Adverse Event Of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Treatment In Medan Among Pulmonary Adenocarcinoma: Focus On Non-Hematologic Toxicity

Putri Wulandari Harahap[1*], Setia Putra Tarigan[2], Noni Novisari Soeroso[3]

[1,2,3] Universitas Sumatera Utara, Medan, Indonesia
[*] Corresponding Author:
Email: putriwulandariharahap@yahoo.com

Abstract.

This study aims to compare the non-hematological toxicities of first and second-generation Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKIs) in pulmonary adenocarcinoma patients with positive EGFR mutations in Medan. Utilizing a retrospective cross-sectional design, data were collected from medical records of 66 patients at three hospitals between January 2017 and December 2022. The study population included all patients meeting the specific criteria, and a total sampling technique was used. The collected data on demographics and non-hematological side effects were analyzed using the SPSS program, with the Kolmogorov-Smirnov and chi-square tests. The results indicate that second-generation TKIs exhibit lower non-hematological toxicities, specifically for skin rash, stomatitis, and diarrhea, compared to first-generation TKIs. However, a significant association was found between second-generation TKIs and a higher incidence of paronychia. All observed side effects were low-grade. The study's limitations include its retrospective nature and focus on non-hematological toxicities. Future research should investigate the toxicity profiles of second-generation TKIs further, including hematological side effects.

Keywords: *Adenocarcinoma; EGFR; Lung Cancer; Side Effects and Tyrosine Kinase Inhibitor.*

I. INTRODUCTION

Cancer remains a formidable global health challenge, responsible for approximately 10 million deaths in 2020, which is equivalent to nearly one in six deaths worldwide [1]. According to the International Agency for Research on Cancer's Global Burden of Cancer (GLOBOCAN) 2020 data, lung cancer ranks as the second most common cancer and a leading cause of malignancy-related mortality [2]. The situation is particularly concerning in Indonesia, where lung cancer is the third most common cancer, leading to over 30,000 deaths annually [3]. Local data from H Adam Malik Hospital in Medan further highlight this issue, with 278 lung cancer patients recorded in 2019 [3].The complex pathophysiology of lung cancer often begins with repeated exposure to carcinogens, leading to genetic mutations that disrupt the normal cell cycle and trigger carcinogenesis [4]. A common genetic mutation in non-small cell lung carcinoma (NSCLC) is found in the epidermal growth factor receptor (EGFR) gene [4]. This mutation is especially prevalent in lung adenocarcinomas, affecting up to 50% of the Asian population [5]. As EGFR plays a crucial role in regulating cell growth and proliferation, its mutation promotes unregulated cell division, tumor-induced angiogenesis, and metastasis [6]. This critical function makes EGFR an attractive and important target for modern cancer therapy [7].The determination of a patient's EGFR mutation status is essential for making informed treatment decisions [8]. For patients with positive EGFR mutations, tyrosine kinase inhibitors (TKIs) are recommended as a first-line therapy [8]. These low molecular weight inhibitors work by competing with ATP to bind to the intracellular tyrosine kinase site of the EGFR, thereby blocking its catalytic activity and inhibiting downstream signaling pathways [7].

While TKIs have shown significant anti-tumor activity [7], their effectiveness is often limited by the development of resistance mechanisms, such as the T790M point mutation in exon 20 [9], [10]. This resistance, which occurs in over 50% of cases treated with first and second-generation TKIs, results in a loss of tumor control [10].The issue of TKI resistance has driven the development of newer generations of inhibitors. However, regardless of their therapeutic benefits, all TKIs are associated with various side effects, which can have a significant impact on a patient's quality of life and treatment adherence [11]. The management of these adverse events, particularly the non-hematological toxicities, is a critical component of

successful treatment [12]. Understanding the distinct side effect profiles of different TKI generations is therefore crucial for clinicians to optimize patient care and improve outcomes.The objective of this study is to compare the non-hematological toxicities of first and second-generation EGFR TKIs in pulmonary adenocarcinoma patients in Medan. The urgency of this research stems from the need for local data to guide clinical practice, as the side effect profiles of these drugs may vary among different populations. The findings of this study will provide unique insights into the effectiveness and tolerability of EGFR TKI treatments in the specific demographic of Medan, a topic that has not been extensively explored. The novelty of this research lies in its specific regional focus and its direct comparison of the non-hematological toxicity between TKI generations, offering valuable data to improve patient management and treatment strategies in the local context.

