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Cost-effectiveness analysis of tyrosine kinase inhibitors (erlotinib *vs*. gefitinib *vs*. afatinib) in non-small-cell lung cancer

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ABSTRACT

Tyrosine kinase inhibitors (TKIs; e.g., erlotinib, gefitinib, and afatinib) are the first-line therapy for non-small-cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) (+) common mutation. The study's objective was to analyze the cost-effectiveness of erlotinib, gefitinib, and afatinib in NSCLC patients. The subjects of the study were NSCLC patients with EGFR (+) mutation receiving either erlotinib, gefitinib, or afatinib from January 2017 to December 2019. The exclusion criteria were patients receiving the respective therapy for less than 2 months and patients unable to complete the treatment until after December 2019. The parameter of treatment effectiveness was progression-free survival (PFS), which was measured as the time from initiation of the therapy until disease progression occurred or a patient became deceased. Direct medical costs, from the hospital perspective, were calculated during the treatment. A nonparametric Kruskal–Wallis test was conducted to compare the median PFS and direct medical cost between the three treatment groups. The median PFS of patients receiving erlotinib, gefitinib, and afatinib was 8 months, 12 months, and 5 months, respectively. There were significant differences in the monthly direct medical costs between the study groups: erlotinib (IDR 13,545,116), gefitinib (IDR 14,727,887), and afatinib (IDR 12,146,834). The cost-effectiveness ratio of the study groups was as follows: erlotinib IDR 1,693,139.50/months; gefitinib IDR 1,227,323.92/months; and afatinib IDR 2,429,366.80/months. Gefitinib was the most cost-effective TKI, followed by erlotinib and afatinib.

INTRODUCTION

According to the 2018 data from the Indonesian Ministry of Health, the cancer incidence in Indonesia was 136.2/100,000 population. The prevalence of cancer in Indonesia ranked 8th in Southeast Asia and 23rd across Asia. In Indonesia, the type of cancer with the highest incidence in males is lung cancer, equal to 19.4 per 100,000 population, with an average death rate of 10.9 per 100,000 population (Balitbang Kemenkes Republik Indonesia, 2018).

Globocan data mentioned that lung cancer was the leading cause of death from cancer in 2018, with deaths of nearly 2.1 million people (World Health Organization, 2018). Lung cancer is a type of lung disease requiring prompt and targeted treatment. Lung cancers are defined as all malignancies occurring in the lung, which include malignancies originating from the lungs themselves (from epithelium/carcinoma of the bronchi) as well as external malignancies (metastatic tumors in the lungs) (Perhimpunan Dokter Paru Indonesia, 2003).

The most common histopathological type of lung cancer is non-small-cell lung cancer (NSCLC), which accounts for 80%–85% of all lung cancers. Most NSCLC patients have advanced-stage cancers and metastases. Guidelines recommend epidermal growth factor receptor (EGFR) mutation examination as the pioneer study (prospective study about EGFR epidemiology) states the Asian population has a high prevalence of EGFR mutation, equal to 51.4% (Sari and Purwanto, 2016).

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In Indonesia, EGFR mutation frequency was 44.4%, comprising 57.1% common EGFR mutation sensitive to tyrosine kinase inhibitor (TKI) (insertion/deletion exon 19, L858R), 29% uncommon mutation (G719X, T790M, and L861Q), and approximately 13.9% mixed mutation (common and uncommon) (Syahruddin *et al*., 2018).

The National Comprehensive Cancer Network recommended TKIs (i.e., erlotinib, gefitinib, or afatinib) as first-line therapy for NSCLC patients that have never received chemotherapy (Planchard *et al*., 2018). A meta-analysis study by Liu *et al*. (2017) revealed no significant differences in the therapeutic effectiveness of erlotinib or gefitinib across all measured parameters. The parameters in the aforementioned study were complete response, partial response, stable disease, progressive disease, overall response rate, disease control rate, progression-free survival (PFS), and median survival time outcomes (Liu *et al*., 2017).

A systematic review conducted by Köhlera and Schuler (2013) stated that afatinib was superior to platinum-based chemotherapy. The results of the study show that afatinib therapy was superior to erlotinib and gefitinib as first-line therapy for NSCLC that is EGFR (+). However, afatinib caused more side effects than the other TKIs; the side effects that occurred were mainly related to skin disorders and diarrhea (Köhler and Schuler, 2013).

