ORIGINAL ARTICLE

The Time to Progression in Lung Adenocarcinoma Patients Receiving First- and Second-Generation EGFR-TKI in Indonesia

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ABSTRACT

Introduction: Targeted therapy, particularly epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), is the first-line treatment for non-small cell lung cancer (NSCLC). However, drug resistance has grown in the last few decades. This study compared the progression time of lung cancer patients treated with first- and second-generation EGFR-TKI.

Methods: Based on cytology and histological results, this cross-sectional study included 1,008 participants diagnosed with lung adenocarcinoma (LUAD) from 11 Indonesian Respiratory Centers. Every three months, the response to treatment was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria in 1.1. Significant differences in the clinical features of the three TKI treatment groups were identified using logistic regression analysis, the median time to disease progression was estimated using the Kaplan-Meier technique, and independent prognostic factors related to the time to progression (TTP) were assessed using Cox proportional hazards regression.

Results: This study examined 505 patients, the majority of whom were females (50.9%), never smoked (59.8%), diagnosed at an advanced stage (99.2%), and had an Eastern Cooperative Oncology Group (ECOG) scale of 0-1 (83.2%). Approximately 98.1% of patients were treated with afatinib (14.8%), erlotinib (18.6%), and gefitinib (66.1%) due to common mutations. The groups did not differ significantly ($p>0.05$). The median overall survival (OS) rate was 9 months. The time to LUAD progression in lung cancer was significantly impacted by poor performance ($p=0.001$).

Conclusion: Epidermal growth factor receptor-tyrosine kinase inhibitor treatment can only prolong the TTP of LUAD by up to 9 months, and the performance scale when receiving the EGFR-TKI significantly affects the prognosis.

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INTRODUCTION

Lung cancer is still a primary global health concern. In 2020, the highest cancer-related death rate was recorded.[1] With 2,206,771 new cases annually, or roughly 11.4% of all new malignancies diagnosed in both sexes, lung cancer is the second most frequent malignancy.[1] With 1,796,114 deaths from lung cancer in 2020, or 18% of all cancer fatalities, lung cancer has emerged as the primary cause of cancer mortality.[1] Lung cancer continues to be the most common cancer in Indonesia among males, with 36,783 new cases (14.1% of all cancers) and a 13.2% mortality rate (30,843 deaths).[2]

This high mortality rate has forced researchers to identify new treatment approaches for controlling the progression of lung cancer. However, disease progression continues to increase despite all treatment approaches, including targeted therapy and immunotherapy.[3] The progression of lung cancer was objectively defined using the Response Evaluation Criteria in Solid Tumours (RECIST) category. The RECIST criteria are based on imaging measurements of the targeted lesions. Progressive disease was defined as an increased tumor size of 20% or a new targeted or non-targeted lesion.[4] Several specific studies or data supporting this claim showed a significant improvement in progression-free survival with targeted therapy compared with systemic chemotherapy.[5,6]

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) were introduced in 2003 and have been shown to substantially improve overall survival (OS) and progression-free survival (PFS) in lung cancer patients.[7–9] Few studies have examined the efficacy of EGFR-TKIs of the first and second generations, including afatinib, erlotinib, and gefitinib.[8,10,11] Although the longevity of first- and second-generation EGFR-TKIs did not differ significantly, one trial found that afatinib was more beneficial for patients with brain metastases from non-small cell lung cancer (NSCLC).[11] In Indonesia, a previous study showed that EGFR mutations accounted for 44.4% of all mutations, consisting of 57.1% common mutations, 29% uncommon mutations, and 13.9% mixed mutations.[12] After a few years of follow-up, 48.7% of the subjects with TKI resistance manifested progressive disease.[12] This study assessed the time to progression (TTP) of NSCLC with variations in EGFR mutations in Indonesia.