II. METHODS

Research Methods

This study utilized a retrospective cross-sectional design to analyze the non-hematological toxicities of EGFR TKI treatment in pulmonary adenocarcinoma patients in Medan. As noted by Sudaryono (2021) and other scholars, this method is ideal for reviewing historical patient data over a specific period to identify relevant patterns and causal relationships [13], [14]. Data were collected from the medical records of patients at Haji Adam Malik Hospital, Elisabeth Hospital, and Pirngadi Hospital from January 2017 to December 2022. The use of secondary data from medical records is a practical and efficient approach for retrospective studies, as it allows access to a large volume of patient information [15].The study population included all patients diagnosed with pulmonary adenocarcinoma who had a positive EGFR mutation and had undergone TKI treatment. A total sampling technique was employed, which, according to Sugiyono (2021), includes all members of the population who meet the research criteria without exception [16]. This technique was chosen because the population of patients with these specific characteristics is generally not large, which allows for a comprehensive analysis of the available data [17]. Inclusion criteria were: patients diagnosed with NSCLC within the specified timeframe, aged over 18 years, with positive EGFR test results for exons 18, 19, and/or 21 (single or combined), who had received first-, second-, or third-generation TKIs for at least three months, and had complete medical record data. Patients with other malignancies, those receiving TKI treatments from other generations, or those with negative EGFR mutations were excluded from the study.

The research procedure began with the collection of lung cancer patient data from the chemotherapy departments of the respective hospitals. Subsequently, relevant information was extracted from medical records using a specifically designed Case Report Form (CRF) to record patient demographics and toxicity data [18]. The data collected included the adenocarcinoma diagnosis, EGFR mutation test results, TKI type (first, second, or third generation), and non-hematological side effects such as skin rash, stomatitis, paronychia, and diarrhea. After the data collection process was complete, analysis was performed using the SPSS program [19].The data analysis was conducted in several stages. First, univariate analysis was performed to describe the characteristics of the research subjects [20]. The Kolmogorov-Smirnov test was then used to check the distribution of the numerical data [21]. Normally distributed data were presented as mean and standard deviation, while non-normal data were presented as median and range. The final stage, bivariate analysis, was conducted using the chi-square test to compare the toxicity between the first- and second-generation TKI groups [22]. The results were considered statistically significant if the p-value was less than 0.05. According to Emzir (2022), this series of analyses represents a robust methodological approach for testing hypotheses and obtaining valid findings [24].

III. RESULTS AND DISCUSSION

Results

Demographic Characteristics of Research Subjects

In this study, 66 research subjects were obtained who were diagnosed with non-small cell lung carcinoma (NSCLC) with positive EGFR mutations and were treated with TKI based on medical record data

at Haji Adam Malik General Hospital, Elisabeth General Hospital, and Pirngadi Hospital from January 2017 to December 2022. The characteristics of the research subjects are presented in Table 1.

Table 1. Characteristics of Research Subjects

Characteristics	Mean ± SD / n (%)
Age by (years)	59,08 ± 10,82
Gender	
Male	33 (50,0)
Female	33 (50,0)
Occupation	
Working	38 (57,7)
Not working	28 (42,3)
Smoking	
Yes	22 (33,3)
No	44 (66,7)
Location of mutation	
Multiple	4 (6,1)
Single	62 (93,9)
Histopathology type	
Adenocarcinoma	66 (100)

The subjects of this study had an average age of 59.08 ± 10.82 years. Most of the subjects of this study were non-smokers (66.7%), single cancer mutation location (93,9%), and histopathology type adenocarcinoma (100%). A total of 50.0% of the subjects were male and 50,0% of the subjects were employed. The characteristics of the subjects based on TKI treatment are presented in Table 2.

Table 2. Characteristics of TKI treatment

Characteristics of TKI treatment	Mean ± SD / n (%)
TKI Generation	
Generation 1	30 (45,4)
Generation 2	36 (54,6)
Drug name	
Erlotinib	37 (56,2)
Gefetinib	6 (9,0)
Afinitib	23 (34,8)
Duration of TKI treatment (months)	9,04 ± 5,89
Drug response	
Stable disease	61 (92,4)
Progressive disease	4 (6,1)
Partial response	1 (1,5)
Stage	
IIIA	13 (19,6)
IIIB	8 (12,2)
IVA	42 (63,7)
IVB	3 (4,5)

In this study, patients only received 1st and 2nd-generation TKIs. As many as 54,6% of patients received 2nd generation TKI therapy and as many as 45,4% received 1st generation therapy. In the 2nd generation, all received afinitib therapy, while in the 1st generation, 37 patients received Erlotinib and only 6 patients received Gefitinib therapy. The study subjects received TKI therapy for an average of 9.04 ± 5.89 months. As many as 92.4% of patients had stable disease drug response, and 64.2% stage IVA.

