Research Article

Outcomes and Prognostic Factors in Patients with EGFR Mutant Metastatic Non-Small Cell Lung Cancer Who Treated with Erlotinib

Izzet Dogan[1*], Nijat Khanmammadov[1], Melin Aydan Ahmed[1], Anıl Yıldız[1], Pinar Saip[1], Adnan Aydiner[1], Sezai Vatansever[1]

[1]*Istanbul University Institute of Oncology, Medical Oncology, Istanbul, Turkey.*

Abstract

The study's goal is to evaluate the effectiveness of erlotinib in patients with EGFR mutant metastatic non-small cell lung cancer (mNSCLC). The patient's medical data were analyzed retrospectively. Erlotinib's effectiveness was assessed by the radiological response. Survival analyzes were done for prognostic factors. Eighty-five patients were included in the study. 49 (57.6%) of the patients were female, and the average age was 60 (range, 33-85). Exon 19, exon, 21, and other mutations were detected in 62.4%, 24.7%, and 12.9%, respectively. Brain metastases were present in 25.9% and liver metastases in 17.6% of patients. Before erlotinib treatment, 25.9% of the patients received chemotherapy, and 43.5% received radiotherapy. With erlotinib treatment, complete response was found in 15.3%, partial response in 51.8%, and stable response in 10.6% of patients. Median PFS was 22.3 (95% CI, 11.0-33.5) months. Grade 1-2 side effects were observed in 29.1% of the patients, and grade 3-4 side effects in 7.1%. The median OS was found as 37.5 (95% CI, 22.6-52.4) months. The 5-years overall survival rate was found to be 32.2%. In this study, we showed outcomes of erlotinib therapy in patients with EGFR mutant mNSCLC. Erlotinib has been well-tolerated and effective in disease control. Age, number of metastases, and EGFR mutation type predict treatment-related prognosis.

Keywords: *Lung cancer, EGFR mutations, Erlotinib, Metastasis, Prognosis*

Introduction

Lung cancer is the third most diagnosed cancer globally, and it is the leading reason of cancer-related deaths.[1] Although smoking is the major risk factor in the development of lung cancer, many risk factors such as radiation, air pollution, occupational exposure, and chemical exposure have been defined.[2] Non-small cell lung cancer (NSCLC) is the most diagnosed subtype divided into multiple pathological subtypes, including adenocarcinoma, large cell cancer, and squamous cell cancer. If patients in the high-risk group for lung cancer are screened for early diagnosis, the mortality associated with lung cancer can be reduced by 20%.[3] The most essential factor determining the prognosis of lung cancer is the presence of metastases; however, poor performance status, age, gender, weight loss, and smoking status were also identified as prognostic factors affecting survival.[4-6]

The prognosis of lung cancer is poor, 45% of the patients have advanced disease at diagnosis, and the five-year life expectancy in these patients is around 7%.[1] In patients with NSCLC, the prognosis of the disease is improved with the use of agents targeting driver mutations.[7] A driver mutation can be detected in 60 percent of the lung adenocarcinoma subtype.[8] Although the frequency of EGFR mutation varies according to race, gender, age, and smoking status in mNSCLC patients, it can be detected at a rate of approximately 22-64%.[9] Exon 21 L858R mutations and exon 19 deletions are the most detected EGFR mutations.[10] Many tyrosine kinase inhibitors, including 1st generation erlotinib, 2nd generation gefitinib and afatinib, and 3rd generation osimertinib, have been developed for the management of patients with EGFR mutant mNSCLC in recent years.[11]

Numerous studies showed that these tyrosine kinase inhibitors are superior to cytotoxic chemotherapy in the case of advanced disease, especially in first-line therapy.[12] The number of studies investigating which subgroup of patients diagnosed with EGFR mutant mNSCLC has the most significant clinical benefit

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Address for correspondence:
Izzet Dogan,
Istanbul University Institute of Oncology, Medical Oncology, Istanbul, Turkey.
E-mail: dr.izzetdogan@gmail.com

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from tyrosine kinase inhibitors is limited. The purpose of this research was to evaluate treatment-related outcomes in patients with mNSCLC receiving erlotinib treatment and to evaluate clinical and pathological factors affecting treatment-related prognosis.

