






Original Article

Evaluation of Treatment Efficacy of Tyrosine Kinase Inhibitors in Rare Single EGFR Exon 21 L861Q Mutation: Single Center Experience

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Abstract

OBJECTIVE: Epidermal growth factor receptor mutations are the second most common oncogenic driver event in non-small cell lung cancer. We aimed to compare the first generation erlotinib treatment with the second generation afatinib treatment in patients with non-small cell lung cancer with epidermal growth factor receptor exon 21 L861Q mutation.

MATERIAL AND METHODS: Progression-free survival and overall survival of 30 non-small cell lung cancer patients treated with erlotinib or afatinib due to single epidermal growth factor receptor L861Q positivity were compared retrospectively. The number of patients included in the first, second, and third treatment line was 15 (50.0%), 11 (36.7%), and 4 (13.3%), respectively.

RESULTS: There were 23 patients in the erlotinib arm and 7 patients in the afatinib arm. Median progression-free survival was 12.8 months in the erlotinib group and 9.3 months in the afatinib group. Median overall survival in erlotinib and afatinib groups was 77.9 months and 30.3 months, respectively. No statistically significant difference was found in the comparison of these survival times.

CONCLUSION: Survival times of erlotinib and afatinib treatment are similar in patients with a single epidermal growth factor receptor L861Q mutation. In patients receiving tyrosine kinase inhibitors treatment, the female gender has a positive effect on progression-free survival, and being a non-smoker has a positive effect on overall survival. In patients with rare mutation exon 21 L861Q positivity, both first-generation and second-generation tyrosine kinase inhibitors should be considered.

KEYWORDS: Non-small cell lung cancer, exon 21, L861Q, erlotinib, afatinib

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death worldwide.¹ Epidermal growth factor receptor (EGFR) mutation in NSCLC is the most common mutation after K-RAS. Epidermal growth factor receptor mutation is found in 10-15% of all NSCLC cases in Western European populations, while the rate of EGFR mutation is 30% in East Asian populations.² Exon 19 and exon 21 L858R are called "classic EGFR mutations" and account for 85% of EGFR mutations.³ These classic EGFR mutations show high sensitivity to treatment with tyrosine kinase inhibitors (TKI). Studies have shown that TKI therapy results in prolongations in progression-free survival (PFS) compared to cytotoxic chemotherapy in these patients.⁴ Exon 18, exon 20, and exon 21 L861Q mutations are rarer mutations and their response to TKI and their prognosis are unclear.^{5,6}

Erlotinib and gefitinib are reversible first-generation TKIs, and afatinib is irreversible second-generation TKIs.^{7,8} In studies with classical EGFR mutations, both first-generation TKI and second-generation TKI responses were found to be similar. Post-hoc analyses of LUX-lung 2, LUX-lung 3, and LUX-lung 6 studies have shown that "rare mutations" such as exon 18, exon 20, and exon 21 L861Q are more susceptible to the second generation TKI.⁹

The exon 21 L861Q mutation accounts for 3% of EGFR mutations, and this mutation is usually found in "complex" with G719X and exon 19 del. While many studies have reported TKI response for complex mutations, the number of studies with single exon 21 L861Q mutation is very limited.¹⁰

The aim of our study is to determine the characteristics of the rare single exon 21 L861Q patient group and to show whether there is a difference between the survival times according to the TKI used.

MATERIAL AND METHODS

Patients

Patients who were followed up at the hospital between 2010 and 2020 and received TKI for single EGFR exon 21 L861Q-positive metastatic NSCLC were included in the study. Patients with other mutations and complex mutations for EGFR

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were excluded from the study. Epidermal growth factor receptor mutation positivity in patients with NSCLC was determined by the pyrosequencing method. Age, gender, smoking status, performance score, stages, metastasis sites, treatments received before and after, side effects, and date of death of the patients were recorded. The general characteristics of these patients and the effectiveness of their treatment with TKI were evaluated retrospectively.

Ethical Considerations

This study was approved by the Ege University ethical committee of (decision number: (21-7T/4). All patients gave their written informed consent.

Statistical Analysis

The Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Whether the data was normally distributed was determined by Kolmogorov–Smirnov and Shapiro–Wilk tests. Mann–Whitney *U* test was used to compare continuous variables between groups, and chi-square test and Fisher’s exact test were used to compare categorical variables. Kaplan–Meier test was used for survival analysis. Results are presented as, median (min-max) and number (percentage). A *P* value <.05 was considered statistically significant in all statistical analyses.

