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Evaluation of Progression-Free Survival and Overall Survival of Epidermal Growth Factor Receptor-Positive Metastatic Lung Adenocarcinoma Patients Treated with Erlotinib

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Abstract

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib and gefitinib have shown promising efficacy and tolerability in patients with advanced NSCLC. Identifying subgroups of patients who benefit from EGFR-TKI treatment may help achieve better treatment responses. Therefore, this study was performed to evaluate the indicators of response to treatment, including progression-free survival (PFS) and overall survival (OS) of patients.

Methods: The study was performed as a prospective cohort in patients referred to Hazrat Rasoul Akram Hospital in Tehran for two years (April 2019-April 2021). Erlotinib was administered to patients at 100-150 mg daily. After completion or discontinuation of erlotinib, patients were followed up every three months to evaluate clinical outcomes.

Independent t-test or Man-Whitney test was used to compare quantitative variables, chi-square or Fisher exact test was used to compare qualitative variables, and correlation test was used to determine the relationship between quantitative data. Analysis of overall survival and progression-free survival was performed using the Kaplan-Meier test. Significant levels less than 0.05 were considered.

Results: Thirty-two patients participated in the final analysis. Out of 32patients, 21 (65.6%) were female, and 11 (34.4%) were male. The mean age was 59.12±14.17years (32–89years). The mean PFS was 11.44±9.35months and, the OS of patients was 21.78±14.35months. Of the 32 patients, 4 (12.5%) had a history of smoking and, the rest had no history of smoking.

Conclusion: Finally, according to the findings of the present study, the use of erlotinib can be considered as an effective first-line treatment option with controllable toxicity in patients with advanced or metastatic NSCLC with positive EGFR. In addition, metastatic progression asymptomatic disease has been identified as the predominant pattern of disease progression. It can be stated that smoking history can play a risk factor in reducing PFS time.

Keywords: Lung Cancer, Erlotinib, Epidermal Growth Factor Receptor, Overall Survival, Progression-Free Survival

Conflicts of Interest: *None declared*
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Introduction

Non-small cell lung cancer (NSCLC), which accounts for more than 85% of lung cancers, is the leading cause of

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↑What is "already known" in this topic:

Non Small cell lung cancer (NSCLC) is the leading cause of death worldwide. Treatment has changed as individual therapy based on the molecular characteristics of the tumor. Epidermal growth factor receptor (EGFR) is one of the variables in the treatment of NSCLC. EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib have shown promising efficacy and tolerability in patients with advanced NSCLC. Identifying subgroups of patients who benefit from EGFR-TKI treatment may help achieve better treatment.

→What this article adds:

The present study showed that the use of erlotinib can be considered as an effective first-line treatment option with controllable toxicity in patients with advanced or metastatic NSCLC with positive EGFR. Smoking history can play a risk factor in reducing progression free survival (PFS) time.

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death worldwide. Most patients with N SCLC have advanced local disease or disease metastasis in the initial evaluation (1, 2). Standard first-line treatment typically involves platinum-based combination chemotherapy, but this treatment provides moderate overall survival (OS) for the patient (3, 4). Treatment has changed as individual therapy based on the molecular characteristics of the tumor with the advancement of molecular technology (5). Epidermal growth factor receptor (EGFR) is one of the crucial variables in the treatment of NSCLC. Epidermal growth factor receptor (EGFR) is commonly expressed or overexpressed in NSCLC and has become a valid treatment target (6). Gradually, tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib, erlotinib, and afatinib and the third generation of these drugs, Osimertinib, became available to patients. EGFR tyrosine kinase inhibitors (EGFR-TKIs) inhibit the intracellular portion of EGFR tyrosine kinase, thereby blocking signal transduction pathways involved in cancer cell survival (6, 7). EGFR-TKIs such as erlotinib and gefitinib have shown promising efficacy and tolerability in patients with advanced NSCLC. Numerous clinical factors affect the response to EGFR-TKIs. Identifying subgroups of patients who benefit most from EGFR-TKI treatment may help achieve better therapeutic responses (8, 9). Studies show that erlotinib is more effective in Asian patients, women, and people without a smoking history and EGFR mutations are usually more common in these subgroups (10, 11).

The presence of EGFR-activating mutations is associated with a better therapeutic response by EGFR-TKI in patients with advanced NSCLC (11, 12). Patients with mutations in exon 21 of the L858R gene and exon 19, which processes the tyrosine kinase portion of the EGFR gene, have much better therapeutic results in treating of EGFR-TKIs than in standard platinum therapy. Therefore, EGFR-TKIs are currently used as a first-line standard in NSCLC patients with EGFR mutations (12, 13).

