer at significant levels compared to those who were T790M-negative (N = 87), and those with EGFR-positive T790M without other 3G-EGFR-TKI treatment. The study also found longer durations for PFS at initial treatment with EGFR-TKIs, which was associated with T790M mutation at significant levels. They also found that patients who with T790M mutation after initial EGFR-TKIs resistance might have longer PFS when compared to those without T790M mutation (17).

There were several limitations in our study. Firstly, the data were collected retrospectively from one single institution, and the sampling size was small, the timing of rebiopsy varied in patients, and was not consistent (as expected in a prospective study). Secondly, the T790M status was analyzed only in rebiopsy areas and not in the entire tumor. In an individual patient, T790M mutation status was reported as spatiotemporally heterogeneous because of selective pressure of EGFR-TKIs (28). There were no patients undergoing rebiopsy for brain or bone progression lesions. Subsequently, rebiopsy areas might have caused biased detection of T790M mutation. In addition, waiting for the results of the liquid biopsy, which is a more non-invasive examination at first, and sending the patient to tissue biopsy also causes a waste of time.

In conclusion, this study conducted in the Turkish population found that the survival time was longer in the T790M positive group compared to the T790M negative group, thatwasstatistically significant. In addition, it was also found that a liquid biopsy could be sent several times in patients who do not want to have a tissue biopsy, especially in patients with progression of EGFR-TKI drugs who do not want to undergo a tissue biopsy.

Ethics Committee Approval: This is a retrospective study, local ethical approval was received and ethical approval date and number 28.02.2020-3. The study protocol was approved by the İzmir Dr. Suat Seren of the Chest Diseases and Surgery Training Hospital.

Conflict of Interest: The author declare there are no potential conflicts of interest.

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