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Effectiveness of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) on Life Expectancy in Non-Small Cell Lung Cancer Patients in Medan City

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ABSTRACT

Introduction: Non-small cell lung cancer (NSCLC) is strongly linked to epidermal growth factor receptor (EGFR) mutations, with tyrosine kinase inhibitors (TKIs) serving as a primary treatment. While TKIs demonstrate substantial antitumor effects, resistance differs across generations. This study evaluates the impact of first- and second-generation EGFR TKIs on the survival outcomes of NSCLC patients in Medan.

Method: A retrospective cross-sectional study was conducted on 67 EGFR-positive NSCLC patients treated with TKIs between 2017 and 2022. Medical records from four hospitals-Haji Adam Malik Hospital, Elisabeth Hospital, Prof. Dr. Chairuddin Panusunan Lubis USU Hospital, and Pirngadi Hospital-were analyzed. Patients aged >18 years with EGFR mutations (exon 18, 19, or 21) and complete records were included. Survival outcomes, including Progression-Free Survival (PFS), Median Survival Time (MST), and Overall Survival (OS), were compared using the Mann-Whitney test.

Results: All 67 The patients received either first-- or second-generation TKIs. Statistical analysis revealed that patients treated with second-generation TKIs had significantly better PFS, MST, and OS than those receiving first-generation TKIs ($p < 0.05$).

Conclusion: This retrospective study faced limitations due to incomplete data and did not assess adverse effects. However, findings indicate that second-generation EGFR TKIs provide superior survival benefits for NSCLC patients compared to first-generation TKIs. Further prospective studies are needed to validate these results and explore the impact of treatment-related toxicity.

Keywords

Life Expectancy, Effectiveness, Epidermal Growth Factor Receptor, Non-Small Cell Lung Cancer, Tyrosine Kinase Inhibitor

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INTRODUCTION

Cancer is a leading cause of mortality, with an estimated 10 million deaths in 2020, or almost 1 in 6 deaths globally.[1] Breast cancer is the most prevalent cancer, with approximately 2.3 million newly diagnosed cases (11.7 %) according to the 2020 Global Burden of Cancer (GLOBOCAN) estimates of the International Agency for Research on Cancer. It is succeeded by gastric (5.6%), prostate (7.3%), colorectal (10.0%), and lung cancer (11.4%).[2]

Lung cancer is the most prevalent type of cancer globally, representing 11.4% of all diagnosed cancer cases, and is a significant contributor to mortality due to cancer. Indonesia has three times as many cases of lung cancer as any other cancer type, followed by breast and cervical cancers, with over 30,000 deaths attributed to it. In North Sumatra, data from Haji Adam Malik Hospital in Medan recorded 278 lung cancer

cases in 2019, comprising 180 men, 98 women, and 68 deaths.[3] Lung cancer has a complicated pathogenesis that remains poorly understood. Exposure to carcinogens, especially smoking, is believed to result in dysplasia of lung epithelial cells. Continuous exposure can cause genetic changes that affect protein production, disturb normal cell cycle regulation, and promote cancer development. MYC, BCL2, and p53 are frequently associated with genetic mutations in small-cell lung cancer (SCLC), while EGFR, KRAS, and p16 are commonly involved in mutations of non-small-cell lung cancer (NSCLC).[4-6]

EGFR frequently undergoes mutations in NSCLC, especially in approximately 50% of lung adenocarcinoma cases in Asian populations. EGFR plays a physiological role in regulating the development and homeostasis of epithelial tissues. G protein-coupled receptors can transactivate EGFR which can affect the proliferation and growth of cells through many signal transduction pathways. Mutations in the EGFR gene may cause overactivation of its tyrosine kinase domain, leading to unchecked cell growth and proliferation.[7]

Tumour cell proliferation, apoptosis suppression, tumour-driven angiogenesis, metastasis, and DNA damage repair are significantly affected by EGFR activation. Thus, EGFR is a key target for cancer therapy, particularly in lung cancer. Chemotherapy and radiotherapy may be improved by inhibiting EGFR.[8] Thus, identifying cancer genotypes enables a more targeted approach for lung cancer treatment. The extracellular ligand-binding region of EGFR has been the target of a class of monoclonal antibodies since its discovery in 1962, blocking receptor activation and reducing its surface expression through antibody-induced receptor dimerisation. Additionally, EGFR is inhibited by small-molecule tyrosine kinase inhibitors (TKIs) via competition with ATP to attach to the intracellular tyrosine kinase subunit, suppressing the receptor's catalytic activity and downstream signalling pathways. TKIs have shown substantial antitumor efficacy in cancers characterized by EGFR overexpression.[8]