Despite the benefits of EGFR-TKI treatment in lung cancer with EGFR mutation, the development of therapeutic resistance is one of the leading clinical problems (14, 15). It is not clear if the treatment with EGFR TKI is beneficial when the disease progresses; but in practice, it is commonly used (16). Each patient probably has multiple tumor clones that each of these clones may develop resistance through different mechanisms. Continuous suppression of these clones through EGFR-TKIs can essentially prevent disease progression. Also, at the time of treatment discontinuation, the rapid progress of the disease in 20% of individuals indicates the importance of continuing treatment (17).

However, pharmacodynamics interactions, toxicity, costs, and high molecular strength, including T790M mutations, can limit the benefits of continuing treatment with drugs such as erlotinib (17, 18). No study has been performed in Iran on the response of NSCLC patients with EGFR mutation to EGFR-TKIs, including erlotinib. Therefore, this study aimed to evaluate the treatment response index, including progression-free survival (PFS) and overall survival (OS) of metastatic lung adenocarcinoma patients treated with erlotinib.

Methods

The study was performed as a prospective cohort in patients referred to Hazrat Rasool Akram Hospital in Tehran for two years (April 2019-April 2021). Data were collected after the approval of the Iran University of Medical Sciences (IR.IUMS.FMD.REC.1398.315). Written consent was obtained from all patients stating their consent to enter the project. The information obtained from the patients was considered confidential.

Patients with the following criteria were included in the study: histology or pathology confirming metastatic or advanced NSCLC, confirmed EGFR activating mutation (mutation in exons 18-21 of EGFR gene), candidate for erlotinib. Excluded criteria included: history of receiving systemic chemotherapy for advanced or metastatic disease, neoadjuvant or adjuvant chemotherapy less than six months ago, history of radiotherapy 14 days before erlotinib. Sampling was done randomly, and all patients who met the inclusion criteria were included. Sampling was continued until the number of samples considered was completed.

Erlotinib (which was different in the brand) was administered to patients at 100-150$_{mg}$ daily. Patients were visited every two months based on the patient's treatment plan. Patients were followed up every three months to evaluate clinical outcomes. The progression-free survival was considered as the primary outcome and the overall survival was considered as the secondary outcome. The pattern of disease progression was determined based on the presence of cancer-related symptoms (symptomatic or asymptomatic) and the location of progression as follows: Local progression (tumor size increases), metastatic disease (at least one new lesion), overall progression (increased tumor size in two or more tumor lesions that initially responds to or has undergone erlotinib treatment).

After completing the checklists, their information was entered into SPSS 21 software. In the descriptive analysis, mean and standard deviation were used. Independent t-test or Man-Whitney test was used to compare quantitative variables, chi-square or Fisher exact test was used to compare qualitative variables, and correlation test was used to determine the relationship between quantitative data. Analysis of overall survival and disease-free survival was performed using the Kaplan-Meier test. Significant levels less than 0.05 were considered.

Results

During the study period, 32 people participated in the final analysis after completing the required data. Out of 32 patients, 21 (65.6%) were female and, 11 (34.4%) were male. The mean age was 59.12 ± 14.17$_{years}$ (32–89years). The mean PFS was 11.44 ± 9.35 months and, the OS was 21.78 ± 14.35$_{months}$. Of the 32 patients, 4 (12.5%) had a history of smoking and, the rest had no history of smoking.

Analysis of OS and PFS was performed using the Kaplan-Meier test (Figs. 1 and 2). There was no statistically significant difference between OS and PFS between men and women (P=0.310, P=0.375, respectively) (Figs. 3 and 4). Statistical analysis of the data showed a statistical-

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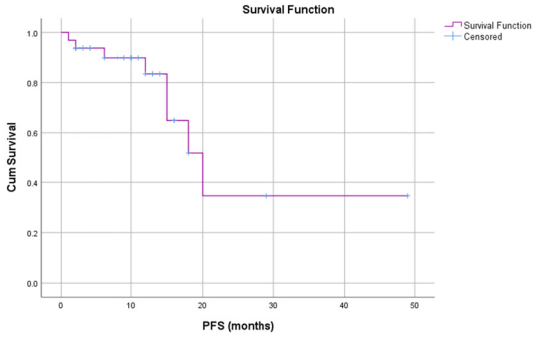

