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 EGFR TKI, is the first-line treatment for non-small cell lung cancer (NSCLC). However, drug resistance has grown in the last few decades. Few studies tried to compare the time of progression among NSCLC and showed inconsistent findings. This study compares the progression time of lung cancer patients treated with first- and second-generation EGFR-TKI.
Methods: This cross-sectional study included 1.008 participants diagnosed with lung adenocarcinoma from 11 Indonesian Respiratory Centers based on cytology and histological results. Every three months, the response to treatment was assessed using the 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 were assessed using Cox proportional hazards regression.
Results: This study examined 505 patients, the majority of whom were female (50.9%), never smoked (59.8%), diagnosed at an advanced stage (99.2%), and had an ECOG 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 ($p > 0.05$), and the median overall survival rate was 9 months. The time to LUAD progression in lung cancer was significantly impacted by poor performance ($p = 0.001$).
Conclusion: EGFR-TKI treatment can only prolong the time to progression of lung adenocarcinoma by up to nine months, and the performance scale when receiving the EGFR TKI significantly affects the prognosis.

INTRODUCTION

Lung cancer is still a major global health concern; in 2020, the highest cancer-related death rate was recorded. 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. 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 men, 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 RECIST category. The RECIST criteria are based on imaging measurements of the

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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 that support this claim show that there is a significant improvement in progression-free survival with targeted therapy compared with systemic chemotherapy.

EGFR-TKIs were first introduced in 2003 and have been shown to substantially improve overall survival and progression-free survival in lung cancer patients[5–7]. Few studies have examined the efficacy of EGFR-TKIs of the first and second generations, including afatinib, erlotinib, and gefitinib[6,8,9]. 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[9]. 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[10]. After a few years of follow-up, 48.7% of the subjects with TKI resistance manifested progressive disease[10]. This study aimed to assess the time to progression 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. 2) activated positive EGFR mutation without T790M mutation; 3) pathological staging of I or IV; 4) age ≥18 years; 5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2; 6) first-line treatment with gefitinib, erlotinib, and afatinib; 7) presence of brain metastasis and pleural effusion were the inclusion criteria. The following were the exclusion criteria: 1) Double primary or synchronous adenocarcinoma, and 2) pathologically secondary adenocarcinoma. The patient has provided written informed consent to participate in this study. The Health Research Ethics Committee, Faculty of Medicine, USU No. 148r/KEPK/USU/2024, has approved this study.

Time to progression (TTP) was the main outcome of this t rial, while progression-free survival 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 Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria. Time from treatment initiation until disease progression or death was known as progression-free survival.

Administration of EGFR TKI Treatment

Gefitinib, erlotinib, and afatinib were administered to every patient in this trial. 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 SPSS. Significant differences in clinical characteristics among the three TKI treatment groups were determined using logistic regression.

RESULTS

Of the 1008 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 CT scan with IV contrast for RECIST (Figure 1).

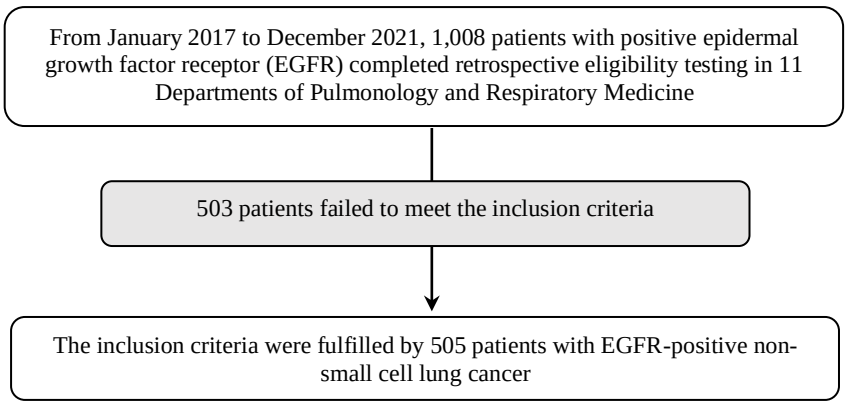

Figure 1. Retrospective study flow chart for EGFR-tyrosine kinase inhibitors therapy in Indonesia

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 are nevertheless common, even though patients are typically diagnosed with intrathoracic metastases, including pleural effusions, at an advanced stage. Additionally, the performance scale, which had an ECOG 0–1, was 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 time to progression 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 time to progression is presented in Table 2.

