ORIGINAL RESEARCH

Predictive Value of *EGFR* Mutation Status for First-Line Tyrosine Kinase Inhibitor Treatment in Patients with Advanced Lung Cancer

Youqin Xie, MD; Jinliang Chen, PhD; Wen Zhu, MD; Zhihui Ye, MD; Xuedong Lv, MD

ABSTRACT

Objective • This study aims to investigate and analyze the correlation between EGFR-TKI first-line therapy and *EGFR* mutation status in patients with advanced lung cancer.

Methods • We selected 60 patients with advanced lung cancer and *EGFR* mutations (diagnosed as stage IIIb or IV) from our hospital between January 2019 and November 2022. Each patient underwent an *EGFR* mutation test and was categorized into two groups based on their mutation status: 28 patients with exon 21 mutations and 32 with exon 19 deletions. After three months of therapy, we assessed treatment efficacy and adverse reactions.

Results • Our data revealed that in the *EGFR* exon 21 mutation group, the objective response rate (ORR) and disease control rate (DCR) were 57.14% and 60.71%, respectively. In the EGFR exon 19 deletion group, the ORR and DCR were 68.75% and 84.38%, respectively. There were significant differences in DCR and ORR between the two *EGFR* mutation states, with statistical significance ($P < .05$). The progression-free survival (PFS) in the *EGFR* exon 21 mutant group was 8.4 months after third-generation EGFR-TKI treatment, while the EGFR exon 19 deletion group had a PFS of 12.7 months after the same treatment, with a statistically significant difference ($P < .05$). Cox regression analysis showed that female patients with no smoking history and an adenocarcinoma pathological type had significantly better PFS after treatment compared to male patients with a smoking history and squamous cell carcinoma type, with statistical significance ($P < .05$). Age and clinical stage did not significantly impact PFS after third-generation *EGFR*-TKI treatment ($P > .05$). Adverse reaction incidences, such as nausea, fatigue, diarrhea, vomiting, and rash, did not significantly differ in either the EGFR exon 21 mutation group or the EGFR exon 19 deletion group ($P > .05$).

Conclusion • The status of *EGFR* mutations serves as a predictive factor for PFS, DCR, and ORR in lung cancer patients undergoing EGFR-TKI first-line therapy. This status can be a valuable predictive indicator of lung cancer treatment efficacy, with potential applications in clinical practice. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Lung cancer is a common malignant tumor.[1] The incidence of lung cancer has increased rapidly in recent years, leading to higher mortality rates.[2] Approximately 781 000 people in China are diagnosed with lung cancer each year.[2,3] Moreover, there is a noticeable trend of younger individuals being affected by this disease.[2] In clinical practice, a significant number of lung cancer patients are diagnosed at an advanced stage or present with metastases, often rendering them ineligible for surgical intervention. Currently, targeting EGFR (Epidermal Growth Factor Receptor) inhibitors represents an effective approach for the treatment of patients with advanced tumors.[4]

EGFR therapy is a targeted treatment approach in the field of oncology. It specifically targets and inhibits the activity of *EGFR*, a protein involved in cell growth and proliferation. In the context of cancer treatment, EGFR therapy aims to block the signals that promote the uncontrolled growth of cancer cells driven by abnormal *EGFR* activity. This therapy plays a crucial role in managing certain types of cancer, particularly non-small cell lung cancer, by slowing down or inhibiting tumor growth and improving patient outcomes.[4-6]

However, clinical practice has demonstrated that patients undergoing EGFR inhibitor therapy often develop

drug resistance, primarily due to *EGFR* gene mutations. Enhancing the efficacy of targeted drugs for advanced tumor patients necessitates a more effective and precise approach to monitoring gene mutations, highlighting its paramount importance.[5-7] Therefore, this study was conducted to understand the relationship between EGFR-TKI therapy and *EGFR* gene mutations in lung cancer patients. Considering the emerging issue of drug resistance and the growing incidence of lung cancer, this study holds significance. It aimed to provide insights into optimizing treatment strategies, potentially prolonging progression-free survival, and improving the quality of life for patients with advanced lung cancer.

MATERIALS AND METHODS

Study Design

A retrospective clinical design was adopted, and a cohort of 60 patients diagnosed with *EGFR*-mutated lung cancer at stage IIIb or IV were enrolled from our hospital from January 2019 to November 2022. Complete clinical data of these patients were systematically analyzed to examine the correlation between the effectiveness of first-line EGFR-TKI treatment and the *EGFR* gene status in patients with advanced lung cancer. This study received ethical approval from the Ethical Committee of Nantong No.1 People's Hospital.