Materials and Methods

Patient inclusion and data collection

A retrospective cross-sectional design was used for creating our study. Before the study, academic and ethical committee approvals were obtained. The Declaration of Helsinki and standards for good clinical practice were followed when conducting the study. Patients who were followed up in an outpatient clinic at a single cancer facility between 2016 and 2020 made comprised the study's patient population. The study's participants were detected using the hospital's database. All patients with a diagnosis of mNSCLC and an EGFR mutation detected by the standard approach were included in the study. The study excluded patients whose data were insufficient for statistical analysis. The radiological, pathological, and other data of the patients were noted from the patient hospital files. The chemotherapy drugs, radiotherapy treatments, and surgeries that were taken before and after erlotinib treatment were noted. The smoking history of the patients was divided into two groups as current smokers and never smokers. EGFR mutations were examined by DNA-specific allele-based polymerase chain reaction (PCR) method.

Erlotinib was used at 150 mg once a day. The treatment-related response was evaluated radiologically and clinically every 2 or 3 months. Treatment-related responses were assessed according to RECIST 1.1 standards. Erlotinib-related adverse events were recorded at each visit. Adverse events were evaluated based on the CTCAE v5 scale.

The duration from erlotinib onset to disease progression or dead was defined as progression-free survival (PFS). Univariate analysis of clinical and pathological parameters affecting PFS was performed. Multivariate analysis was done using the findings found to be significant in the univariate analysis in our study and the factors found to be significant in the literature. The duration from the onset of metastasis to death from any cause was defined as overall survival (OS). The Ministry of Health's death notification system was used to determine whether the patients were still alive.

Statistical analysis

Statistics related to the study were made with SPSS version 25. Continuous variables were represented by a median value, whereas categorical variables were indicated by numbers and percentages. The Kaplan Meier method was used to plot survival curves. Univariate analysis was conducted using the log-rank test. Multivariate analyzes were done by the Cox regression model. Statistically significant findings were presented as a hazard ratio with a confidence interval.

Results and Discussion

Patient characteristics and treatment modality

A total of 85 participants were enrolled in the study. The patient's median age of the patients was 60 (33-85). The female-to-male ratio was 1.36. The primary tumor originated predominantly from the right lung (61.2%). The most common histopathological subtype was adenocarcinoma. The most frequent EGFR mutations were exon 19 (62.4%), exon 21 (24.7%), and other rare (12.4%) subtypes, respectively. The number of de-novo metastatic patients was 71 (83.5%). The most extrapulmonary metastases sites were bone (61.2%), brain (25.9%), and liver (17.6%). 22 (25.9%) patients received palliative chemotherapy before erlotinib, and 37 (43.5%) patients received palliative radiotherapy. The pathological and clinical features of the patients are listed in **Table 1**.

Table 1. Clinical, pathological, and treatment features of mNSCLC patients with EGFR mutation

Characteristics	Number of patients Total number: 85	%
Age		
<65	54	63.5
≥65	31	36.5
Gender		
Male	36	42.4
Female	49	57.6
Smoking history		
Current smoker	41	48.2
Never smoker	28	32.9
Unknown	16	18.8
Primary tumor location		
Right side	52	61.2
Left side	33	38.8
Histopathology		
Adenocarcinoma	80	94.1
Other	5	5.9
Type of EGFR mutation		
Exon 19	53	62.4
Exon 21	21	24.7
Other types	11	12.9
Stage at diagnosis		
Stage 1	5	5.9
Stage 2	5	5.9
Stage 3	4	4.7
Stage 4	71	83.5
Primary lung surgery		
Yes	10	11.8
No	75	88.2
Number of metastatic sites		
1	25	29.4
2	31	36.5
≥ 3	29	34.1
Metastatic sites		
Bone	52	61.2
Brain	22	25.9
Liver	15	17.6
Adrenal gland	9	10.6

Other sites	6	7.1
Treatments before erlotinib		
Palliative chemotherapy	22	25.9
Palliative radiotherapy	37	43.5
Metastasectomy	4	4.7

The number of patients with an objective response to erlotinib treatment was 57 (67.1%), and the disease control rate was 77.7% **(Table 2)**. At the time of analysis, disease progression was developed in 62 (72.9%) patients, and three (3.5%) patients discontinued erlotinib due to toxicity. Grade 1 and 2 adverse events were detected in 25 (29.4%) patients. grade 3-4 side effects developed in 6 (7.1%) patients. The most prevalent side effect was rash, which occurred in 22 (25.9%) of the individuals. T790M resistance mutation was evaluated in 49 (57.6%) patients after disease progression by taking either liquid (72.4%) or a new tissue biopsy (27.7%). T790M resistance mutation developed in 33 (57.6%) of these patients. 28 (32.9%) patients received osimertinib after progression under erlotinib treatment, and 8 (9.4%) patients received palliative chemotherapy.