METHODS

Eligibility Requirements and Study Design

Patients from several cancer institutes in Indonesia, including Jakarta, Surabaya, Medan, Makassar, Solo, Surabaya, Padang, Malang, Riau, Semarang, Bali, Kalimantan, and Palembang, were recruited for this retrospective cohort study between 2017 and 2021. The inclusion criteria were: 1) Pathologically confirmed diagnosis of adenocarcinoma (NSCLC); 2) Activated positive EGFR mutation without T790M mutation; 3) Pathological staging of I or IV; 4) Aged ≥18 years old; 5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2; 6) First-line treatment with gefitinib, erlotinib, and afatinib; and 7) Presence of brain metastasis and pleural effusion. The exclusion criteria were double primary or synchronous adenocarcinoma and pathologically secondary adenocarcinoma. The patients provided written informed consent to participate in this study. The Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara, Medan, approved this study (No. 148r/KEPK/USU/2024).

Time to progression was the primary outcome of this trial, while PFS was the secondary outcome. The amount of time between a lung cancer diagnosis and the cancer's progression was known as the "time to progression." Subjects receiving TKI were considered progressive if they met the RECIST 1.1 criteria. The time from treatment initiation until disease progression or death was known as PFS.

Administration of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Treatment

Gefitinib, erlotinib, and afatinib were administered to every patient in this study. The dosages of gefitinib, erlotinib, and afatinib were given orally at 250 mg once daily, 150 mg once daily, and 40 mg once daily each (every 28 days as a single cycle).

Analysis of Statistics

All demographic data are shown as frequencies and percentages. Kaplan–Meier technique was used to estimate median time to disease progression and Cox proportional hazards regression to assess independent prognostic factors associated with PFS. The demographic data were gathered and analyzed using the Statistical Package for the Social Sciences (SPSS). Significant differences in clinical characteristics among the three TKI treatment groups were determined using logistic regression.

RESULTS

Of the 1,008 subjects enrolled in this study, 505 fulfilled the inclusion criteria and could be followed up after three months of therapy after the first RECIST. Other subjects were lost to follow-up, alive, or died before three months. Those with follow-up had a chest computed tomography (CT) scan with IV contrast for RECIST (Figure 1).

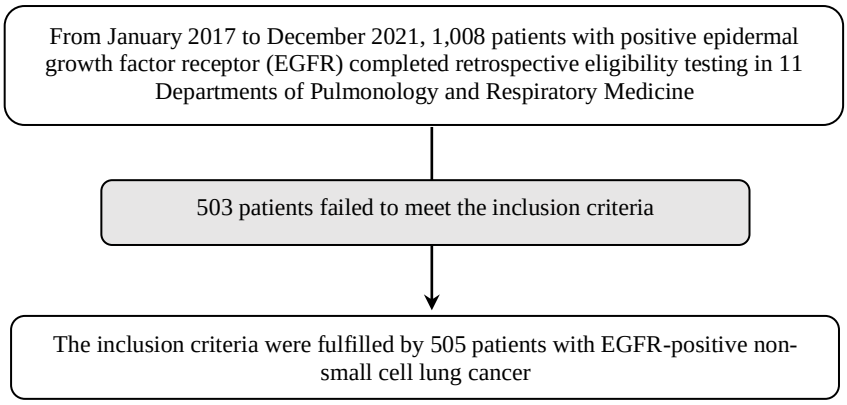

Figure 1. Retrospective study flow chart for EGFR-tyrosine kinase inhibitors therapy in Indonesia

The majority of the subjects had no history of smoking or cancer. The sex differences between the TKI groups were not statistically significant. Brain metastases and other extra-thoracic metastases were nevertheless common, even though patients were typically diagnosed with intrathoracic metastases, including pleural effusions, at an advanced stage. The performance scale, which had an ECOG 0–1, was also in good condition. Table 1 displays the further demographic details.