Lung Cancer Diagnosis Criteria

Pathological Examination. The criteria for diagnosing lung cancer encompass multiple methods. The gold standard for diagnosis is a pathological examination, which involves obtaining tissue samples through various techniques, including bronchoscopy for central tumor sampling, punctures for peripheral lesions, and biopsies guided by CT and B-ultrasound to identify the tumor's cell type, whether it is small-cell lung cancer, squamous cell carcinoma, adenocarcinoma, or other variants. In this study molecular pathological testing was performed on the acquired tissue to identify meaningful target genes, guiding the selection of appropriate targeted therapies. This minimally invasive approach enable precise tumor treatment.

Alternative Diagnostic Methods. In cases where pathological diagnosis was unavailable, alternative diagnostic methods awere adopted. Imaging examinations such as CT, PET-CT, X-ray, and serum tumor markers, including carcinoembryonic antigen, served as clinical references, indicating the potential presence of a tumor, though without providing a definitive diagnosis. These alternative methods were valuable in situations where pathological examination is not feasible or inconclusive.

Lung cancer presents diagnostic challenges due to its similarity to other diseases, including tuberculosis and fungal infections. Imaging examinations often produce results that can resemble those of a tumor, making it imperative to rely on pathological examination as the definitive diagnostic method. Therefore, pathological examination remained the gold standard for confirming the diagnosis of lung cancer in this study, offering the most accurate and conclusive results in distinguishing it from other potential conditions.[4-7]

Patient Selection Criteria

All patients included in this study met the specified inclusion criteria: (1) they had cytological or histological evidence of stage IIIb-iv lung cancer; (2) they had at least one measurable lesion; (3) their specimens met the requirements for *EGFR* gene testing, ensuring sufficient tumor tissue or cell specimens submitted for testing; (4) adherence to specimen treatment standards; (5) their cytological specimens tested after smear and pathological tumor cell diagnosis; (6) patients without a surgical history and those with accurate and complete clinicopathologic data were included in this study.

Exclusion criteria were as follows: (1) individuals who did not meet inclusion criteria; (2) cases where pathological specimens did not meet the necessary criteria for *EGFR* detection; (3) patients who had undergone prior anti-tumor therapies, such as chemoradiotherapy and EGFR-TKI treatments, were excluded from the study.

Patient Stratification

After meeting the inclusion criteria, each patient underwent *EGFR* mutation testing. Subsequently, they were categorized into two distinct groups based on the mutation status revealed by the EGFR mutation test. The resulting groups comprised 28 patients with exon 21 mutations and 32 patients with exon 19 deletions. This stratification was critical for analyzing the impact of different *EGFR* mutation types on treatment outcomes.

Treatment Methods

All subjects participating in this study received third-generation EGFR-TKI, specifically Osetinib, administered orally at a daily dosage of 250 mg.

Mechanism of Osetinib. Osetinib was selected due to its documented efficacy in inhibiting *EGFR*-sensitive mutations. Notably, it also demonstrates inhibitory effects against the *T790M* mutation on exon EGFR20. This specific mutation accounts for resistance, occurring in over 50% of patients previously treated with first- and second-generation EGFR-TKI therapies.

Efficacy and Adverse Reaction Evaluation. Following a three-month course of oral therapy, the patients were subjected to comprehensive evaluations to assess both treatment efficacy and the presence of any adverse reactions. These evaluations are crucial for understanding the impact of the treatment regimen on the patients and its overall effectiveness.

Evaluation Criteria for Efficacy and Adverse Reactions

In this study, the evaluation of treatment efficacy and adverse reactions was based on established criteria. Specifically, we referred to RESIST 1.1 guidelines for efficacy assessment and employed the toxicity classification evaluation criteria for

anticancer drugs provided by the World Health Organization as a reference. These standardized criteria allowed for a comprehensive and reliable assessment of treatment outcomes and the presence of any adverse reactions.

Statistical Analysis

The statistical analysis was perfomed using SPSS 22.0 software (IBM, Armonk, NY, USA). The results for counting data are presented as frequency and component ratios using a chi-square test (χ^2) to compare two groups. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and a *t* test was employed to make comparisons between the groups. A significance level of $P < 0.05$ served as the threshold to determine statistical significance.