Limwattananon *et al*. (2018) conducted a cost-utility analysis of TKI drugs (erlotinib, gefitinib, and afatinib) compared with platinum chemotherapy. The results of their study found that the incremental cost-utility ratio (ICUR) of erlotinib was $ 46,783/ quality of life year (QALYquality life year) over platinum-based drugs, which was followed by afatinib, with an ICUR of $198,961/ QALY over erlotinib. In the 2018 Indonesian National Formulary and its amendment, the therapy aimed at lung adenocarcinoma patients with NSCLC type with EGFR (+) mutation was TKIs, namely, erlotinib and gefitinib. On the contrary, afatinib was specified for patients with a specific mutation of exons 19 and 21 that had received prior lung cancer therapy (Kementrian Kesehatan Republik Indonesia, 2018). A review of various studies conducted on the use of erlotinib, gefitinib, and afatinib was not able to adequately prove a superior TKI (Institute for Clinical and Economic Review, 2016). Therefore, more pharmacoeconomic studies are required to provide evidence for determining the best choice of medication.

Persahabatan General Hospital is a national referral hospital with excellence in respiratory care that continues to provide quality health services, particularly in respiratory health, including services for people with lung cancer. Therefore, this study aimed to analyze and compare the effectiveness and costs of using erlotinib, gefitinib, or afatinib in the treatment of NSCLC.

MATERIALS AND METHODS

The study type used was an analytic observational retrospective cohort study. The subjects of the study were NSCLC patients with EGFR (+) mutation who were treated with a full course of erlotinib, gefitinib, or afatinib, according to hospital protocol. Patients were included in the study period of January 2017 to December 2019 until they experienced disease progression or became deceased. The exclusion criteria were patients obtaining therapy of less than 2 months duration and patients who did not complete treatment during the study period. Data were collected from patients' medical records and financial records. We collected financial data (i.e., direct medical costs) from the initiation to the cessation of TKI treatment. The perspective of the pharmacoeconomic study was payer (the perspective point of the hospital).

The patient data that was collected included demographic and clinical characteristics (gender, age, cancer stage, presence of side effects, comorbidities, and other cancer therapy measures). The cancer treatment effectiveness parameter used was the PFS. PFS was measured by calculating the time from initiation of treatment with a TKI until a patient experienced either disease progression or death. PFS was calculated in months (Gutman *et al*., 2013). PFS measurements have shown several advantages in cancer drug effectiveness studies. PFS can be measured in a shorter time period than can overall survival); therefore, observation costs can be reduced. Additionally, PFS is appropriate for the use in determining the success of TKI therapy (U.S. Department of Health and Human Services *et al*., 2018). The cost-effectiveness ratio (CER) can be calculated by dividing the average total direct medical cost by the median PFS.

Data were managed to Statistical Package for the Social Science version 23.0 for analysis. The assessment of the treatments' effectiveness (PFS) and direct medical cost significance was analyzed using the bivariate Kruskal–-Wallis test. The *post-hoc* analysis determined the significance among groups.

The systematic research procedure is shown in Figure 1. Study permission and ethical clearance were obtained from the study hospital. The ethical approval was obtained from Persahabatan Hospital in Jakarta, number 81/KEPK-RSUPP/12/2019 and date 31 December 2019.

RESULTS

A total number of 440 patients were treated with a TKI between January 2017 and December 2019, comprising 138 erlotinib 138 patients, 218 gefitinib patients, and 84 afatinib patients. The patient screening process is shown in Figure 2.

Patient characteristics

The patient characteristics in Table 1 reveal the comorbidities in TKI therapy for NSCLC accompanying the process of providing TKI, which could affect the cost. Among the diseases were diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and tuberculosis. There were 69 patients with comorbidities (53.5%). Patients suffering from cancer metastases in the brain underwent radiotherapy, while those with bone metastases received bisphosphonate therapy, as stated in the Clinical Practice Guide (KSM Paru RSUP Persahabatan, 2017).