Fig. 1. Disease-free survival in participants

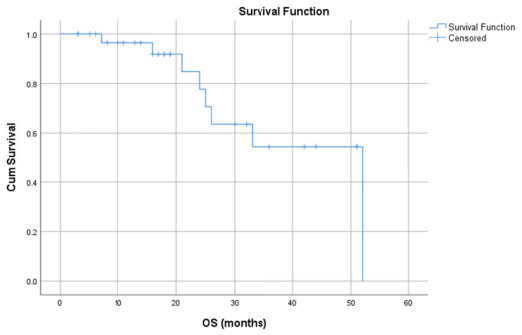

Fig. 2. Overall survival in participants

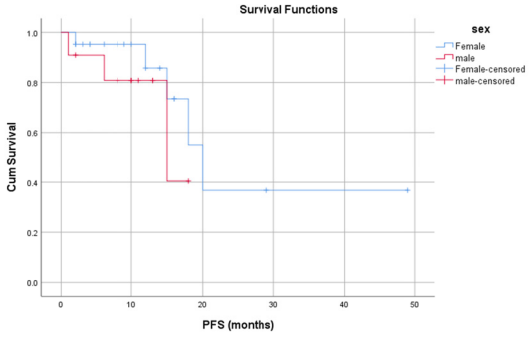

Fig. 3. Disease-free survival in participants according gender

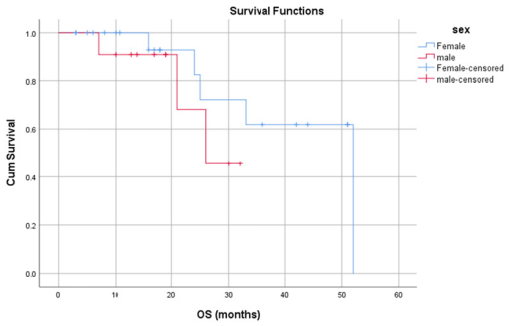

Fig. 4. Overall survival in participants according gender

ly significant difference between the study of PFS between smokers and non-smokers (Log Rank=3.390, P=0.036) so that non-smokers survived without disease longer than smokers (Fig. 5), However, there was no statistically significant difference between the OS of smokers and non-smokers (Log Rank=3.289, P=0.070) (Fig. 6).

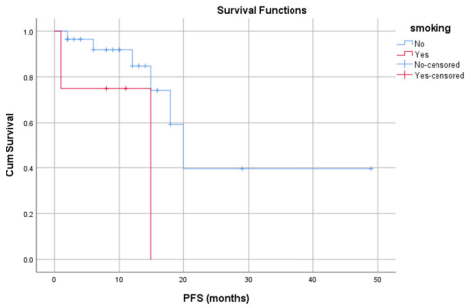

Fig. 5. Disease-free survival in participants according smoking

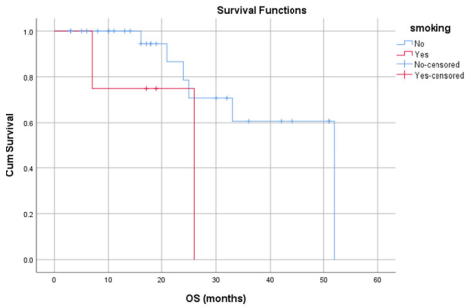

Fig. 6. Overall survival in participants according smoking

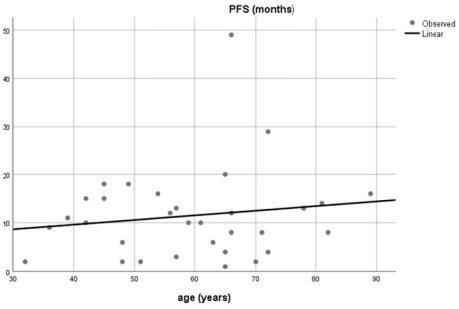

Fig. 7. Scatter plot with fitted regression line between disease-free survival and age (Standardized Coefficients. Beta= -0.145, R= 0.145, P= 0.427)

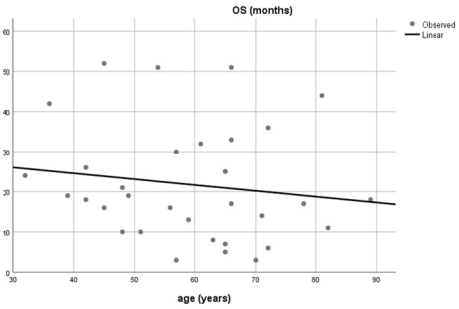

Fig. 8. Scatter plot with fitted regression line between overall survival and age (Standardized Coefficients, respectively. Beta= -0.143, R= 0.433)

There was no significant correlation between age and PFS and between age and OS (Standardized Coefficients Beta=-0.145, R=0.145, P=0.427 and Standardized Coefficients, respectively. Beta=-0.143, R=0.433) (Figs. 7 and 8).