Determining the correct treatment for patients with NSCLC is crucial, and this involves assessing the EGFR mutation status. Patients with EGFR mutations should receive TKIs as the first-line therapy. For patients with wild-type EGFR, TKIs are also possible treatment options, but they should be considered for second or third-line therapy.[9] TKIs like erlotinib, have shown efficacy in halting tumour progression in EGFR-mutated NSCLC. However, tumor control may be lost as resistance mechanisms evolve, such as the mutation in exon 20 known as T790M.[10]

In previous studies, the T790M mutation was stated to be the leading pathway of acquired resistance in more than half of patients treated receiving first- and second-TKIs for EGFR-mutated NSCLC.[5] This resistance can affect treatment outcomes, including life expectancy. The data indicates different survival outcomes associated with various TKIs, with afatinib showing a progression-free survival (PFS) of 19.1 months, gefitinib at 13.7 months, and erlotinib at 14.0 months.[11] Regarding overall survival (OS), the results showed that afatinib had a 22.8-month OS, erlotinib a 17.8-month OS, and gefitinib a 15.5-month OS.[12] TKI resistance in the first and second generations, which can affect life expectancy in EGFR-positive lung cancer, makes researchers interested in researching the effectiveness of TKIs on life expectancy in EGFR mutation-positive NSCLC patients in Medan.

METHOD

This study had a retrospective, cross-sectional design. A total sampling method was used to select the sample, and all population members meeting the research criteria were included. The subjects were patients diagnosed with NSCLC with positive EGFR mutations and treated with TKIs, based on medical records from Haji Adam Malik Hospital, Medan, Elisabeth Hospital, Prof. Dr. Chairuddin Panusunan Lubis USU Hospital, and Pirngadi Hospital.

Patients diagnosed with NSCLC between January 2017 and December 2022, aged over 18 years, with EGFR mutation results positive for exons 18, 19, or 21 (single or combination), who received first-, second-, or third-generation TKIs, and with complete medical record data were included in this study. Exclusion criteria included patients with other malignancies; those treated with TKIs outside of the first, second, or third generation; and patients negative for EGFR mutations.

The data obtained were analysed using SPSS. A univariate analysis was performed to examine the descriptive aspects of the data. The distribution of the numerical data was evaluated using the Kolmogorov-

Smirnov test. Distributions were reported using means and standard deviations, whereas non-normal data were reported as medians and ranges. Bivariate analysis employed hypothesis testing with an independent sample t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data to assess the effectiveness of the two sample groups.

Data normality was determined using the Shapiro-Wilk test. Kaplan-Meier survival analysis was used to assess the effectiveness of two or more sample groups. The log-rank test was used to evaluate the differences in effectiveness across the groups. The survival proportion difference between the groups was significant if the p-value was less than 0.05, and the chi-square value was greater than the critical value. Because data will be collected from medical records, not all subjects of this research will be asked for consent. The Health Research Ethics Committee of Universitas Sumatera Utara approved this study.

RESULTS

In this study, 67 research participants were diagnosed with NSCLC and EGFR mutations. They were treated with TKIs based on medical records from Haji Adam Malik Hospital Medan, Elisabeth Hospital, Prof Dr. Chairuddin Panusunan Lubis USU Hospital, and Pirngadi Hospital from January 2017-December to 2022. Table 1 presents the baseline characteristics of the study participants.

Table 1. Demographic and Clinical Characteristics

Characteristics	Mean ± SD / n (%)
Age, by year	59,08 ± 10,82
≤ 60 years	29 (43,3)
> 60 years	38 (56,7)
Gender	
Male	34 (50,7)
Female	33 (49,3)
Working	
Yes	39 (58,2)
No	28 (41,8)
Smoking	
Yes	23 (34,3)
No	44 (65,7)
Location of mutation	
Multiple	4 (6,0)
Single	63 (94,0)
Histopathology Type	
Adenocarcinoma	66 (98,5)
Squamous Cell Carcinoma	1 (1,5)