Table 1. Clinical characteristics subjects with epidermal growth factor receptor-tyrosine kinase inhibitors treatment

Parameters		Total (n= 505)		Afatinib (n = 75)		Erlotinib (n = 94)		Gefitinib (n = 334)		p	HR	95%CI	
		n	%	n	%	n	%	n	%			Lower	Upper
Sex	Male	248	49.1	34	45.3	43	45.7	170	50.9	0.50	1.09	0.84	1.43
	Female	257	50.9	41	54.7	51	54.3	164	49.1				
Smoking history	None	302	59.8	49	65.3	52	55.3	200	59.9	0.60	0.93	0.71	1.22
	Yes	203	40.2	26	34.7	42	44.7	134	40.1				
Cancer history	None	473	93.7	73	97.3	90	95.7	308	92.2	0.90	0.98	0.65	1.46
	Yes	32	6.3	2	2.7	4	4.3	26	7.8				
Brain metastases	None	505	100.0	75	100.0	94	100.0	334	100.0				
Pleural effusion	None	195	38.6	28	37.3	34	36.2	131	39.2	0.13	1.16	0.96	1.41
	Yes	310	61.4	47	62.7	60	63.8	203	60.8				
Staging	Early	4	0.8	1	1.3	1	1.1	2	.6	0.58	0.72	0.23	2.27
	Advanced	499	99.2	74	98.7	93	98.9	332	99.4				
ECOG	0-1	420	83.2	60	80.0	77	81.9	282	84.4	0.09	0.81	0.63	1.04
	2-4	85	16.8	15	20.0	17	18.1	52	15.6				

*Smoking history: Yes (current smoker, ex-smoker <15 years, and passive smoker); HR: hazard ratio; 95%CI: 95% confidence interval; ECOG: Eastern Cooperative Oncology Group

The total median TTP after four years of follow-up was nine months (Figure 2a), with no discernible difference between the three patient groups who received first-generation TKI, which included gefitinib and erlotinib or second-generation TKI, which included afatinib. All subjects had nine months of median PFS, but in subjects treated with erlotinib, the median PFS increased 0.7 months compared with others (Figure 2b). Detailed TTP is presented in Table 2.

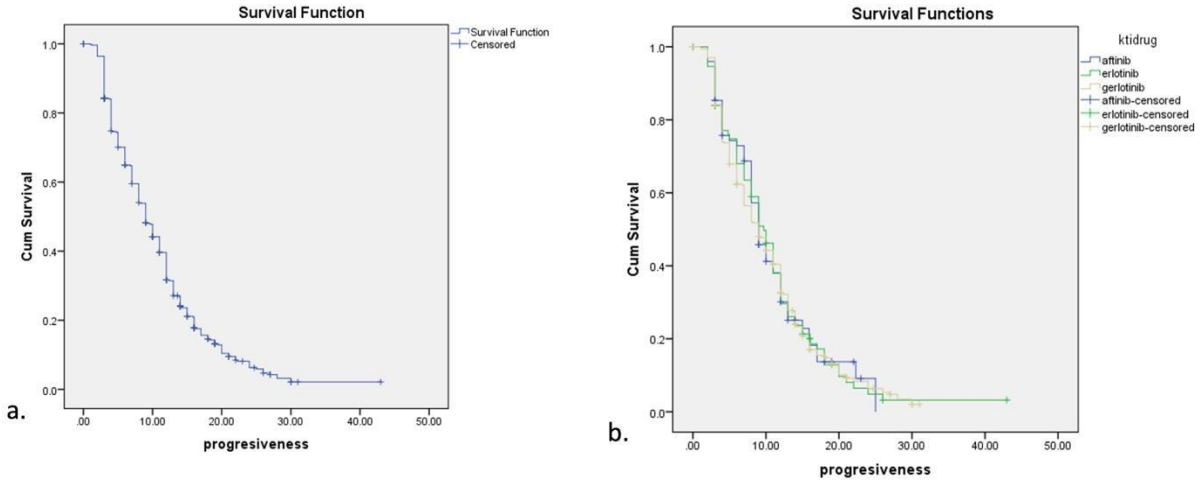

Figure 2. Median time to progression of tyrosine kinase inhibitors (TKI) treatment. 2a) The overall median to progression in TKI treatment; 2b) Median of each subject group with TKI treatment. Blue line for afatinib, green line for erlotinib, and yellow line for gefitinib groups.