Table 2. Responses to erlotinib in mNSCLC patients with EGFR mutation

	Number of patients Total number:85	%
Response ratios		
Complete response	13	15.3
Partial response	44	51.8
Stable disease	9	10.6
Progresssşon	19	22.4
Objective response ratio	57	67.1
Disease control ratio	66	77.7

Survival outcomes and prognosis

The average follow-up period in the post-metastasis period was 24.7 months. Erlotinib-related PFS was found at 22.3 months (95%, CI, 11-33) **(Figure 1)**. Pathological and clinical parameters affecting PFS were examined **(Table 3)**. In multivariate analysis; age (p=0.02), EGFR mutation type (p=0.01), and metastatic site number (<0.001) were determined as factors affecting erlotinib-associated PFS. At the time of study analysis, 50 (58.8%) of the patients had died. Median OS was determined as 37.5 months (95% CI, 22.6-52.4) from the post-metastasis period **(Figure 2)**. The five-year overall survival rate was found as 32.2%.

Table 3. Univariate and multivariate analysis for PFS in the EGFR mutant mNSCLC patients who were treated with erlotinib

	Univariate analysis	Multivariate analysis	
	P-value	P-value	HR (95% CI)
Age (<65 vs. ≥65)	0.36	**0.02**	2.5 (1.1-5.6)
Gender (Male vs. Female)	0.75	0.09	1.9 (0.8-4.5)
Smoking history (Yes vs. No)	0.90	0.31	0.6 (0.2-1.5)
Primary tumor site (Right vs. Left)	0.28		
Histopathology (Adenocarcinoma vs. another type)	**0.01**	0.42	2.3 (0.2-19.3)
Type of EGFR mutation (Exon 19 vs. Exon 21)	0.29	**0.01**	2.6 (1.1-6.0)
Primary surgery (Yes vs. No)	0.20		
De-novo metastatic disease (Yes vs. No)	0.13	0.09	2.8 (0.8-9.8)
Number of metastatic sites			
1	**<0.001**	**<0.001**	1
2		**0.01**	3.5 (1.3-9.6)
≥ 3		**<0.001**	15 (4.3-52.3)
Brain metastasis (Yes vs. No)	0.36	0.62	1.2 (0.5-2.9)
Liver metastasis (Yes vs. No)	0.25		
Adrenal gland metastasis (Yes vs. No)	**<0.001**	0.11	2.6 (0.8-8.7)

Multivariate analysis model p-value <0.001

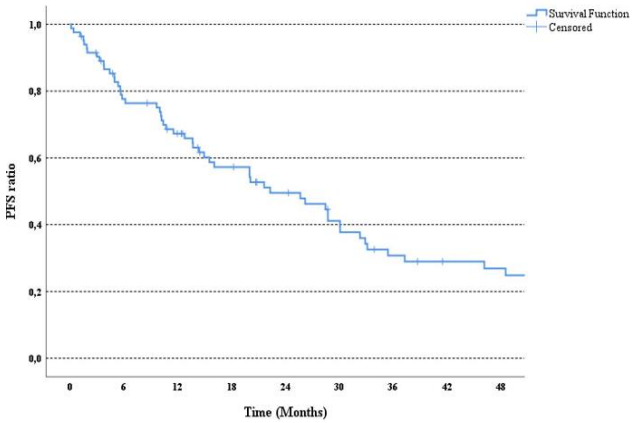

Figure 1. Kaplan Meier Curve for PFS in EGFR mutant mNSCLC patients treated with Erlotinib