The mean age of the subjects in this study have a mean age of 59.08 ± 10.82 years. Most participants were nonsmokers (65.7%), had a single cancer mutation site (94.0%), and presented with adenocarcinoma histopathology (98.5%). Among the study participants, 50.7% were male, and 58.2% were employed. The characteristics of the subjects based on TKI treatment are detailed in Table 2

The patients received either first- or second-generation TKIs. While 44.8% received first-generation treatment, 55.2% received second-generation TKIs. In the second-generation group, all the patients received afatinib treatment. In the first-generation group, 37 patients were administered erlotinib, and 6 underwent gefitinib treatment. The average duration of TKI therapy was 9.04 ± 5.89 months. The treatment resulted in a stable disease response in 92.6% of the patients, and 64.2% of the patients were at stage IVA.

The efficacies of first- and second-generation TKIs in NSCLC patients with positive EGFR mutations were compared in terms of PFS, Median Survival Time, and OS (Table 3).

As shown in Table 3, PFS, median survival time, and OS were significantly higher in EGFR mutation-positive NSCLC patients receiving second-generation TKIs than in those receiving first-generation TKIs ($p < 0.05$). Figure 1 presents a comparison of the findings.

Table 2 Characteristics of TKI Treatment

Treatment Characteristics	Mean ± SD / n (%)

Generation of TKI	
Generation 1	30 (44,8)
Generation 2	37 (55,2)
Drug	
Erlotinib	37 (55,2)
Gefitinib	6 (9,0)
Afinitib	24 (35,8)
Duration of TKI treatment (months)	9,04 ± 5,89
Drug response	
Stable disease	62 (92,6)
Progressive disease	4 (6,0)
Partial response	1 (1,5)
Stage	
IIIA	13 (19,4)
IIIB	8 (11,9)
IVA	43 (64,2)
IVB	3 (4,5)

Table 3. Characteristics of TKI Treatment Effectiveness of TKIs in NSCLC Patients With Positive EGFR Mutations

Characteristics	Progression (Months)	CI 95%	P-Value
Progression Free Survival			
Generation 1	8,00	6,670-9,330	<0,001**
Generation 2	11,00	9,819-12,181	
Median Survival Time			
≤ 60 years	4,00	3,335-4,665	<0,001**
> 60 years	5,00	4,958-6,042	
Overall Survival			
Male	8,00	6,670-9,330	<0,001**
Female	11,00	9,515-12,485	

Notes: Kaplan–Meier and log-rank tests, *Significant at $p < 0.05$, **Significant at $p < 0.001$.