Table 2. Time to progression in subjects with TKI treatment in Indonesia

Parameters	Median	95%CI		p-value
		Upper	Lower	
Afatinib	9.0	7.5	10.4	<0.001(a-e)*
Erlotinib	9.7	8.2	11.2	0.008(a-g)*
Gefinitib	9.0	7.6	10.4	0.001(e-g)*
Overall	9.0	8.1	9.8	<0.001

*Mann Whitney; 95%CI: 95% confidence interval

Table 3. Factors affecting progression-free survival

	Patient No. (%)	mPFS (months)	Multivariate Analysis	
			HR (95% CI)	p-value
Smoking history				
No	69 (65.7)	13.0	0.84 (0.51-1.42)	0.519
Yes	36 (34.3)	11.0		
ECOG PS				
0-1	81 (77.1)	13.0	0.44 (0.27-0.73	0.001
≥2	24 (22.9)	8.0		
Tumor stage				
3-4A	73 (69.5)	13.0	1.07 (0.64-1.78)	0.812
4B	32 (30.5)	11.0		
Baseline brain metastases				
No	76 (72.4)	13.0		
Yes	29 (27.6)	11.0	0.98 (0.59-1.63)	0.947
EGFR mutation type				
Common	103 (98.1)	13.0	1.82 (0.25-12.38)	0.558
Uncommon	2 (1.9)	22.0		

*Logistic regressions; mPFS: median progression-free survival; 95%CI: 95% confidence interval; ECOG: Eastern Cooperative Oncology Group; PS: performance status; EGFR: epidermal growth factor receptor

Several factors have been analyzed to predict the TTP in patients with lung cancer. This study showed that only the performance scale (ECOG scale) substantially predicted TTP in patients with NSCLC harboring EGFR mutations. A good performance scale (0-1) showed a longer time to progress than a poor performance scale (>2). Other factors, including smoking history, stage, brain metastases, and EGFR mutations, did not significantly predict the TTP of NSCLC harboring EGFR mutations (Table 3).

DISCUSSION

Epidermal growth factor receptor-tyrosine kinase inhibitor is the first-line treatment for individuals with lung cancer who have these mutations at the age of targeted therapy.[13] Females who have never smoked are frequently found to have EGFR mutations.[14,15] Smoking plays a significant role in the onset and spread of NSCLC. Smoking history affects the incidence of EGFR mutations in NSCLC.[16] Patients with NSCLC who have

never smoked frequently have EGFR mutations.[17] For patients receiving ongoing pemetrexed maintenance therapy for advanced non-squamous NSCLC without EGFR mutations, current smoking is a separate negative prognostic risk for survival.[18] A newly published large population-based study indicated that NSCLC in patients who had never smoked differed clinically from NSCLC linked to smoking.[19] The study found that patients who never smoked had a longer OS than those who smoked.[19] According to earlier meta-analyses, the effect of smoking status on the effectiveness of EGFR-TKIs about PFS in NSCLC is conflicting.[20,21] A meta-analysis of OS by Sohn, *et al.* (2015) found that EGFR-TKI therapy seems to show longer OS in nonsmoking NSCLC patients than in smokers compared to chemotherapy or a placebo.[22] On the other hand, Lee, *et al*. (2017), stated that there was no difference in OS between patients with NSCLC receiving EGFR-TKI treatment and those receiving chemotherapy based on smoking status.[23] However, this study did not find any significant variations in smoking history or sex among individuals with EGFR mutations. This is consistent with other studies conducted in Indonesia, which demonstrated that EGFR mutations are more common among smokers and males.[12,24] However, the time it takes for lung cancer to progress is unaffected by either of these factors. These findings revealed unique molecular alterations in Indonesian lung cancer patients.