Non-Hematologic Toxicity Of Tyrosine Kinase Inhibitors In Patients With Adenocarcinoma With Positive EGFR Mutations

In this study, a comparative analysis of non-hematological toxicity in the form of skin rash, stomatitis, paronychia, and diarrhea from tyrosine kinase inhibitor treatment in adenocarcinoma patients with positive EGFR mutations between first-generation and second-generation TKIs was conducted, the results of which are presented in Table 3.

Table 3. Non-Hematologic Toxicity Of Tyrosine Kinase Inhibitors In Patients With Non-Small Cell Lung Carcinoma (NSCLC) With Positive EGFR Mutations

Non-Hematologic Toxicity	Generation 1	Generation 2	P-value
	n (%)	n (%)	
Skin rash			
None	11 (36,7)	31 (86,2)	
Grade 1	15 (50,0)	4 (11,1)	0,000**
Grade 2	4 (13,3)	1 (2,7)	
Stomatitis			
None	12 (40,0)	33 (91,6)	0,000**
Grade 1	11 (36,7)	3 (8,4)	
Grade 2	7 (23,3)	-	
Paronychia			
None	16 (53,3)	5 (13,8)	
Grade 1	9 (30,0)	14 (38,9)	0,001*
Grade 2	5 (16,7)	17 (47,3)	
Diarrhea			
None	9 (30,0)	30 (83,4)	
Grade 1	14 (46,7)	3 (8,3)	0,000**
Grade 2	7 (23,3)	3 (8,3)	

**Chi-square test, *Significant at p < 0.05; **Significant at p < 0.001.*

Based on Table 3, the results show that most patients who received 1st generation TKI had grade 1 skin rash side effects (50.0%), while most patients who received 2nd generation TKI did not have skin rash side effects (86.2%). The results of statistical tests showed that there was a significant difference in skin rash side effects between patients who received 1st generation and 2nd generation TKI, with a p value <0.05. Patients who received 1st generation TKI had grade 1 stomatitis side effects of 36.7% and grade 2 of 23.3% while patients who received 2nd generation TKI only had grade 1 stomatitis side effects of 8.4%. The results of statistical tests showed that there was a significant difference in stomatitis side effects between patients who received 1st generation and 2nd generation TKI, with a p value <0.05. Most patients who received 1st generation TKI did not have paronychia side effects (53.3%), 30.0% had grade 1 side effects, and 16.7% had grade 2 side effects, while most patients who received 2nd generation TKI had grade 2 paronychia side effects (47.3%) and 38.9% had grade 1 side effects. The results of statistical tests showed that there was a significant difference in paronychia side effects between patients who received 1st and 2nd generation TKI, with a p value <0.05. Most patients who received 1st generation TKI had grade 1 diarrhea side effects (46.7%), while most patients who received 2nd generation TKI did not have diarrhea side effects (83.4%). The results of statistical tests showed that there was a significant difference in diarrhea side effects between patients who received 1st and 2nd generation TKI, with a p value <0.05. Thus, 2nd generation TKIs have better side effects on skin rash, stomatitis, and diarrhea compared to 1st generation TKIs, but not on paronychia side effects.

Table 4. The Use Of Side Effects Therapy Due To Tyrosine Kinase Inhibitors In Patients With Adenocarcinoma With Positive EGFR Mutations

Side effects of therapy	Generation 1	Generation 2	P-value
	n (%)	n (%)	
Yes	9 (30,0)	13 (36,1)	0,502
No	21 (70,0)	23 (63,9)	

**Chi-square Test*

Table 4 shows that both patients who received EGFR TKI generation 1 and generation 2 mostly did not receive side-effect therapy. The results of statistical tests showed that there was no significant difference between the use of side effect therapy between EGFR TKI generation 1 and generation 2.