RESULTS

Demographic and Clinical Characteristics of Study Groups

In the exon 21 mutant group, there were 13 female patients and 15 male patients, with an average age of 56.8±11.1 years. In the exon 19 deletion group, there were 14 females and 18 males, with an average age of 57.1±12.6 years. No statistically significant differences were observed in age, gender, pathological types, or other general information between the two groups ($P > .05$), indicating that the groups were comparable.

Relationship Between Short-Term Efficacy and EGFR Mutation Status

The findings revealed that the patients in the EGFR exon 21 mutant group exhibited an objective response rate (ORR) of 57.14% and a disease control rate (DCR) of 84.37%. In contrast, patients in the EGFR exon 19 deletion group demonstrated an ORR of 68.75% and a DCR of 87.50%. Notably, there were significant differences in DCR and ORR between patients with these distinct *EGFR* mutation states, and these differences held statistical significance ($P < .05$). The detailed findings are presented in Table 1.

Relationship Between Patient Survival and EGFR Mutation Status

In the EGFR exon 21 mutant group, the progression-free survival (PFS) was recorded at 8.4 months following third-generation EGFR-TKI treatment. In contrast, patients in the EGFR exon 19 deletion group demonstrated a significantly extended PFS of 12.7 months after third-generation EGFR-TKI treatment, with a statistically significant ($P < .05$) difference between the two groups.

To further analyze these findings, the study employed the Cox regression method for a multivariate regression analysis. The results revealed that in comparison to male patients with a history of smoking and a pathological diagnosis of squamous cell carcinoma, female patients with no history of smoking and a pathological diagnosis of adenocarcinoma experienced significantly improved PFS after treatment, with statistical significance ($P < .05$). Furthermore, it was found that factors such as age and clinical stage had no significant impact on PFS after third-generation EGFR-TKI treatment ($P > .05$), refer to Table 2.

Table 1. Comparison of Short-Term Efficacy Between the Two Groups [n (%)]

Group	n	ORR	DCR
Exon 21 Mutants	28	16(57.14)	17(60.71)
Exon 19 Mutants	32	27(84.37)	28(87.50)
χ^2		5.454	5.714
P value		.019	.016

Abbreviations: ORR, Objective Response Rate; DCR, Disease Control Rate.

Table 2. Multivariate Analysis of EGFR Mutation Status After First-Line Treatment with EGFR-TKI in Lung Cancer Patients

Variable	95%CI	OR	*P* value
Smoking History	1.828-39.216	11.612	.001
Gender	1.607-7.357	5.219	.021
Age	0.541-3.841	1.538	.675
Pathological Type	1.278-2.526	1.942	<.001
Clinical Staging	0.003-1.169	0.851	.765

Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Table 3. Comparison of the Incidence of Adverse Reactions After Treatment Between the Two Groups [n (%)]

Group	n	Diarrhea	Rash	Vomit	Nausea	Fatigue
Exon 21 Mutants	28	9(32.14)	12(42.86)	2(7.14)	6(21.43)	6(21.43)
Exon 19 Mutants	32	9(28.13)	13(40.63)	3(9.38)	6(18.75)	7(21.88)
χ^2		0.115	0.031	0.097	0.067	0.002
P value		.734	.860	.755	.795	.964

Variations in Adverse Reactions after Treatment Among Patients with Distinct *EGFR* Mutation Status

The findings indicated that there were no notable differences in the incidence of adverse reactions, encompassing symptoms like nausea, fatigue, diarrhea, vomiting, and rash, after treatment. This observation was true for both the EGFR exon 21 mutant group and the EGFR exon 19 deletion group. Consequently, no statistically significant differences were identified in the occurrence of adverse reactions between patients with these diverse *EGFR* mutation profiles after treatment ($P > .05$), refer to Table 3.

DISCUSSION

EGFR mutation is a prominent genetic anomaly in non-small cell lung cancer, boasting a mutation rate of approximately 46%.[8] Notably, within the Asian lung cancer population, the prevalence of *EGFR* gene-sensitive mutations is higher. This higher prevalence indicates that Asian individuals are more likely to benefit from the effectiveness of EGFR inhibitors.[8-9] Therefore, the detection of *EGFR* gene mutations is strongly recommended for all lung cancer patients. This recommendation is reinforced by major guidelines and is actively implemented in clinical settings in China, where it is an essential requirement for initiating targeted therapy.

