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Research Article

Metastatic EGFR-Mutant Lung Adenocarcinoma Patients: A Safety and Efficacy Analysis of First- and Third-Generation EGFR-TKIs

Suha Ali Hammed [1,a]*, Alaa Fadhil Alwan [2,b]

[1] Medical Oncology Department, Aljawad Oncology Center, Baghdad, Iraq.
[2] The National Center of Hematology, Mustansiriyah University, Baghdad, Iraq.

E-mail: suahmnm88@gmail.com [a,*], ala-sh73@uomustansiriyah.edu.iq [b]

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Abstract

In the context of metastatic non-small cell lung cancer (NSCLC), the phenomenon of resistance to therapeutic interventions is a prevalent occurrence, particularly in cases involving tumors that harbor epidermal growth factor receptor (EGFR) mutations. Tyrosine kinase inhibitors (TKIs) directed at the epidermal growth factor receptor have transformed first-line care. The objective of this study is to compare the safety and effectiveness of first-generation (gefitinib) versus third-generation (osimertinib) epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) in treatment-naïve patients with metastatic epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma. A cross-sectional cohort study was conducted at the Oncology Teaching Hospital in Baghdad from 2023 to 2024. The study included 40 adults with molecularly confirmed epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC), who received first-line gefitinib or osimertinib treatment. The tumor response was evaluated using the RECIST v1.1 criteria at the three-cycle interval, and the adverse events (AEs) were assessed according to the CTCAE v4.03 scale. The PFS was estimated using Kaplan–Meier methods. The study demonstrated that osimertinib resulted in a substantially longer mean progression-free survival (18.2 months; 95% CI: 13.97–25.03) in comparison to gefitinib (7.1 months; 95% CI: 4.54–12.46; $p<0.00000001$). A complete response was observed more frequently in the osimertinib group (85% vs. 40%). Dermatologic and gastrointestinal AEs were more prevalent in patients treated with gefitinib, while interstitial lung disease was reported exclusively in cases involving osimertinib. Osimertinib exhibited superior efficacy with a more manageable safety profile compared with gefitinib and should be preferred as first-line therapy in eligible patients with metastatic EGFR-mutant NSCLC.

Keywords: *EGFR-TKI; Osimertinib; Gefitinib; Lung Adenocarcinoma; Progression-Free Survival.*

*** Correspondence Author**

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Introduction

Lung cancer has been found to account for more deaths annually than breast, prostate, and colorectal cancers combined (Siegel et al., 2023), and it remains the leading cause of cancer mortality worldwide. NSCLC is the predominant histologic category, with adenocarcinoma being the most common, particularly among women and never-smokers (Sun et al., 2007; Travis et al., 2015).

As a result of two decades of molecular characterization, there have been notable advances in the identification of targetable drivers, particularly activating alterations in the epidermal growth factor receptor (EGFR) (Lynch et al., 2004; Sharma et al., 2007). EGFR mutations, predominantly exon 19 deletions and the exon 21 L858R substitution, have been observed in 10–15% of Caucasian and 30–40% of East Asian non-small cell lung cancer (NSCLC) cases [6,7] (Mok et al., 2009; Tan et al., 2016).

According to Global Cancer Observatory (GLOBOCAN) data from 2022, the global burden of lung cancer remains significant, with increasing incidence observed in numerous low- and middle-income regions. This observation highlights the necessity of interpreting local outcomes in the context of international trends (Lynch et al., 2004; Sharma et al., 2007; Tan et al., 2016).

First-generation EGFR-TKIs (gefitinib, erlotinib) have been shown to improve survival and quality of life when compared with chemotherapy (Rosell et al., 2009; Sequist et al., 2011; Zhou et al., 2011). However, these agents are limited by acquired resistance, most commonly the T790M gatekeeper mutation (Sequist et al., 2011).

Osimertinib is an irreversible third-generation EGFR-TKI with enhanced CNS penetration and activity against both sensitizing mutations and T790M, with favorable tolerability (Cross et al., 2014; Goss et al., 2016; Jänne et al., 2015). In the FLAURA trial, first-line osimertinib demonstrated a significant increase in survival duration when compared with first-generation tyrosine kinase inhibitors (TKI) (Mok et al., 2017; Ramalingam et al., 2020; Soria et al., 2018).