RESULTS

Patient Characteristics

Thirty patients who received TKI therapy for metastatic NSCLC single exon 21 L861Q mutation positivity were included in the study. The pathological type of all patients was adenocarcinoma. The median age was 70 (52.0-84.0), 14 patients (46.7%) were female, and 16 patients (53.3%) were male. Demographic and clinical characteristics of the patients are presented in Table 1. Twenty-three (76.7%) patients received first-generation TKI, and 7 (23.3%) patients received second-generation TKI. Tyrosine kinase inhibitors were used in the first-line treatment in 15 (50%) patients, in the second-line treatment in 11 (36.7%) patients, and in the tertiary treatment in 4 (13.3%) patients. The treatments received by the patients before and after TKI are shown in Table 2. None of the patients underwent metastasectomy and none of the patients received radiotherapy.

MAIN POINTS

- L861Q mutation is a rare epidermal growth factor receptor (EGFR) mutation. While many studies have reported tyrosine kinase inhibitor (TKI) response for complex mutations, the number of studies with single exon 21 L861Q mutation is very limited.
- There is no study in the literature comparing the first generation EGFR-TKI and the second generation EGFR-TKI with single exon 21 L861Q mutation.
- Survival times of erlotinib and afatinib treatment are similar in patients with a single EGFR L861Q mutation
- In patients receiving TKI treatment, the female gender has a positive effect on progression-free survival, and being a non-smoker has a positive effect on overall survival.

Table 1. Demographic Data and Clinical Characteristics

Patients Characteristics	n (%)
Age (mean) (min-max)	70.0 (52.0-84.0)
Sex, n (%)	
Female	14 (46.7%)
Male	16 (53.3%)
Smoking status, n (%)	
Non-smoker	16 (53.3%)
Ex-smoker	14 (46.7%)
Smoking package*year (min-max)	50.0 (30.0-60.0)
ECOG performance status (%)	
0	3(10%)
1	18 (60 %)
2	9 (30%)
3	0 (0 %)
Stage n (%)	
I	-
II	4 (13.3%)
III	-
IV	26 (86.7%)
Metastasis n (%)	
Solitary	12 (40.0%)
Multiple	18 (60.0%)
Brain metastases, n (%)	5 (16.7%)
Bone metastases, n (%)	12 (40.0%)
TKI type, n (%)	
Erlotinib	23 (76.7%)
Afatinib	7 (23.3%)
TKI treatment, n (%)	
First line	15 (50.0%)
Second line	11 (36.7%)
Third line	4 (13.3%)

TKI, tyrosine kinase inhibitor.

Progression-free survival and OS

Progression-free survival was found to be 13.2 months (95% CI: 7.8-18.7) in all patient groups. The PFS was 12.8 months (95% CI: 7.2-18.4) in the erlotinib group, and 9.3 months

Table 2. The Treatments Received by the Patients Before and After Tyrosine Kinase Inhibitors

Type of Treatment Received	First Line (n)	Second Line (n)	Third Line (n)
Paclitaxel-platinum	1	2	0
Docetaxel-platinum	5	0	5
Pemetrexed -platinum	6	3	0
Gemcitabine-platinum	0	4	0
Vinorelbine -platinum	3	0	0
Others	0	0	0