EGFR plays an important role in mammals by promoting the actions of epidermal growth factor. This receptor is expressed on the cell membrane surfaces of various human cell types, including keratinocytes, epithelial cells, glial cells,

and fibroblasts.[10] Upon activation, *EGFR* serves as a conduit for transmitting signals related to cell proliferation and differentiation. The gene encoding *EGFR* is located on the short arm of chromosome 7.[10,11]

Notably, when *EGFR* gene mutations lead to overexpression, it triggers a cascade of events, including the promotion of tumor cell proliferation, angiogenesis, invasion, and metastasis, while simultaneously inhibiting tumor cell apoptosis. This intricate network of actions highlights the significance of *EGFR* in the context of cancer development and progression.[10]

The *EGFR* gene is comprised of 28 exons, with a significant concentration found in exons 18 to 21, particularly within the tyrosine kinase region. Within this genetic landscape, researchers have identified over 30 distinct mutations, both common and rare, that have been linked to lung cancer. Among these mutations, two main categories stand out: exon deletions (Del19) and exon point mutations (L858R). These two types collectively account for more than 80% of all *EGFR* mutations, emphasizing their importance in the field of *EGFR*-associated lung cancer.[11]

Tyrosine kinase inhibitors (TKI) act by competitively binding to the ATP binding site within the tyrosine kinase domain of the *EGFR* gene. This binding effectively inhibits the expression of *EGFR* and disrupts the transmission of growth signals. Therefore, TKIs play a crucial role in restraining the proliferation and metastasis of tumor cells [12]. Notably, the 19Del and L858R mutations within the *EGFR* gene trigger the activation of the tyrosine kinase domain. These specific mutations exhibit increased sensitivity to TKIs, leading them to be referred to as EGFR-TKI-sensitive mutations.[12]

The binding sites of TKI vary based on their distinct structural properties, which consequently leads to differing drug effects and potential adverse reactions. In the current Chinese market, three generations of EGFR-TKI are available, namely Ocitinib, Ametinib, and Vometinib.[13] A key unifying characteristic among these three generations of TKIs is their ability to not only inhibit *EGFR*-sensitive mutations but also target the *T790M* mutation situated on exon EGFR20.

The emergence of the *T790M* mutation, accounting for resistance, is a common challenge encountered in more than 50% of patients following the administration of first and second-generation EGFR-TKIs.[14] This multi-generational approach to treatment addresses this critical concern and enhances the therapeutic potential for patients with EGFR-mutated lung cancer.

In this study, advanced lung cancer patients with EGFR exon 19 deletion received first-line treatment with EGFR-TKI. In comparison to advanced lung cancer patients with EGFR exon 21 mutation, their short-term efficacy and PFS exhibited significant improvements, with statistically significant differences observed. The subsequent multivariate stratified analysis revealed that female patients with no history of smoking and a pathological diagnosis of adenocarcinoma displayed significantly enhanced PFS after first-line treatment with EGFR-TKI, in contrast to male patients with a history of smoking and a pathological diagnosis of squamous cell carcinoma, where the differences were once again statistically significant. These findings highlight the considerable impact of *EGFR* mutation type, gender, smoking history, and pathological diagnosis on the effectiveness of EGFR-TKI treatment.[14]

These results highlight the critical role of *EGFR* mutation type and individual patient characteristics in tailoring treatment strategies. This study highlights the factors that influence treatment outcomes and also contributes to the development of more personalized and effective approaches for managing advanced lung cancer.

Study Limitations

We acknowledge a few limitations in this study. Firstly, the study's retrospective design may introduce inherent biases and limit the ability to establish causal relationships. Secondly, the patient sample is drawn from a single hospital, potentially limiting the generalizability of the findings to broader populations. Additionally, the study's focus on short-term efficacy and progression-free survival may not provide a comprehensive picture of the long-term outcomes and potential adverse effects associated with EGFR-TKI treatment. Furthermore, the study does not consider other potential confounding variables that could impact treatment response. These limitations should be taken into consideration when interpreting the results and designing future research endeavors in this field.

CONCLUSION

This study highlights the important role of EGFR mutation status in determining treatment outcomes for lung cancer patients undergoing first-line EGFR-TKI therapy. The findings indicate that *EGFR* mutation status serves as a predictive marker for PFS, DCR, and ORR, thus offering a valuable tool for assessing treatment efficacy. These results hold significant clinical implications, suggesting that *EGFR* mutation status can be effectively employed as a predictive index in the realm of lung cancer management. By incorporating this information into clinical practice, healthcare professionals can better tailor treatment strategies and optimize therapeutic outcomes for patients with EGFR-mutated lung cancer, ultimately enhancing the quality of care in this patient population.

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CONFLICT OF INTERESTS
The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS
The data supporting the findings of this study are available from the corresponding author upon request, subject to reasonable conditions.

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