Lung cancer is usually asymptomatic until it spreads and invades adjacent organs. Therefore, it is mainly diagnosed at an advanced stage.[25] This study also presented similar data showing that 99.2% of subjects had advanced-stage disease. However, this study also showed that there was no difference between the progression time of patients using EGFR-TKI stage III-IVA compared to stage IVB. Another retrospective study showed similar results: stage III, IVA, and IVB lung adenocarcinoma (LUAD) patients treated with EGFR-TKI had no significant difference in OS and TTP.[26] Pleural effusions and brain metastases are the most common types of lung cancer and are poor predictors of lung cancer. This study showed that pleural effusion and brain metastasis were detected in 61.4% and 27.6% of subjects, respectively. However, neither of these metastases significantly affected the TTP of the lung cancer treated with EGFR-TKIs.

Epidermal growth factor receptor mutations were defined as either common or uncommon. Common mutations include exons 19 and 21 L858R mutations, whereas uncommon mutations include exons 18, 20, and T861Q. Different types of EGFR mutations play a role in different responses to TKI and later affect the TTP and survival rate in lung cancer patients, particularly the adenocarcinoma type.[27,28] Lung cancer patients with EGFR mutations had longer PFS and OS than those with uncommon mutations.[29] In this study, only two subjects had uncommon mutations. Therefore, it could not represent the population to determine whether subjects with uncommon mutations had a shorter or longer TTP than those with common mutations.

Currently, there are three generations of TKI, each with a different mechanism of action. First-generation EGFR-TKI (gefitinib and erlotinib) reversibly bind to EGFR. Meanwhile, second-generation EGFR-TKI (afatinib) irreversibly bind to all relevant homodimers and heterodimers of ErbB family receptors, including EGFR, ErbB2, and ErbB4.[30,31] This makes second-generation EGFR-TKI superior to first-generation TKIs in determining the prognosis of lung cancer.[32] However, this study showed no difference in the TTP for afatinib, gefitinib, and erlotinib. Studies in Poland and Indonesia showed that afatinib, gefitinib, and erlotinib had the same effectiveness in NSCLC harboring EGFR mutations.[33,34] Meanwhile, a different study from Indonesia showed longer PFS and greater cost-effectiveness in the gefitinib group compared to afatinib and erlotinib.[35] Furthermore, a meta-analysis showed no significant difference in efficacy between afatinib, gefitinib, and erlotinib.[36] However, afatinib showed greater side effects than the others.[36]

In patients with EGFR-mutant LUAD, the time to disease progression while receiving first- and second-generation EGFR-TKI therapies varies based on drug generation, mutation type, and individual response factors. First-generation EGFR-TKIs commonly yield a median PFS of about 10–14 months. Despite their initial effectiveness, acquired resistance often limits long-term outcomes, leading to progression around this median range.[37,38] Second-generation EGFR-TKIs generally show similar PFS with a slightly extended duration due to its irreversible EGFR binding mechanism. Studies have reported median PFS times close to 12–16 months in patients with common EGFR mutations (e.g., exon 19 deletions, L858R).[39,40] However, resistance mutations develop over time and influence the progression timeframe.[39,40] Overall, second-generation EGFR-TKIs may offer a modestly longer PFS than first-generation, though both face challenges with resistance leading to eventual disease progression. While second-generation TKIs often provide longer TTP than first-generation, patients commonly face resistance within about a year of treatment.

Epidermal growth factor receptor-tyrosine kinase inhibitors of the first and second generations have shown promise in treating EGFR-mutant NSCLC, despite differences in response length and effectiveness. First-generation EGFR-TKIs were the initial targeted therapies for EGFR-mutated NSCLC and improved PFS

to an average of 10–14 months. However, patients often develop resistance due to secondary mutations (e.g., T790M) or other resistance mechanisms, limiting their long-term effectiveness.[39] Second-generation EGFR-TKIs are irreversible inhibitors, offering a broader and more durable response, especially for patients with uncommon mutations. Second-generation TKIs can extend PFS slightly longer than first-generation drugs, often exceeding 12 months, due to their more potent inhibition of EGFR signaling. A previous study showed that they might be more effective, especially in never-smoker patients and those with certain mutation profiles.[41] In summary, while both generations provide significant benefits, second-generation TKIs may offer extended PFS in specific patient subgroups. However, both face eventual resistance, leading to a need for third-generation options in resistant cases.