Statistical analysis was conducted to determine whether there were significant differences in patient characteristics that may have affected therapy effectiveness; this analysis was conducted in order to avoid bias in the interpretation of the cost and effectiveness. In the analysis of patient characteristics, significant differences were observed between treatment groups in terms of stage of disease and comorbidities (Table 2). However, the higher stages of disease and presence of comorbidities did not decrease therapeutic effectiveness. In fact, patients with higher stages of disease and more comorbidities even trended toward increased

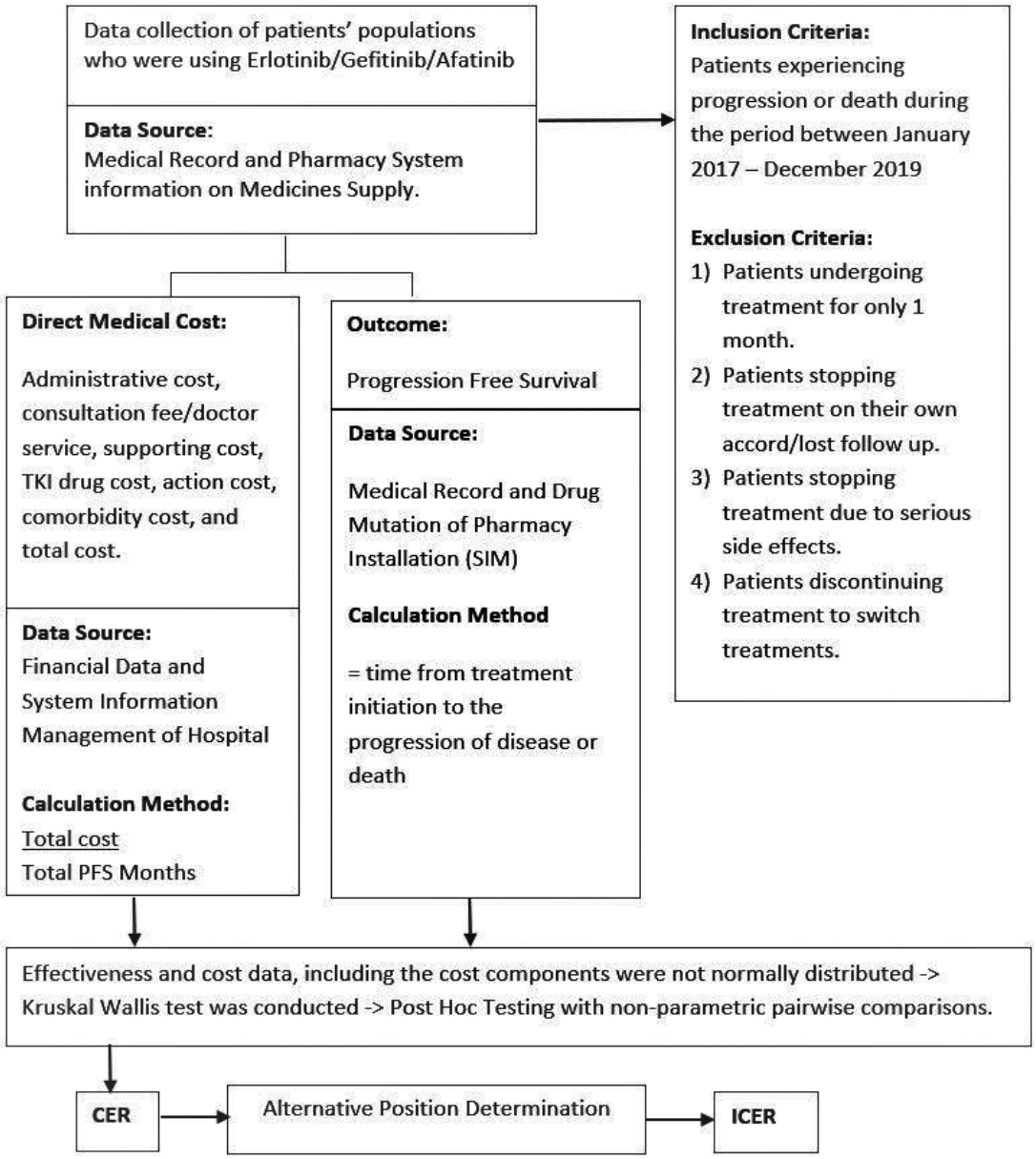

Figure 1. Flowchart of the research procedure.