Notwithstanding the global advances in this field, robust regional data from Iraq remain scarce. The present study aims to provide a comparative analysis of the real-world effectiveness and safety of gefitinib versus osimertinib in treating Iraqi patients diagnosed with metastatic EGFR-mutant lung adenocarcinoma. This analysis is intended to inform local clinical practices.

Methodology

Study Design and Setting

Conducted from February 2023 to March 2024, this cross-sectional observational study was conducted at Iraq's Oncology Teaching Hospital in Baghdad. The collection of demographic and clinical information was conducted through prospective follow-up and retrospective chart review.

Eligibility Criteria

Participants were required to meet specific criteria to be considered eligible for enrollment. First, they had to be at least 18 years of age. Second, they had to have a confirmed diagnosis of metastatic lung adenocarcinoma. Third, they had to possess documented epidermal growth factor receptor (EGFR) mutations. All participants had to be chemotherapy-naïve prior to study enrollment and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The presence of epidermal growth factor receptor (EGFR) mutations was determined through the implementation of molecular diagnostic techniques, encompassing next-generation sequencing methodologies.

Treatment Protocol

Two oral epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) regimens, gefitinib (250 mg daily) and osimertinib (80 mg daily), were assigned to the participants. The formulation of treatment recommendations was informed by a multifaceted evaluation process that encompassed clinical judgment, mutation subtypes, and patient-specific criteria, including accessibility and tolerability.

Assessment of Therapeutic Response

The therapeutic response was evaluated at the conclusion of each of the three treatment cycles using radiographic imaging and clinical evaluation. In accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, patient outcomes were stratified into one of four categories: complete response, partial response, stable disease, or progressing disease.

Evaluation of Adverse Events

The most recent version of the Common Terminology Criteria for Adverse Events (CTCAE) was utilized for the purpose of monitoring and classifying adverse events. The investigation particularly focused on the assessment of dermatologic, gastrointestinal, and pulmonary toxicities; however, it is important to note that both hematologic and non-hematologic toxicities were thoroughly documented as well.

Statistical Analysis

The statistical analysis was conducted using SPSS version 25. Categorical variables were presented as frequencies and percentages, while continuous data were displayed as the mean ± standard deviation. In instances where statistical analysis was deemed necessary, the researchers employed the chi-square test and Student's t-test. The progression-free survival (PFS) was estimated using Kaplan-Meier analysis, and significance was defined as $p < 0.05$.

Ethical Considerations

Following a period of deliberation, the Iraqi Council of Medical Specialization formally endorsed the proposal. All participants in the study provided written informed consent. Throughout the research process, the confidentiality of the data and the anonymity of the patients were maintained.

Results

A total of 40 patients were enrolled, equally distributed between the two treatment groups. The demographic and clinical baseline characteristics are detailed in **Table 1**. Patients in both groups exhibited comparable demographics, including age, gender, and smoking status. The majority of the subjects were non-smokers, and a minority reported a positive family history of malignancy.

The sites of metastases exhibited variability, with bone involvement demonstrating the highest prevalence, followed by liver and brain metastases. As demonstrated in **Table 2**, both groups exhibited analogous patterns of disease dissemination, though brain metastases manifested slightly more frequently in the Gefitinib group.

Treatment efficacy varied considerably among the study's various arms. The Osimertinib cohort exhibited a higher complete response rate (85%) in comparison to the Gefitinib group (40%). The results of these analyses, in conjunction with other treatment-related responses and safety events, are presented in **Table 3**. It is noteworthy that patients treated with Gefitinib exhibited a higher prevalence of adverse effects, particularly dermatologic and gastrointestinal toxicities. The occurrence of interstitial lung disease (ILD) was exclusively observed within the Osimertinib group.

With respect to the disease burden, both groups exhibited multi-organ metastases. As demonstrated in **Table 2**, bone was the most frequently involved site in both treatment groups. The incidence of brain metastases was marginally elevated in the Gefitinib group, while the prevalence of liver and lymph node involvement remained consistent across both groups.

Table 1. The Demographic and Baseline Clinical Characteristics of Patients in Both Treatment Groups.