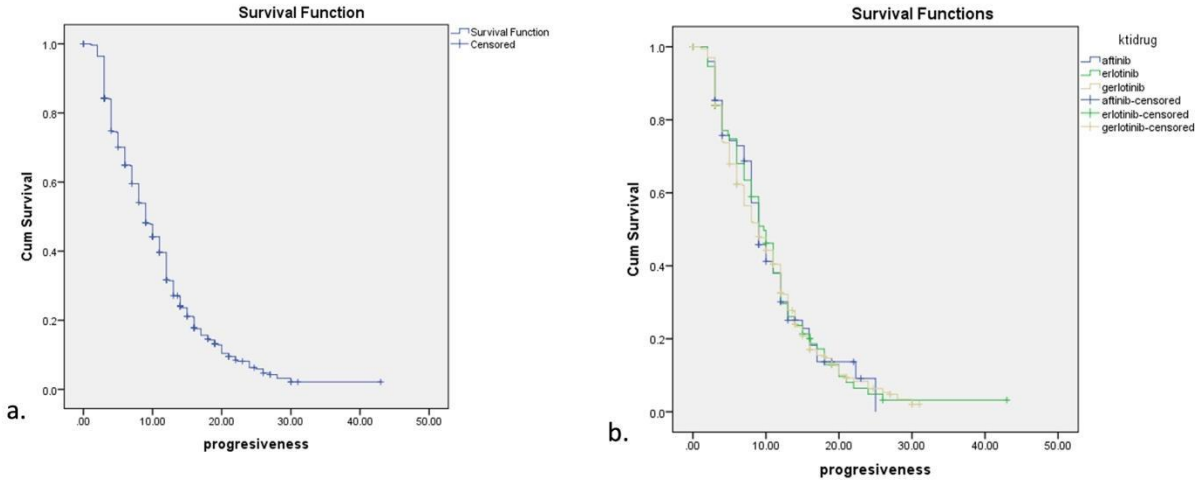

Figure 2. Median time to progression of tyrosine kinase inhibitors (TKI) treatment. 2a) The overall median to progression in TKI treatment; 2b) Median of each subject group with TKI treatment. Blue line for afatinib, green line for erlotinib, and yellow line for gefitinib groups.

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 time to progression in patients with lung cancer. This study showed that only the performance scale (ECOG scale) played a substantial role in predicting the time to progression 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 time to progression of NSCLC harboring EGFR mutations (Table 3).

DISCUSSION

EGFR-TKI is the first-line treatment for individuals with lung cancer who have these mutations at the age of targeted therapy[11]. Females who have never smoked are frequently found to have EGFR mutations[12,13]. Smoking plays a significant role in the onset and spread of NSCLC. Smoking history affects the incidence of EGFR mutations in NSCLC[14]. Patients with non-small cell lung cancer who have never smoked frequently have EGFR mutations[15]. For patients receiving ongoing pemetrexed maintenance therapy for advanced non-squamous non-small cell lung cancer

(NSCLC) without EGFR mutations, current smoking is a separate negative prognostic risk for survival[16]. A newly published large population-based study indicated that NSCLC in patients who had never smoked differed clinically from NSCLC linked to smoking. The study found that patients who never smoked had a longer Overall Survival (OS) than those who smoked[17]. According to earlier meta-analyses, the effect of smoking status on the effectiveness of EGFR-TKIs about PFS in NSCLC is conflicting[18,19]. According to a meta-analysis of OS by Sohn et al.[20], EGFR-TKI therapy seems to show longer OS in nonsmoking NSCLC patients than in smokers, when compared to chemotherapy or a placebo. According to Lee et al.[21], however, there was no difference in OS between patients with NSCLC receiving EGFR-TKI treatment and those receiving chemotherapy based on smoking status. However, we did not find any significant variations in smoking history or sex among individuals with EGFR mutations in our investigation. This is consistent with other research conducted in Indonesia that demonstrated that EGFR mutations are more common among smokers and men[10,22]. 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 mostly diagnosed at an advanced stage[23]. This study also presented similar data showing 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 also showed similar results that stage III, IVA, and IVB lung adenocarcinoma treated with EGFR-TKI had no significant difference in overall survival and time to progression[24]. 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 time to progression of the lung cancer treated with EGFR-TKIs.