Discussion

In this study, patients with Adenocarcinoma with positive EGFR mutations had an average age of 59.08 ± 10.82 years. Similar results in a study in Algeria showed that the age of patients with Adenocarcinoma with positive EGFR mutations was 59 years, with a range of 44-94 years [11]. Similar results were reported in a study in China, where the median age of patients with Adenocarcinoma with

positive EGFR mutations was 60.6 years, with a range of 33-78 years [12].Most patients with Adenocarcinoma with positive EGFR mutations did not smoke. A higher frequency of EGFR mutations occurred in the group who had never smoked (42.5%) compared to active smokers (4.9%) or former smokers (13.5%). High exposure to smoke from coal combustion is considered one of the factors causing lung cancer. Air pollution is a significant predictor of lung cancer [13]. Most EGFR mutation-positive tumors occur in patients who have never smoked or are light smokers. Because of the increasing prevalence of nonsmoking behavior, more female patients have EGFR mutations than male patients [14]. Smoking is a major risk factor for lung cancer. There are significant differences in the pattern of gene mutations between lung cancer patients who smoke and never smoke.

The frequency of EGFR gene mutations is higher in nonsmokers with lung adenocarcinoma than in smokers. In lung cancer, KRAS mutations are found in 15% to 25% of lung cancer patients, but these mutations are rare in squamous lung carcinoma, a tumor that contains mutations in EGFR [15].In this study, 50.0% of the study subjects were male, and 50.0% of the study subjects were employed. Similar results were reported in a study in China of non-small cell lung carcinoma (NSCLC) patients with positive EGFR mutations, where 44.7% were male [16]. In a study in Taiwan, it was reported in a study in China of non-small cell lung carcinoma (NSCLC) patients with positive EGFR mutations, 52.1% were male [17].Most patients with non-small cell lung carcinoma (NSCLC) with positive EGFR mutations have a single cancer mutation location, mostly exon 19. Common mutations in patients with non-small cell lung carcinoma (NSCLC) with EGFR are mutations in exon 19 (Del 19) and L858R mutations in exon 21, approximately 90% of all mutations and are associated with sensitivity to EGFR tyrosine kinase inhibitors. Mutations in exon 18 are rare and detected in 3.6%. Patients with lung adenocarcinoma who have a rare exon 18 deletion may respond to afatinib, a second-generation TKI [18].Most patients with EGFR mutation-positive non-small cell lung carcinoma (NSCLC) have adenocarcinoma histopathology. Similar results were found in a study in Algeria, where the age of patients with EGFR mutation-positive non-small cell lung carcinoma (NSCLC) mostly had adenocarcinoma histopathology [19].

Adenocarcinoma is the most common type of lung cancer, accounting for 60% of NSCLC. Lung adenocarcinoma typically forms a peripherally located mass with central fibrosis and pleural wrinkling. It can also have a variety of other gross appearances, including a centrally located mass, diffuse lobar consolidation, bilateral multinodular distribution, and pleural thickening. Lung adenocarcinoma is a malignant epithelial neoplasm with glandular differentiation or mucin production [20].Most patients with adenocarcinoma with positive EGFR mutations are mostly stage IVA. This result is in line with the study of Setiawan et al. that as many as 54.71% of patients with non-small cell lung carcinoma (NSCLC) with positive EGFR mutations in Malang have stage IVA [21]. In stage IVA, especially with early symptoms of pleural seeding, surgery is not recommended. EGFR-TKI treatment provides a good response in cancer control, increases PFS, and has a chance of survival of more than five years [22].A total of 54.6% of patients received 2nd-generation TKI therapy and 45.4% received 1st-generation therapy. In generation 2, all received afatinib therapy, while in generation 1, 37 patients received Erlotinib and only 6 patients received Gefitinib therapy. In the study of Wu et al., non-small cell lung carcinoma (NSCLC) patients with positive EGFR mutations in China received treatment with Gefitinib 71.1%, Erlotinib 25.7% and Afatinib 3.2% [17]. In this study, 2nd generation TKIs had better side effects on skin rash, stomatitis, and diarrhea compared to 1st generation TKIs, but not on paranoia side effects. However, in general, 1st and 2nd generation TKIs have tolerable non-hemorrhagic toxicity.