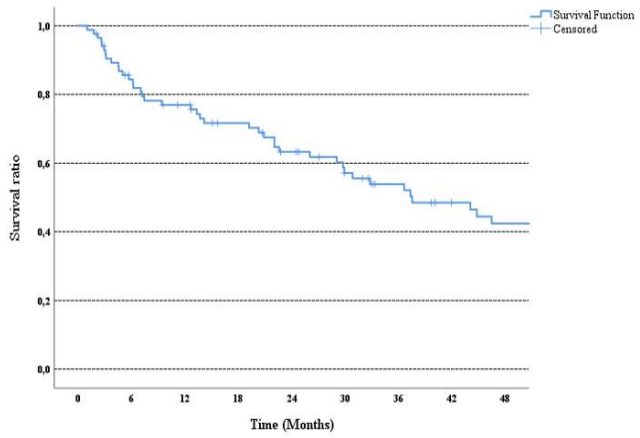

Figure 2. Kaplan Meier Curve for OS in EGFR mutant mNSCLC patients

In our study, we showed that erlotinib benefits survival and is safe in patients with EGFR mutant mNSCLC. Numerous randomized controlled studies have shown that EGFR inhibitors were superior to standard chemotherapy in EGFR mutant mNSCLC patients. In the OPTIMAL study, the results of which were announced in 2011, in the first-line treatment, median PFS was found to be 13.1 months in the erlotinib arm, while it was 4.6 months in the chemotherapy arm with more toxicity.[13] In the EURTAC and ENSURE studies conducted in patients with EGFR mutant mNSCLC, although the erlotinib arm was superior in terms of median PFS when compared with the combination of platinum-based cytotoxic chemotherapy, both treatment arms were similar in terms of median OS; and median OS was observed more than two years.[14, 15] In these studies, the most important grade 3-4 side effect associated with erlotinib was detected as rash, approximately 10%. In our study, EGFR-related PFS was found to be higher with a median of 22.3 months compared to other studies. This can be explained by the fact that erlotinib's efficacy varies depending on the country. The frequency of EGFR mutations and the rates of EGFR mutation types in patients with lung cancer vary according to countries and regions. In a worldwide analysis, exon 19 mutations were found at a rate of 45%, and exon 21 L858R mutations at a rate of 44% in lung cancer tissue samples.[16] In our study, the frequency of exon 19 mutation was determined as 62.4%. In the subgroup analysis of the ENSURE study, patients with exon 19 mutations benefit more from erlotinib treatment compared to patients with exon 21 L858R mutation.[15] This situation may explain the better outcome in erlotinib-associated PFS in our study. In the patient group in our study, the median OS was found as 37.5 months. These better results can be explained by the good rate of erlotinib-associated PFS, and the use of osimertinib, a third-generation EGFR mutation inhibitor, in 28 (32.9%) patients after progression. Twenty-two (25.9%) of the patients in our study had received palliative chemotherapy before erlotinib treatment. In a phase 3 study evaluating the effectiveness of erlotinib in maintenance treatment in patients who had previously received chemotherapy, erlotinib provided better PFS compared to placebo in patients who had not had progressive disease after four cycles of cytotoxic chemotherapy.[17]

We identified patient groups that benefited more from erlotinib in our study. Age, number of metastatic sites, and EGFR mutation type predict treatment-related prognosis. In our study, we found that the patients over 65 years of age benefited less from erlotinib treatment compared to the patients under 65 years of age. In a study conducted by the Cancer Institute of Canada, the efficacy of erlotinib in the patient group with mNSCLC was found to be similar in the population above and below 70 years of age.[18] However, in this investigation, there was a statistically significant difference in past chemotherapy treatment between the groups. The population under 70 years of age had received more intensive cytotoxic chemotherapy before erlotinib. This may have reduced the effectiveness of erlotinib in the young population under 70 years of age. In this study, we showed that patients with mNSCLC with exon 19 mutations benefited more from erlotinib treatment than patients with exon 21 mutations. Similar to the results in our study, in a retrospective study, the median OS was found as 34 months in patients with mNSCLC with exon 19 mutation who were used with erlotinib and gefitinib, while it was 8 months in patients with exon 21 mutation.[19] In another study evaluating 77 Korean patients with EGFR mutant mNSCLC received gefitinib and erlotinib, better PFS was found in patients who had exon 19 mutations compared to patients who had exon 21 mutations; however, Response rates and median OS were not different.[20]

Our study had some limitations. Because our study was retrospectively designed, the patient group was heterogeneous, and some data were missing. There is a risk of selection bias in retrospective and single-center studies.

Conclusion

In our study, we demonstrated the real-life outcomes of erlotinib in patients with EGFR mutant mNSCLC. Erlotinib was found to be effective in our patient group and was well tolerated. In our study, we showed that people over 65 years of age, patients with more than one metastasis site, and patients with exon 21 mutations (versus exon 19) under erlotinib treatment have a worse prognosis than other patients. In the future, with a better understanding of the genetic and molecular structure of lung cancer, it is expected that more effective and less toxic treatments targeting these mutations will be developed.

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Conflict of interest
None.

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Ethics statement
The local ethics committee approved this study at the Istanbul University Faculty of Medicine (Number:2021/266748).

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