EGFR mutations were defined as either common or uncommon. Common mutations include mutations in exons 19 and 21 L858R, whereas uncommon mutations include mutations in exons 18, 20, and T861Q. Different types of EGFR mutations play a role in different responses to TKI and later affect the time to progression and survival rate in lung cancer patients, particularly the adenocarcinoma type[25,26]. Patients with lung cancer with EGFR mutations had longer progression-free and overall survival than those with uncommon mutations[27]. In this study, only two subjects had uncommon mutations, so it could not represent the population to determine whether subjects with uncommon mutations had a shorter or longer time to progression 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, while second-generation EGFR TKI (afatinib) irreversibly bind to all relevant homodimers and heterodimers of erbB family receptors, including EGFR, erbB2, and erbB4[28,29]. This makes second-generation EGFR TKI superior to first-generation TKIs in determining the prognosis of lung cancer[30]. However, this study showed no difference in the time to progression 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[31,32]. Meanwhile, a different study from Indonesia showed longer PFS and greater cost-effectiveness in the gefitinib group compared to afatinib and erlotinib[33]. Furthermore, a meta-analysis also showed no significant difference in efficacy between afatinib, gefitinib, and erlotinib; however, afatinib showed greater side effects than the others[34].

In patients with EGFR-mutant lung adenocarcinoma, the time to disease progression while receiving first- and second-generation EGFR-TKI (tyrosine kinase inhibitors) therapies varies based on drug generation, mutation type, and individual response factors. First-generation EGFR-TKIs (e.g., gefitinib and erlotinib), these drugs commonly yield a median progression-free survival (PFS) of about 10–14 months. Despite their initial effectiveness, acquired resistance often limits long-term outcomes, leading to progression around this median range[35,36]. Second-generation EGFR-TKIs (e.g., afatinib and dacomitinib), this generation 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). However, the progression timeframe is also influenced by resistance mutations that develop over time[37,38]. 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.

EGFR tyrosine kinase inhibitors (TKIs) of the first and second generations have shown promise in treating EGFR-mutant non-small cell lung cancer

(NSCLC), despite differences in response length and effectiveness. First-Generation EGFR TKIs (e.g., gefitinib, erlotinib), were the initial targeted therapies for EGFR-mutated NSCLC and improved progression-free survival (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[37]. Second-Generation EGFR TKIs (e.g., afatinib, dacomitinib), 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. Studies have shown that they may be more effective, especially in never-smoker patients and those with certain mutation profiles[39]. 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 tyrosine kinase inhibitors (TKIs) are an important advancement for patients with EGFR-mutant non-small cell lung cancer (NSCLC) who develop resistance to first- and second-generation TKIs. Osimertinib is the primary approved third-generation EGFR TKI and is designed to target EGFR T790M mutations, a common resistance mechanism following earlier-generation TKI therapies[40]. The key benefits of third-generation EGFR TKIs include extended progression-free survival (PFS), osimertinib shows a longer PFS compared to previous TKIs, making it a standard treatment option in both first-line and second-line settings for patients with T790M-positive mutations[41]. 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[42].

Third-generation EGFR TKIs, notably osimertinib, are recognized for their superior CNS penetration, making them more effective against brain metastases in patients with EGFR-mutant non-small cell lung cancer (NSCLC). Osimertinib achieves higher CNS drug concentrations, which is important for controlling brain lesions—an area where previous-generation TKIs were limited[43]. Studies show osimertinib's efficacy in delaying the progression of CNS metastases and providing longer CNS progression-free survival. High-dose approaches with third-generation TKIs are under exploration to further enhance CNS efficacy while maintaining tolerable side effects[44]. 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 continue to assess third-generation TKIs' efficacy and mechanisms to overcome the resistance that can eventually develop to these drugs, highlighting the need for ongoing research and novel treatments[41.]

In lung adenocarcinoma patients in Indonesia with EGFR mutations, the use of first- and second-generation EGFR-TKI therapies such as gefitinib, erlotinib (first-generation), and afatinib, dacomitinib (second-generation) has shown varied time to progression (TTP) results. Typically, these time-to-progression durations differ based on patient factors, mutation types, and the generation of EGFR-TKI used. Studies show the following trends for first-generation EGFR-TKIs (eg, gefitinib, erlotinib), where patients receiving these TKIs showed a median time to progression ranging between 8 and 14 months. 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 disease[45]. Second-generation EGFR-TKI (e.g., afatinib, dacomitinib), these drugs generally offer slightly improved time to progression (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[46,47]. 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 time to progression between patients with lung cancer who had EGFR mutations. The average PFS was nine months. Poor lung cancer was independently predicted by the performance scale score. 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

The authors declared there is no conflict of interest.

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Authors' Contributions

All authors contributed and approved the final version of the manuscript.

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