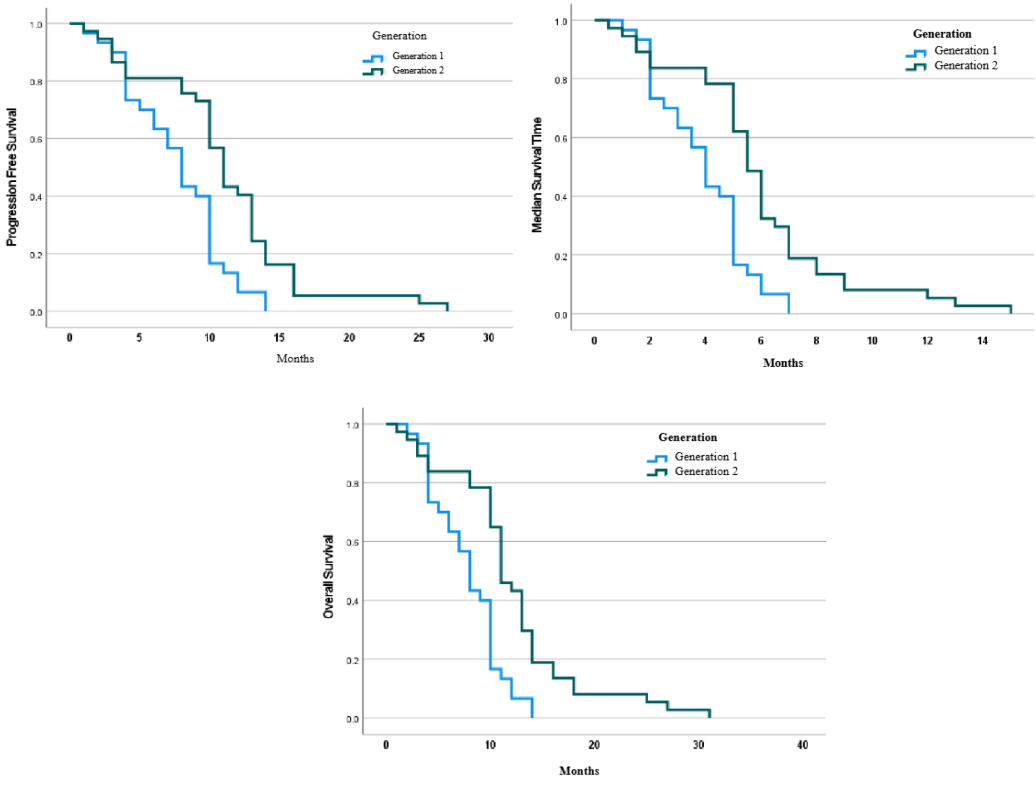

Figure 1. Differences in (a) PFS, (b) MST, and (c) OS between first and second-generation TKI

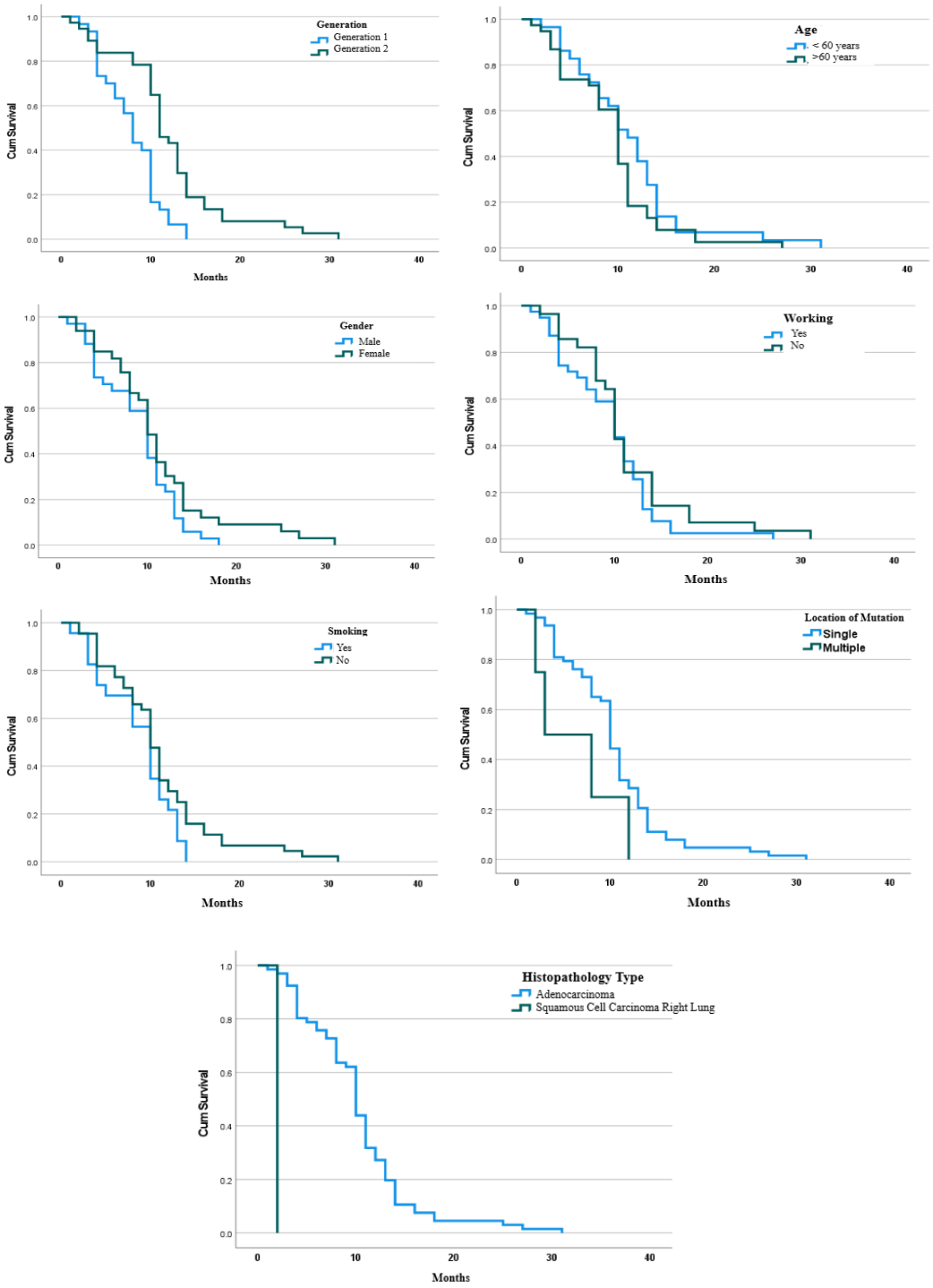

Figure 2. Differences in Length of Life Based on The Characteristics of Research Subjects

The results of the analysis of the length of life using the Kaplan-Meier method and log-rank test are presented in Table 4.