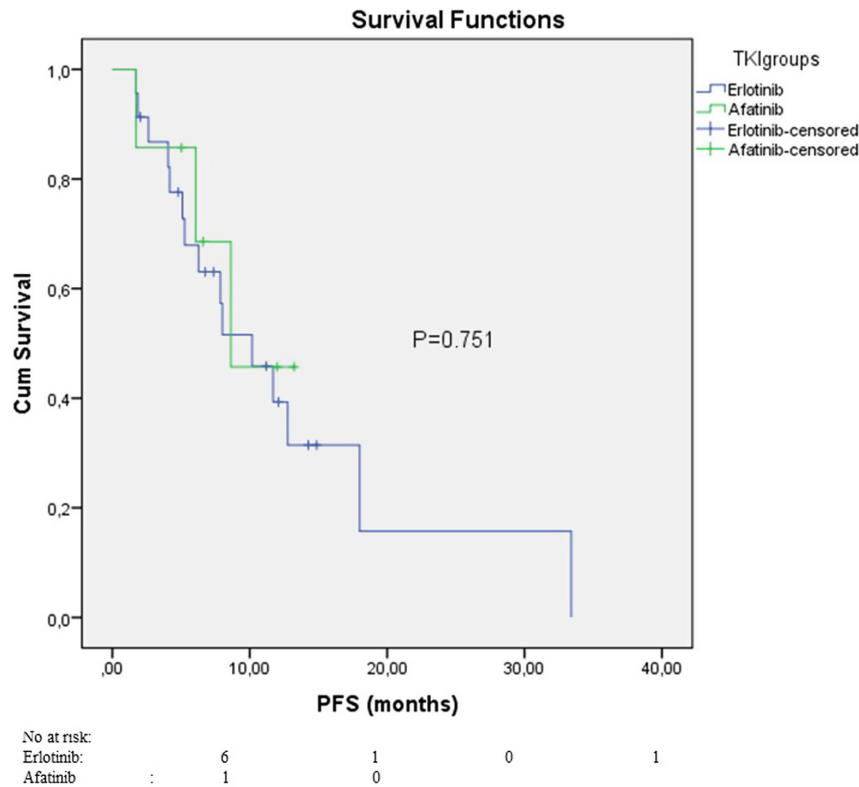


Figure 1. Evaluation of PFS according to tyrosine kinase inhibitor types. PFS, progression-free survival.

(95% CI: 6.0-12.6) in the afatinib group, with no difference between the 2 groups ($P = .751$) (Figure 1).

When the PFS was compared according to gender, the PFS of female patients was found to be longer than male patients (19.3 vs. 7.3 $P = .005$). Similarly, there was a statistically significant difference between the PFS of female patients and male patients in the Erlotinib group (19.4 months (95% CI: 8.9-29.8) vs. 7.1 months (95% CI: 4, 7-9.5), respectively $P = .008$). Also, the PFS of female patients was longer in the afatinib group, but no statistical difference was found (10.4 months vs. 7.8 months $P = .823$).

When the PFS was compared according to the smoking status of the patients, the PFS was found to be 13.8 months in the non-smokers group and 9 months in the ex-smokers group ($P = .749$). In the erlotinib group, patients who had never smoked had a longer PFS than patients who had smoked, although it was not statistically significant (14.6 months vs. 8.2 months $P = .320$). In the afatinib group, the PFSs for these patients were found to be 10.9 months and 7.2 months, respectively ($P = .264$).

No better response was observed in any subgroup when PFSs were compared according to tumor stages, number of metastatic sites, and performance status (Table 3).

OS of all patients was 73 months (95% CI: 41.0-104). OS was 77.9 months (95% CI: 44.2-111.5) in the erlotinib group and 30.3 months (95% CI: 30.1-30.5) in the afatinib arm, and there was no statistically significant difference between the 2 groups ($P = .265$) (Figure 2).

When OS was evaluated according to gender, the OS of male patients was found to be longer than female patients (76.1 vs. 37.2, $P = .649$).

When OS was compared by smoking status, OS was statistically significantly longer in the non-smokers group (97.5 months (95% CI: 65.6-129.3) vs. 40 months (95% CI: 26.7-53.2) respectively, $P = .026$). Similar results were also observed in the erlotinib group (97.5 months vs. 45.1 months, respectively, $P = .083$).

In this study, 5 patients (16.7%) had brain metastases. Patients with brain metastases had a PFS of 12.0 months, and patients without brain metastases had a PFS of 14.6 months ($P = .862$). All of these patients received erlotinib treatment, and the PFS of this group was calculated as 12.0 months (95% CI: 4-19.9). The OS of the patients with brain metastases was 40.9 months (95% CI: 20.2-61.6), and the OS of the patients without brain metastases was found to be statistically significantly longer (40.9 months vs. 89.1, respectively, $P = .045$).

Bone metastases are the most common site of metastasis, and there was no difference between the groups with and without bone metastases in terms of both PFS and OS ($P = .407$ vs. $P = .558$).

There was no statistically significant difference between the PFS of the patients who received TKI in first line and those who received TKI in other steps (17.8 months vs. 8.2 months, $P = .082$). However, when the OS was compared between the groups, a statistically significant difference was observed (39.4 months vs. 97.5 months, respectively, $P = .019$).