Previous studies reported that the most common side effects of gefitinib use were skin rash (85.06%), diarrhea (54%), increased liver aminotransferase (70.1%), and side effects that often caused death were interstitial lung disease (1.3%), while the most common side effects of afatinib use were diarrhea 13%, rash or acne (9%) [23]. In this study, patients only experienced low-grade stomatitis. In previous studies, the rate of minor stomatitis (G1-G2) was high, while the incidence of severe stomatitis (G3-G4) was lower [24].This study is different, where the side effect of afatinib use is paronychia. However, the first-generation TKIs gefitinib and erlotinib and the second-generation TKI afatinib have the same degree of toxicity, namely only grade 2 for skin rash, stomatitis, diarrhea and paronychia, which means that all three have acceptable

toxicity.The incidence of diarrhea according to the type of EGFR-TKI and the therapy given varies greatly. The prevalence of diarrhea varies from 1 in every 3 patients to 1 in every 10 patients, as does its onset and duration. Diarrhea can occur as early as 2 days after starting EGFR-TKI and can persist for more than 7 days, often resulting in discontinuation or interruption of therapy. First-generation EGFR-TKIs are more selective than afatinib or dacomitinib.

Diarrhea appears later and is less severe. Diarrhea with first-generation TKIs develops in less than 10% of patients and occurs around day 13 (7–18 days) with erlotinib and day 18 (10–19 days) with gefitinib. In previous studies, Afatinib was associated with a higher incidence of diarrhea because it has a broad spectrum of activity, blocking several members of the ErbB family [25]. In this study, afatinib had a low incidence of diarrhea with only 8.3% Grade 1 and 8.3% Grade 2.Skin rash side effects due to the use of EGFR TKIs because EGFR TKIs interfere with keratinocyte growth, migration and chemokine expression, resulting in inflammatory cell recruitment and skin injury by inhibiting EGFR downstream pathways, such as the mitogen-activated protein kinase (MAPK) pathway [26]. The mechanism by which EGFR-TKIs induce stomatitis involves the abundance of EGFR on undifferentiated keratinocytes and its role in keratinocyte proliferation, migration, differentiation and survival, keratinization and follicle development. EGFR-TKI reduces EGFR phosphorylation in basal stem cells and promotes cell expansion and differentiation in the oral mucosal epithelium. The activation of the PI3K-Akt and Ras-Raf-MAPK signaling pathways is initially inhibited. The cyclin-dependent kinase inhibitor p27 is then upregulated, resulting in G1/S cycle arrest and inhibition of DNA synthesis. However, the apoptotic proteins BCL2 and BCL-XL are up-regulated in normal keratinocytes, which promotes cell apoptosis and ultimately causes significant changes and thinning of the epidermis. Apoptotic cells provide favorable conditions for the reproduction of bacteria, viruses, and fungi. Streptococcus and Staphylococcus species proliferate in areas such as the buccal mucosa, tongue, gingiva, and maxilla, which exacerbates the inflammatory reaction and causes further acute damage to the oral mucosa [27].

EGFR-TKI can cause diarrhea through a secretory mechanism that results in dysfunction of water homeostasis in the colon. When the EGFR receptor is no longer able to negatively control chloride secretion, it can result in constant chloride deposition in the lumen and subsequently cause water accumulation. EGFR TKI can also cause changes in intestinal architecture that cause decreased absorption of nutrients and electrolytes in the intestine [25].The side effects of generation 2, afatinib in this study were in the low category, which were only grades 1 and 2. The greatest side effect in this study was caused by the use of generation 2, namely paronychia. Paronychia is an inflammation of the tissue surrounding the nail [28]. In previous studies, as many as 10 and 15% of patients with first and second generation EGFR TKI suffered from paronychia and this condition usually occurs later during treatment (i.e. 4-8 weeks) [26].The mechanism of paronychia is still unclear. Paronychia occurs in places that are likely to experience compression, either from shoes or activities such as writing and eating. The mechanism of paronychia is an abnormality in local tissue healing during treatment with EGFR TKI. Paronychia may be prevented by avoiding local tissue damage rather than reducing the dose of EGFR-TKI. To minimize unnecessary pressure and trauma and friction on the nail fold, patients should be advised to wear wide-fitting shoes and to avoid nail biting, cutting nails too short, or other potentially damaging effects on the skin around the nail [29]. In contrast to this study, previous studies have shown that the overall toxicity profiles of the three drugs were comparable, although grade 3 or 4 toxicities were more common with afatinib (7.3%) compared with gefitinib (2.6%) or erlotinib (1.8%).