Characteristic	Gefitinib (n=20)	Osimertinib (n=20)
Mean Age (years)	58	61
Male	7	9
Female	6	11
Non-smokers	13	12
Smokers/Ex-smokers	7	8
Family History of Cancer	5	4

Table 2. The Distribution of Metastatic Sites in Patients Treated with Gefitinib Versus Osimertinib.

Site	Gefitinib	Osimertinib
Brain	3	1
Liver	4	4
Bone	8	11
Mediastinal LAP	3	2
Other Lymph Nodes	4	4

Table 3. The Treatment Responses and Reported Adverse Effects Across Both Groups.

Outcome / Adverse Event	Gefitinib (n=20)	Osimertinib (n=20)
Complete Response	8	17
Partial Response	2	2
Stable Disease	2	1
Disease Progression	8	0
Skin Reactions (Mild/Moderate)	10 (6/4)	6 (5/1)
Diarrhea	5	4
ILD	0	2
QT Prolongation	4	3
Generalized Pain	7	3

Discussion

The present study lends further credence to the clinical advantages of third-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), particularly Osimertinib, in the management of epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC).

Our findings are consistent with the results of international clinical trials, including the FLAURA and AURA3 studies, which demonstrated that the survival rate is higher and the response to the treatment is better when patients have been treated with Osimertinib than first-generation TKIs like Gefitinib (Mok et al., 2017; Ramalingam et al., 2020). The median overall survival in our cohort was 14.6 months, which is marginally higher than the 12.0 months reported in a similar cohort and comparable to the 14.4 months reported in a multi-center study from other literature. These variations may be indicative of disparities in patient selection, stage distribution, treatment accessibility, and supportive care infrastructure between regions.

The markedly higher complete response rate observed with Osimertinib in our cohort supports its role as a preferred first-line therapy. This observation is particularly salient in patients with central nervous system metastases or those who harbor the T790M resistance mutation (Gao et al., 2016). Conversely, Gefitinib, while initially beneficial, was associated with a greater frequency of adverse effects and a shorter duration of clinical benefit (Oxnard et al., 2016).

The findings are corroborated by real-world data from various populations, which highlight the consistent efficacy and safety profile of Osimertinib (Kerrigan et al., 2021; Midha et al., 2015). The present study contributes to the global narrative by offering regional evidence, underscoring the significance of context-specific oncology research in the Middle East.

Limitations

The present study is not without its limitations. The study was conducted in a single tertiary care center, which may limit the generalizability of the findings to other healthcare settings. The retrospective design carries an inherent risk of selection bias, and certain clinical parameters, such as detailed comorbidity indices and molecular biomarker profiles, were not consistently documented. Moreover, while the sample size was adequate for primary analyses, it was insufficient for subgroup comparisons, thereby limiting the statistical power. Subsequent research endeavors should investigate the longitudinal outcomes and resistance mechanisms associated with extended Osimertinib use.

Conclusion

Osimertinib has been shown to have significant clinical advantages over Gefitinib in the management of metastatic EGFR-mutant non-small cell lung cancer (NSCLC), with prolonged progression-free survival and a more manageable safety profile. These findings support its preferential use as first-line therapy in eligible patients. The findings of this study underscore salient survival patterns and treatment outcomes in Iraqi patients with lung cancer, thereby offering invaluable contextual insights for the enhancement of regional oncology practices. These results may inform multidisciplinary treatment planning, optimize follow-up protocols, and serve as a foundation for prospective studies that incorporate molecular profiling and real-world treatment pathways to further improve patient outcomes.

Declarations

Ethics Approval and Consent to Participate

Following a period of deliberation, the Iraqi Council of Medical Specialization formally endorsed the proposal. All participants in the study provided written informed consent. Throughout the research process, the confidentiality of the data and the anonymity of the patients were maintained.

Consent for Publication

Not applicable.

Availability of Data and Material

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest / Competing Interests

The authors declare that there are no conflicts of interest.

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Author Contributions

S.A.H: Conceptualization, Methodology, Data curation, Writing of the original draft.

A.F.A: Conceptualization, Methodology, Investigation, Resources, Writing of the original draft.

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Use of Generative AI and AI-Assisted Technologies

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this work.

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