Table 3. Comparison of PFS and OS According to Demographic and Clinical Characteristics

	PFS		OS	
	Median Months (95% CI)	P	Median Months (95% CI)	P
Overall	13.2 (7.8-18.7)		73.0 (41.9-104.1)	
Gender				
Male	7.3 (5.3-9.3)	.005	76.1 (42.2-110)	.649
Female	19.3 (9.8-29.2)		37.2 (33.2-41.2)	
Smoking status				
Non-smoker	13.8 (6.9-20.8)	.749	97.5 (65.6-29.3)	.026
Ex-smoker	9.0 (6.4-11.6)		40.0 (26.7-53.2)	
Stage				
I	-	.282	-	.762
II	12.7 (12.0-13.3)		36.3 (27.8-44.9)	
III	-		-	
IV	12.7 (6.9-18.5)		77.9 (44.2-111.5)	
ECOG				
0	6.0 (5.3-6.7)	.594	-	.160
1	11.6 (8.8-14.5)		86.3 (52.6-119.9)	
2	19.9 (8.8-30.1)		40.9 (20.2-61.6)	
3	-		-	
Metastasis type				
Solitary	8.3 (5.7-10.9)	.341	74.7 (40.2-109)	.448
Multiple	14.9 (7.7-22.1)		37.6 (34.4-40.9)	

PFS, progression-free survival; OS, overall survival.

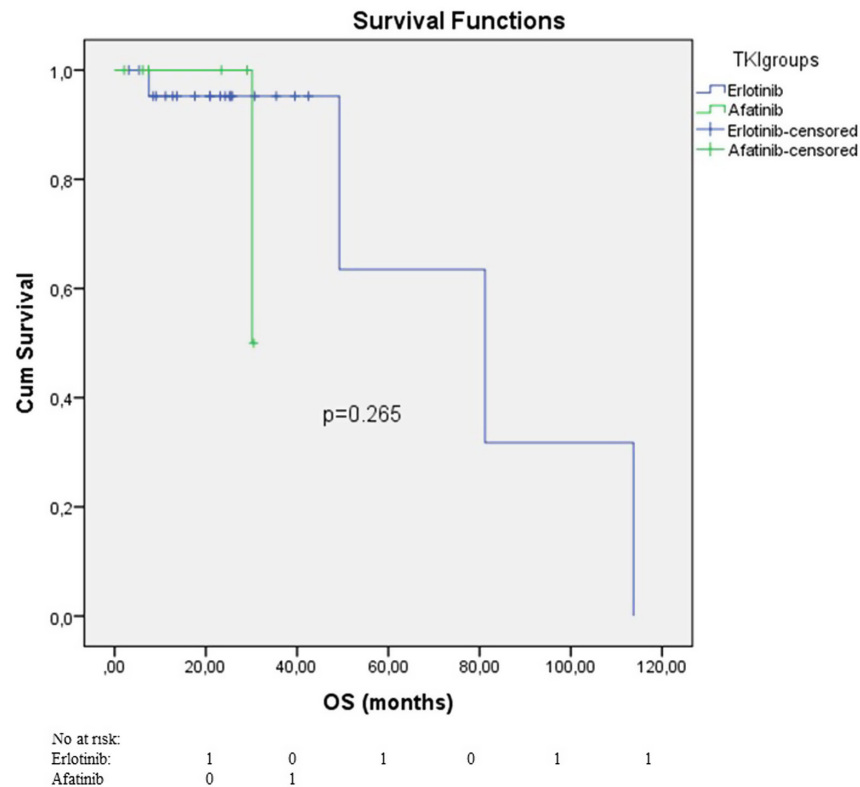
**Figure 2.** Evaluation of OS according to tyrosine kinase inhibitor types. OS, overall survival.

Table 4. Evaluation of Side Effects According to Tyrosine Kinase Type

	Erlotinib		Afatinib	
	Grade 1/2, n (%)	Grade 3/4, n (%)	Grade 1/2, n (%)	Grade 3/4, n (%)
Diarrhea	13 (56.5%)	0	2 (28.5%)	0
Rash	18 (78.2%)	1 (4.3%)	2 (28.5%)	0
Mucositis	11 (47.8%)	0	2 (28.5%)	0
ALT/AST elevation	1 (4.3%)	0	0	0
Paronychia	3 (13.0%)	0	0	0
Anemia	11 (47.8%)	1 (4.3%)	2 (28.5%)	0
Interstitial lung disease	1 (4.3%)	0	0	0

Adverse Effects

The most common side effects associated with erlotinib were rash (82.6%) and diarrhea (56.5%). In the afatinib group, rash was the most common side effect with a rate of 28.5%. Paronychia, which is frequently observed in TKI treatment, was observed in 3 patients (13%), while all patients were in the erlotinib group. When all side effects were evaluated, grade 3-4 side effects were presented with anemia in only 1 patient (4.3%). Interstitial lung disease, especially with a poor prognosis, was seen only in 1 patient (4.3%) who received erlotinib, and treatment-related death was not observed in either group. The side effects observed in patients due to TKI treatment were shown in Table 4.

When the relationship between rash and PFS and OS was evaluated, there was a statistically significant difference between the PFS of the patients with and without rash (10.6 months vs. 12.9 months, $P = .030$, respectively), but there was no difference between the OS ($P = .863$).