Discussion

The study aimed to determine the survival of patients

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with EGFR-positive metastatic lung adenocarcinoma treated with erlotinib. The findings of the study showed that there was no statistically significant difference between PFS and OS of patients according to patient gender. However, PFS was significantly higher in patients without a history of smoking. 25% of patients were still alive at the end of the study and, 75% of patients died.

Most patients with NSCLC and EGFR positive receive first- or second-generation EGFR TKI as primary treatment for metastatic disease. These patients had 60% drug resistance, which is mainly related to genetic mutations. In some treatment regimens, drug combinations are used to overcome drug resistance (19). Treatment should not be stopped if the tumor has not stopped growing. Treatment responses are also expected to differ in some populations due to the cytostatic nature of drugs and racial differences (20).

Metastatic progression by creating new sites of metastasis and asymptomatic disease The predominant patterns of disease progression in first-line treatment with erlotinib in patients with advanced or metastatic NSCLC are carriers of EGFR-activating mutations. Some studies suggest that liver metastasis appears to be an independent prognostic factor for PFS in these patients. This analysis also supports the benefits of first-line erlotinib in patients with advanced or metastatic EGFR mutant NSCLC in a natural environment (21). Efficacy data obtained in the present study suggest that erlotinib is an active treatment in tumor response and survival in patients with NSCLC-enhanced EGFR-positive mutations. As a descriptive comparison, the results of the effectiveness of the present study are consistent with those previously reported in the EUTARC experiment with first-line erlotinib treatment in European patients with NSCLC-positive EGFR mutation (22).

The mean PFS level in the present study was 11.44 months. In the study of Rosell et al., This value was 9.7 months (23). In the Ortega-Granados study, this was 8.8 months (21).

Studies show that Erlotinib prescribed as a first-line treatment is well tolerated in patients with advanced or metastatic NSCLC. Erlotinib toxicity is generally mild and controllable, and no treatment-related mortality has been reported. Less than a quarter of patients experience grade 3 toxicity (23, 24). The most common side effect of erlotinib is skin rash and diarrhea. Although erlotinib is temporarily discontinued in about 30% of patients, it is due to erlotinib poisoning in less than 9% of cases. Liver metastasis appears to be less common in patients with NSCLC who are EGFR positive than brain and bone (25). The presence of liver metastasis is independently associated with PFS. The results of studies show that liver metastasis is associated with an increased risk of PFS reduction in patients with liver metastases treated with erlotinib in a first-line setting (26). Hepatic metastasis also predicts a weak response to erlotinib as a second-and third-line treatment in patients with metastatic lung adenocarcinoma (27). The worse prognosis associated with liver metastasis is probably due to a more invasive disease, usually accompanied by more metastatic sites that predict worse survival (23). Management of liver metastases should be a priority for patients with advanced NSCLC with EGFR mutation for early detection of disease progression. Other prognostic factors in NSCLC, such as age, tumor status, and EGFR mutation status, have not yet been identified as predictors of PFS (27-29).

No difference in PFS based on age and functional status may indicate that elderly patients ($>65_{years}$) can also benefit from erlotinib treatment in first-line settings (30, 31). The predominant pattern of progression in NSCLC is a metastatic progression with the development of new metastatic sites in half of the patients and then local progression with metastatic progression in 30% of patients. Overall, less than 20% of patients had only local progression (21). Thus, erlotinib may be more effective in preventing local progression than developing new metastases (32). In addition, approximately 60% of asymptomatic patients progressed, in whom continued treatment with EGFR-TKI is recommended. Some studies emphasize that EGFR-TKI treatment should be maintained after disease progression (33, 34). However, some guidelines recommend changing platinum-based chemotherapy as the disease progresses to EGFR-TKI therapy (35).

The onset of flare-ups after discontinuation of EGFR-TKI is a concern in patients with NSCLC and EGFR-positive patients progressing in treatment with EGFR-TKI (35, 36).

The main limitation of this study is related to the sample size limit of the study. In addition, the exact period in which patients were to be treated with erlotinib was not specified. Another limitation is the lack of appropriate information about new sites of metastases in the course of treatment of the disease and the therapeutic side effects of erlotinib treatment.

Conclusion

Finally, according to the findings of the present study, the use of erlotinib can be considered as an effective first-line treatment option with controllable toxicity in patients with advanced or metastatic NSCLC with positive EGFR. In addition, metastatic progression asymptomatic disease has been identified as the predominant pattern of disease progression. It can be stated that smoking history can play a risk factor in reducing PFS time.

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Conflict of Interests

The authors declare that they have no competing interests.

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