The analysis showed that the histopathological type, EGFR TKI production, and survival length were significantly correlated ($p < 0.05$). The median survival for second-generation EGFR-TKIs was 11 months, which was longer than first-generation TKIs, which was eight months. Additionally, the median survival for patients with SCC was much lower at two months, compared at ten months for those with adenocarcinoma or NSCLC. Age, sex, occupation, smoking status, and EGFR mutation location were not significantly correlated with survival ($P > 0.05$). Figure 2 compares the survival times based on the characteristics of the study population.

Table 4. Length of Life Analysis on TKIs in NSCLC Patients with Positive EGFR Mutations

Characteristics	Median Length Of Life (Months)	CI 95%	P-Value
EGFR TKI			
Generation 1	8,00	6,670-9,330	< 0,001**
Generation 2	11,00	9,515-12,485	
Age (years)			
≤ 60 years	11,00	8,740-13,260	0,176
> 60 years	10,00	8,705-11,295	
Gender			
Male	10,00	8,413-11,587	0,116
Female	10,00	8,750-11,250	
Working			
Yes	10,00	7,977-12,023	0,241
No	10,00	9,145-10,855	
Smoking			
Yes	10,00	8,209-11,791	0,090
No	10,00	9,001-10,099	
Location of Mutation			
Multiple	3,00	0,000-8,880	0,065
Single	10,00	9,356-10,644	
Histopathology Type			
Adenocarcinoma	10,00	9,341-10,659	< 0,001**
Squamous Cell Carcinoma	2,00	-	

Notes: Kaplan–Meier and log-rank tests, *Significant at $p < 0.05$, **Significant at $p < 0.001$.

DISCUSSION

The average age of NSCLC patients in this study who had positive EGFR mutations was 59.08 ± 10.82 years. Likewise, an Algerian study found that NSCLC patients with positive EGFR mutations ranged in age from 44 to 94 years old, with a mean age of 59.[13] Similar results were found in China, where patients ranged from 33-78 years of age and a median of 60.6 years.[14]

Most patients with EGFR mutations or NSCLC do not smoke. Never-smokers had a higher frequency of EGFR mutations (4.9 %) than active smokers (13.5%) and former smokers (42.5%). Exposure to high levels of smoke from burning coal has been considered a contributing factor to lung cancer, and air pollution is also a significant risk factor.[15] The majority of individuals with EGFR mutations are either moderate smokers or do not smoke. Due to the rising prevalence of non-smoking behaviors, more female patients are found to carry EGFR mutations compared to males.[16] Smoking continues to be a substantial risk factor for lung cancer, and those who smoke and those who do not have been found to have different patterns of genetic alteration. Notably, nonsmokers were more likely than smokers to have mutations in EGFR.

Males comprised 50.7% of the study participants, and 58.2% of them had occupations. Similar outcomes were observed in 44.7% of male patients according to a Chinese study.[14] A different Taiwanese study found that 52.1% of patients with positive EGFR mutations in NSCLC were male.[17,18] The majority of individuals with EGFR mutations in NSCLC have only one mutation, often at exon 19. The exon 19 deletion (Del 19) and the mutation in exon 21 comprise 90% of all EGFR mutations and are associated with sensitivity to EGFR TKIs.[19]

Most EGFR mutation-positive NSCLC patients have adenocarcinoma according to their histopathological type. Research conducted in Algeria has shown similar results, indicating that most NSCLC patients who have positive EGFR mutations also have the adenocarcinoma histological type.[13] Accounting for 60% of NSCLC cases, adenocarcinoma is the most prevalent form of lung cancer. A peripheral mass with central fibrosis and pleural wrinkling is a typical appearance of lung adenocarcinoma. It can also manifest in various ways, including a centrally located mass, diffuse lobar consolidation, bilateral multinodular distribution, or pleural thickening. Histologically, lung adenocarcinoma is defined as a cancerous epithelial tumor with glandular differentiation or mucin secretion.[20]