PFS. Therefore, it can be assumed that these two differences in patient characteristics did not affect the effectiveness of each treatment group.

Treatment effectiveness

The median PFS value was used to measure the effectiveness of each treatment as wide ranges were observed in the minimum and maximum PFS values of each TKI. The highest median PFS value corresponded to the use of gefitinib, followed by erlotinib and then afatinib (Table 3).

There were significant differences in the median PFS when comparing erlotinib versus gefitinib and gefitinib versus afatinib (p-value < 0.05). The median PFS corresponding to erlotinib and afatinib was not statistically significant (p-value = 0.256) (Table 3).

Direct medical cost

The most significant component of the monthly total cost per patient was spent on TKI medications. The proportion of each TKI medication toward total direct medical cost was as follows: erlotinib 75.12%, gefitinib 71.31%, and afatinib 74.62%. The average monthly direct medical cost per patient was significantly different between each group (p-value < 0.05), as shown in Table 4.

With regard to direct medical costs, the only components that significantly differed (p-value < 0.05) between the study groups were supporting cost and TKI medication costs, even though the unit prices of the three TKI drugs were the same, IDR 350,000/tablet, between August 2017 and December 2019. In a routine hospital inpatient visit, the cost components incurred were administrative cost, consultation fee/doctor service, and TKI drug

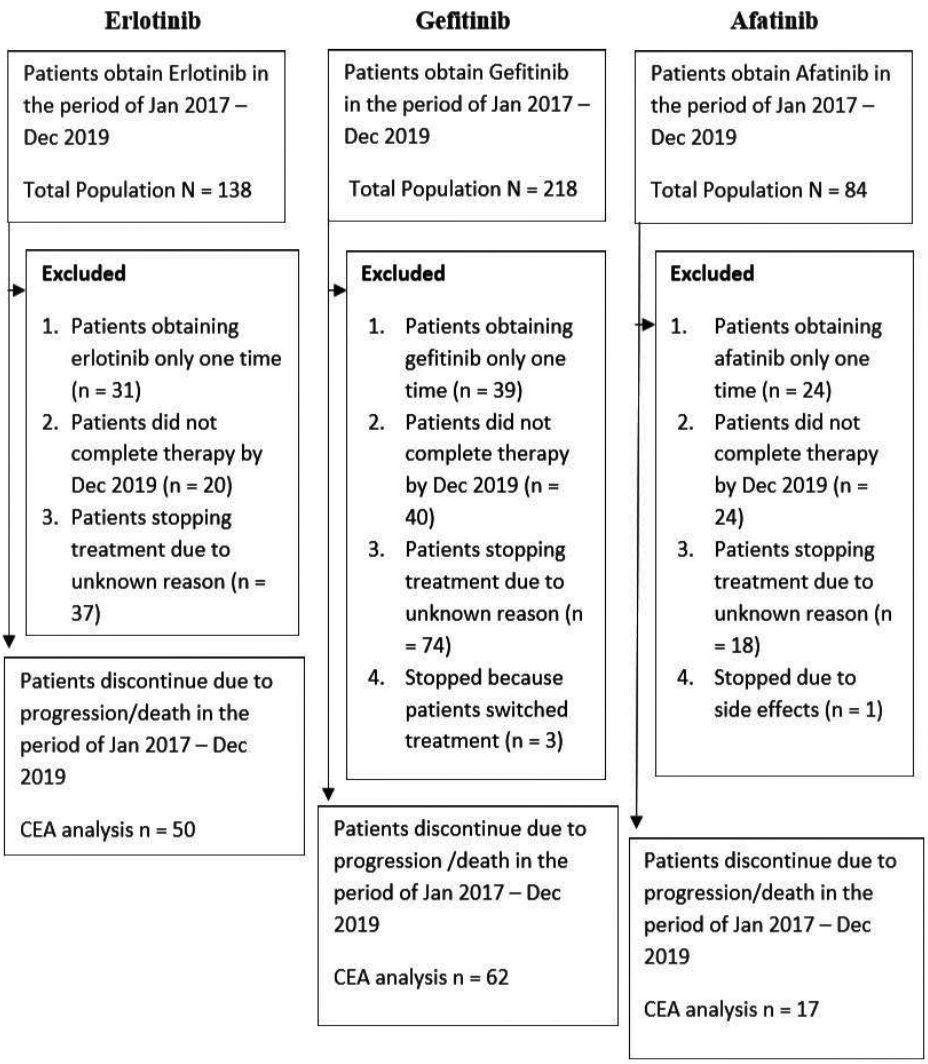

Figure 2. Patient screening flowchart.