Third-generation EGFR-TKIs are an important advancement for patients with EGFR-mutant NSCLC who develop resistance to first- and second-generation TKIs. Osimertinib is the primarily approved third-generation EGFR-TKI and is designed to target EGFR T790M mutations, a common resistance mechanism following earlier-generation TKI therapies.[42] The key benefits of third-generation EGFR-TKIs include extended PFS. Osimertinib shows a longer PFS than previous TKIs, making it a standard treatment option in first-line and second-line settings for patients with T790M-positive mutations.[43] The other advantage of this generation is better central nervous system (CNS) penetration. This generation is particularly effective against brain metastases due to better CNS penetration, addressing a significant unmet need in advanced NSCLC patients with brain involvement.[44]

Third-generation EGFR-TKIs are recognized for their superior CNS penetration, making them more effective against brain metastases in patients with EGFR-mutant NSCLC. Osimertinib achieves higher CNS drug concentrations, which is important for controlling brain lesions, an area where previous-generation TKIs were limited.[45] A previous study showed the efficacy of osimertinib in delaying the progression of CNS metastases and providing longer CNS PFS.[46] High-dose approaches with third-generation TKIs are under exploration to further enhance CNS efficacy while maintaining tolerable side effects.[46] These advances underscore the potential of third-generation EGFR-TKIs to improve the quality of life and survival outcomes in NSCLC patients with CNS involvement. Studies continued to assess the efficacy of third-generation TKIs and mechanisms to overcome the resistance that could eventually develop to these drugs, highlighting the need for ongoing research and novel treatments.[43]

In LUAD patients in Indonesia with EGFR mutations, using first- and second-generation EGFR-TKI therapies such as gefitinib, erlotinib, afatinib, and dacomitinib has shown varied TTP results. Typically, these TTP durations differ based on patient factors, mutation types, and the generation of EGFR-TKI used. A previous study showed the following trends for first-generation EGFR-TKIs, where patients receiving these TKIs showed a median time to progression ranging between 8 and 14 months.[47] This is generally effective for common mutations like exon 19 deletions and L858R mutations but may be less durable for uncommon mutations or patients with more aggressive diseases.[48] Second-generation EGFR-TKIs generally offer slightly improved TTP over first-generation options, averaging between 10 and 16 months. This increase is likely due to their irreversible binding to the EGFR, providing a broader activity spectrum, especially against some resistant mutations.[49,50] Overall, patient outcomes in Indonesia reflect global trends, with newer-generation EGFR-TKIs offering better durability and response, though socioeconomic factors may limit access to optimal therapies.

CONCLUSION

This study found no significant difference in the TTP between patients with lung cancer who had EGFR mutations. The average PFS was nine months. The performance scale score independently predicted poor lung cancer. The patient's condition, insurance coverage, side effects, and the availability of EGFR-TKI at each cancer center must all be considered when selecting a TKI treatment for patients with lung cancer who have EGFR mutations.

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Conflict of Interest
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Authors' Contributions
Concept or idea, design, and research substance: ES, NNS, and LW. Collected data by searching the literature and obtained information: ARS, SE, SDP, AI, NA, SMM, ADP, IAJDK, HH, ND, and MAH. Statistical data analysis and research methodology: NNS and FRA.

Critical revisions: ES and DWTL. Manuscript preparation, editing, and review: ES, NNS, FRA, LW, ARS, SE, SDP, AI, NA, SMM, ADP, IAJDK, HH, ND, MAH, and DWTL. Each author read and approved the manuscript's final draft in addition to making an equal contribution to its creation.

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