Common grade 3 or 4 toxicities with afatinib included diarrhea (3.0%), paronychia (2.4%), and skin rash (1.8%) [30]. In the study by HE et al. (2021) stated that compared to gefitinib, afatinib has higher side effects, including increased skin and gastrointestinal toxicity [31]. Therefore, second-generation EGFR-TKIs have a limited role in patients with developing resistance to first-generation EGFR-TKIs. Further research is needed, especially regarding the toxicity of second-generation TKIs. Dose-limiting toxicity in second-generation EGFR-TKIs, and its severity is dose-dependent. The recommended standard dose of afatinib is 40 mg/day and can be reduced by 10 mg to a minimum of 20 mg if not tolerated [25]. Side effects that have occurred can be overcome by using side effect therapy. In this study, there was no significant relationship

between the use of side effect therapy between patients receiving first-generation and second-generation EGFR TKIs.The study was conducted retrospectively, which experienced limitations related to incomplete data. This study only examined non-hematological toxicity and did not examine hematological toxicity of TKIs. Further research can be conducted by identifying hematological side effects that may occur due to the use of TKI.

IV. CONCLUSION

Based on the findings of this study, it can be concluded that second-generation tyrosine kinase inhibitors (TKIs) demonstrate lower non-hematological toxicities, specifically for skin rash, stomatitis, and diarrhea, when compared to first-generation TKIs in the treatment of pulmonary adenocarcinoma patients with positive EGFR mutations in Medan. However, the study also revealed that the use of second-generation TKIs was associated with a higher incidence of paronychia. Overall, the toxicities of both TKI generations were found to be tolerable, with all observed side effects being low-grade (Grade 1 or 2). A limitation of this study is its retrospective design, which resulted in some incomplete data. Furthermore, the scope was limited to non-hematological toxicities, leaving out any potential hematological side effects. Therefore, for future research, it is recommended to conduct further studies to comprehensively examine the toxicity profiles of second-generation TKIs and to include an analysis of hematological side effects.

REFERENCES

[1] [World Health Organization, "Cancer," 2022. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/cancer.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. ***CA Cancer J. Clin.*** 2021;71(3):209–49.

[3] Fajrinur F, Handini MC, Tarigan FL, Harefa K, Ginting D. Ketidaklengkapan Pengisian Dokumen Clinical Pathway Kanker Paru (Studi Kualitatif di RSUP H. Adam Malik tahun 2021). ***J Healthc Technol Med.*** 2022;8(1):477–88.

[4] Siddiqui F, Vaqar S, Siddiqu AH. Lung Cancer. *StatPearls*. 2023.

[5] Wright NMA, Goss GD. Third-generation epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer. *Transl. Lung Cancer Res.* 2019;8(Suppl 3):S247–64.

[6] Sigismund S, Avanzato D, Lanzetti L. Emerging functions of the EGFR in cancer. *Mol Oncol*. 2018;12(1):3–20.

[7] Bartholomew C, Eastlake L, Dunn P, Yiannakis D. EGFR targeted therapy in lung cancer; an evolving story. *Respir Med Case Reports*. 2017;20:137–40.

[8] Chi A, Remick S, Tse W. EGFR inhibition in non-small cell lung cancer: Current evidence and future directions. *Biomark Res.* 2013;1(1):1.

[9] Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: A systematic review. *Curr Oncol*. 2015;22(3):e183–215.

[10] Tan CS, Kumarakulasinghe NB, Huang YQ, Ang YLE, Choo JRE, Goh BC, et al. Third generation EGFR TKIs: Current data and future directions. *Mol Cancer*. 2018;17(1):1–14.

[11] Lahmadi M, Beddar L, Rouibah AL, Boumegoura A, Boufendi H, Temim A, et al. Analysis of EGFR Mutation Status in Algerian Patients with Non-Small Cell Lung Cancer. ***Asian Pacific J Cancer Prev***. 2021;22(4):1063–8.

[12] Bian D, Sun L, Hu J, Duan L, Xia H, Zhu X, et al. Neoadjuvant Afatinib for stage III EGFR-mutant non-small cell lung cancer: a phase II study. *Nat Commun.* 2023;14(1):1–14.