DISCUSSION

In studies with classical mutations (EGFR exon 19 and exon 21 L858R), a progression-free survival benefit was observed in patients receiving TKI compared with chemotherapy. There are no prospective studies evaluating the efficacy of TKI in rare mutations in the literature. Results evaluating the efficacy of TKI in these patients are generally obtained from post-hoc analyses of other studies or case series. Exon 21 L861Q mutations may be a single mutation or part of complex mutations. Our study is the first in the literature to compare the efficacy of erlotinib and afatinib in a single EGFR exon 21 L861Q mutation-positive patient group.

There are analyses showing that EGFR phosphorylation is preserved in cells expressing L861Q following treatment with first-generation TKI, such as erlotinib, while EGFR phosphorylation is lost after treatment with afatinib. These data suggest that second-generation TKIs may be more effective in targeting L861Q mutations. Moreover, preclinical studies have shown that L861Q mutations are more resistant to first generation-TKIs than L858R mutations and more sensitive to

afatinib and osimertinib treatment.¹¹ The reason for this sensitivity has been shown to be the irreversible covalent binding of these 2 drugs to the cysteine-797 residue in the ATP pocket.^{12,13}

In the post-hoc analysis of LUX-lung 2, LUX-lung 3, and LUX-lung 6 studies, single L861Q positivity was detected in 16 (16.0%) of 100 patients with positive rare mutation.⁹ With afatinib treatment, ORR was 56.3%, PFS was 8.2 months, and OS was 17.1 months in these patients. Yang et al¹⁴ reported that 8.2 months of PFS and 17.1 months of OS were observed in patients receiving afatinib treatment in their series of 12 cases.

In the literature by Chiu et al and Xu et al. in studies with 57 and 15 patients, erlotinib/gefitinib was used in single L861Q-positive patients, and PFS was 8.1 months and OS was 22.0 months.¹⁵ In our study, OS and PFS were found to be longer in both erlotinib and afatinib groups compared to literature results.

The OPTIMAL study is a phase III study comparing erlotinib and chemotherapy in classical EGFR mutation-positive patients. In this study, PFS was 13.1 months and OS was 22.8 months in the erlotinib arm. In our study, while the PFS of the erlotinib arm was the same as in the literature, OS was longer than in the literature. The longer OS may be due to the higher proportion of patients receiving chemotherapy in the next steps.

In the OPTIMAL study, the exon 21 L858R classical mutation was more common in females and non-smokers.¹⁶ In our study, the incidence of L861Q mutation was more common in the non-smoker group, but no difference was found in terms of gender.

Studies on the pharmacokinetics of TKIs have shown that metabolic clearance of TKIs is increased in smokers compared to non-smokers. As a result, patients who were non-smokers provided 36% more benefits.¹⁷ In our study, PFS and OS were found to be longer in both the erlotinib and afatinib arms in non-smokers, and only the OS benefit was found to be statistically significant.

Whether the development of rash is an indicator of TKI effectiveness has been investigated in many studies. Although this predictive effect was found in most of the studies, this relationship could not be clearly demonstrated in a few studies.¹⁸ In our study, unlike the literature, patients who did not develop rash had longer PFS and no difference was found in terms of OS.

The main limitations of our study are the small number of patients and its retrospective nature. Since afatinib treatment receives late repayment in our country, there is a difference in the number of patients between the groups. The TKIs chosen for treatment are the physician’s choice and may affect the results. However, our study has important findings as it is the first study to compare the efficacy of erlotinib and afatinib in a single EGFR exon 21 L861Q mutation-positive patient group.

In conclusion, both PFS and OS were found to be similar with erlotinib and afatinib treatments in rare EGFR exon 21 L861Q mutation-positive patients. In this patient group, the female

gender should be considered in terms of PFS benefit and being a non-smoker should be considered in terms of OS benefit. However, randomized studies with larger numbers of patients are needed for clearer results.

Ethics Committee Approval: This study was approved by Ethics committee of Ege University, (Approval No: 21 7T/4).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.G., B.Ç.; Design – P.G., B.Ç.; Supervision – P.G., B.Ç., D.N., E.G.; Funding – P.G.; Materials – P.G.; Data Collection and/or Processing – P.G., B.Ç., S.Ö.; Analysis and/or Interpretation – P.G.; Literature Review – P.G., B.Ç., S.Ö.; Writing – P.G.; Critical Review – D.N., E.G.

Declaration of Interests: The authors have no conflict of interest to declare.

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