Most patients with EGFR mutation-positive NSCLC are diagnosed with stage IV adenocarcinoma (IVA). These results are in line with those of Setiawan et al. in Malang, who discovered that, 54.71% of patients

with NSCLC and positive EGFR mutations had a stage IVA diagnosis.[21] In this study, 55.2% of the patients received second-generation TKI therapy, while 44.8% received first-generation therapy. In the second-generation group, all the patients received afatinib treatment. Among the first-generation group, 37 patients were administered erlotinib and 6 patients were administered gefitinib. In contrast, a study by Wu et al. in China found that patients with NSCLC who have positive EGFR mutations were treated with gefitinib (71.1%), erlotinib (25.7%), and afatinib (3.2%).[18]

Compared to patients treated with first-generation TKIs, those with EGFR-positive NSCLC who received second-generation TKIs exhibited a longer median PFS, MST, and OS. These findings are similar to those of the LUX-Lung 7 study, which showed that afatinib had a better PFS rate than gefitinib because of its broader inhibitory profile. This broader profile aids in postponing resistance processes, particularly in cases of Leu858Arg mutation and exon 19 deletion.[22] Kim et al. similarly reported that the median PFS durations for afatinib, gefitinib, and erlotinib were 19.1, 13.7, and 14.0 months, respectively.[11] Additionally, Brzozowska et al. discovered that afatinib had a median OS of 22.8 months, longer than erlotinib (17.8) and gefitinib (15.5).[12] Gefitinib and erlotinib are first-generation TKIs that bind to and block EGFR signaling in a reversible manner, whereas afatinib is a second-generation TKI that inhibits ErbB family receptors (EGFR/ErbB1, HER2/ErbB2, ErbB3, and ErbB4) irreversibly. Gefitinib and afatinib are two TKIs that are widely preferred over chemotherapy for NSCLC patients who have EGFR mutations. These TKIs exhibit significantly higher response rates, prolonged PFS, and an enhanced quality of life. Afatinib has demonstrated higher efficacy than gefitinib, with a PFS of 11 months and an OS of 27.9 months in contrast to gefitinib's 24.5 months.[17]

The initial TKI was gefitinib, which attaches to the ATP-binding site of the enzyme. Similarly, erlotinib, another first-EGFR TKI, inhibits the formation of phosphotyrosine residues and associated downstream signalling pathways. In contrast, afatinib achieves irreversible inhibition of ATP binding through the formation of covalent bonds and has demonstrated efficacy in preclinical studies against mutations such as Thr790Met.[22] Afatinib irreversibly binds to all ErbB receptors (EGFR, ErbB2, ErbB4) due to its covalent attachment to the EGFR C797 site, resulting in irreversible EGFR tyrosine kinase inhibition.[23] The activity of afatinib has been shown to target both activating EGFR mutations and the wild-type EGFR. It also shows efficacy against the exon 20 T790M mutation at higher concentrations, the leading cause of secondary resistance to first-generation EGFR TKIs.[16]

The superior efficacy of afatinib in contrast to first-generation TKIs is due to the irreversible inhibition of ErbB, leading to better tumor control and prolonging PFS and OS in EGFR mutations-positive NSCLC patients.[17] Survival in NSCLC patients treated with EGFR-TKIs was not correlated with age, sex, occupation, smoking, or the location of the EGFR mutation. These factors were not confounding variables in the relationship between TKI use and patient survival.

CONCLUSION

This study was conducted retrospectively and experienced limitations related to incomplete data. This study only examined the effectiveness of TKI and not their side effects. Sixty-seven patients diagnosed with NSCLC and EGFR mutations were included in this study. Second-generation TKIs significantly improved PFS, Median Survival Time, and OS compared to first-generation TKIs ($p < 0.05$). Conclusion: Second-generation EGFR TKI were more effective than first-generation TKI in NSCLC.

DECLARATIONS

This study adhered to the procedures and ethical guidelines of The Health Research Ethics Committee of Universitas Sumatera Utara. The ethical clearance certificate issued by the committee was no. 148/KEPK/USU/2024.

CONSENT FOR PUBLICATION

The Authors agree to be published in Journal of Society Medicine.

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All authors significantly contributed to the work reported on execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of this work.

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