[13] Rodak O, Peris-Díaz MD, Olbromski M, Podhorska-Okołów M, Dzięgiel P. Current landscape of non-small cell lung cancer: Epidemiology, histological classification, targeted therapies, and immunotherapy. *Cancers (Basel)*. 2021;13(18).

[14] Hsu WH, Yang JCH, Mok TS, Loong HH. Overview of current systemic management of EGFR-mutant NSCLC. *Ann Oncol*. 2018;29(Suppl 1):i3–9.

[15] Zhang P, Nie X, Bie Z, Li L. Impact of heavy smoking on the benefits from first-line EGFR-TKI therapy in patients with advanced lung adenocarcinoma. *Medicine (United States)*. 2018;97(9):1–5.

[16] Bian D, Sun L, Hu J, Duan L, Xia H, Zhu X, et al. Neoadjuvant Afatinib for stage III EGFR-mutant non-small cell lung cancer: a phase II study. *Nat Commun*. 2023;14(1):1–14.

[17] Wu SG, Chang YL, Yu CJ, Yang PC, Shih JY. Lung adenocarcinoma patients of young age have lower EGFR mutation rate and poorer efficacy of EGFR tyrosine kinase inhibitors. ***ERJ Open Res.*** 2017;3(3).
[18] Kobayashi Y, Togashi Y, Yatabe Y, Mizuuchi H, Jangchul P, Kondo C, et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. *Clin Cancer Res.* 2015;21(23):5305–13.
[19] Lahmadi M, Beddar L, Rouibah AL, Boumegoura A, Boufendi H, Temim A, et al. Analysis of EGFR Mutation Status in Algerian Patients with Non-Small Cell Lung Cancer. ***Asian Pacific J Cancer Prev***. 2021;22(4):1063–8.
[20] Zheng M. Classification and Pathology of Lung Cancer. *Surg Oncol Clin N Am*. 2016;25(3):447–68.
[21] Setyawan UA, Tantular R, Bahar C. Survival Rate of Lung Adenocarcinoma Patients Receiving EGFR - Tyrosine Kinase Inhibitor Targeted Therapy. ***J Kedokt Brawijaya***. 2023;32(3):165–70.
[22] Chen YY, Yen YT, Lai WW, Huang WL, Chang CC, Tseng YL. Outcomes of salvage lung resections in advanced EGFR-mutant lung adenocarcinomas under EGFR TKIs. *Thorac Cancer*. 2021;12(20):2655–65.
[23] Sari S, Andayani TM, Endarti D, Widayati K. Efikasi Afatinib dan Gefitinib pada Pasien Non-small Cell Lung Cancer EGFR Mutasi Positif: Tinjauan Sistematis. ***Indones J Clin Pharm***. 2019;8(4):289.
[24] Arena C, Troiano G, De Lillo A, Testa NF, Lo Muzio L. Stomatitis and VEGFR-Tyrosine Kinase Inhibitors (VR-TKIs): A Review of Current Literature in 4369 Patients. *Biomed Res Int*. 2018;2018:7–12.
[25] Cárdenas-Fernández D, Pina PS, Turcott JG, Chávez-Tapia N, Conde-Flores E, Cardona AF, et al. Management of diarrhea induced by EGFR-TKIs in advanced lung adenocarcinoma. *Ther Adv Vaccines*. 2018;9(6):259–61.
[26] Aw DCW, Tan EH, Chin TM, Lim HL, Lee HY, Soo RA. Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. ***Asia Pac J Clin Oncol***. 2018;14(1):23–31.
[27] Zhu Y, Li L, Zhang P, Zuo Y, Lei Y, Bai J, et al. Severe stomatitis caused by osimertinib combined with gefitinib: A case report. *Clin Case Reports*. 2022;10(2):3–7.
[28] Relhan V, Bansal A. Acute and chronic paronychia revisited: A narrative review. ***J Cutan Aesthet Surg.*** 2022;15(1):1–16.
[29] Masago K, Irie K, Fujita S, Imamichi F, Okada Y, Katakami N, et al. Relationship between Paronychia and Drug Concentrations of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. *Oncology*. 2018;95(4):251–6.
[30] Kim Y, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Efficacy and safety of afatinib for EGFR-mutant non-small cell lung cancer, compared with gefitinib or erlotinib. *Cancer Res Treat*. 2019;51(2):502–9.
[31] HE J, HUANG Z, HAN L, GONG Y, XIE C. Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (Review). ***Int J Oncol***. 2021;59(5):1–20.