Table 1. Patient characteristics' data.

Variable	Erlotinib (*n* = 50)	%	Gefitinib (*n* = 62)	%	Afatinib (*n* = 17)	%	Total (*n* = 129)	%
Gender								
Male	28	55%	35	56%	9	53%	72	55.8%
Female	22	45%	27	44%	8	47%	58	45.0%
Age								
(17–25)	1	2%	0	0%	0	0%	1	0.8%
(26–35)	2	4%	3	5%	0	0%	5	3.9%
(36–45)	6	14%	12	19%	3	18%	22	17.1%
(46–55)	14	27%	19	31%	4	24%	37	28.7%
(56–65)	21	41%	19	31%	4	24%	44	34.1%
6 (> 66)	6	12%	9	15%	6	35%	21	16.3%
Side effect	44		50	81%	13	76%	110	85.3%
Stage								
Stage 3	2	4%	1	1.6%	3	21.4%	6	4.6%
Stage 4	48	96%	61	98.4%	14	78.6%	123	95.6%
Comorbidity	20	40%	40	66%	5	24%	65	53.5%
Other cancer therapies (radiotherapy and bisphosphonates)	16	32%	29	46.8%	4	24%	44	34.1%

Table 2. Differences in patient characteristics among each treatment group.

Variable (average)	Erlotinib	Gefitinib	Afatinib	*p*-value
Stage disease	3.96	3.98	3.82	0.021*
Side effect	1.12	1.19	1.24	0.444
Comorbidity	1.6	1.35	1.71	0.007*
Other cancer theraphies (radiotherapy and bisphosphonate)	1.68	1.56	1.76	0.226
PFS (median)	8	12	5	0.001*

Table 3. PFS erlotinib versus gefitinib versus afatinib.

PFS	Erlotinib (months)	Gefitinib (months)	Afatinib (months)	*p*-value* Kruskal-Wallis test, p = 95%
Median	8	12	5	0.001*
Minimum	2	2	2	
Maximum	25	28	19	
Std. deviation	5.55	7.14	4.21	
Post-hoc test (PFS)				
Treatments	Difference	PFS (months)	Results	*p*-value*Mann–Whitney Test, p = 95%
Erlotinib versus gefitinib	4 months	8 versus 12	Significant	0.033*
Erlotinib versus afatinib	3 months	8 versus 5	Not significant	0.256
Gefitinib versus afatinib	7 months	12 > versus 5	Significant	0.001*

Table 4. Average direct medical cost per patient per month for TKI treatment.

Average direct medical cost per patient per month	Research subject (*n* = 129)						*p*-value Kruskal-Wallis test
	Erlotinib (*n* = 50)		Gefitinib (*n* = 62)		Afatinib (*n* =17)		
	Cost (IDR)	%	Cost (IDR)	%	Cost (IDR)	%	
1. Administrative cost	82,744	0.61%	71,886	0.49%	69,302	0.57%	0.576
2. Consultation fee/doctor service	186,036	1.37%	205,670	1.40%	121,169	1.00%	0.202
3. Supporting fee	1,252,823	9.25%	1,353,283	9.19%	823,166	6.78%	**0.028***
4. TKI drug cost	10,175,061	75.12%	10,502,590	71.31%	9,064,266	74.62%	**0.000***
5. Side effect drug cost	19,176	0.14%	450,286	3.06%	270,119	2.22%	0.056
6. Drug/other health equipment costs	265,792	1.96%	450,286	3.06%	270,119	2.22%	0.627
7. Accommodation cost	187,756	1.39%	247,392	1.68%	182,701	1.50%	0.135
8. Action cost	340,821	2.52%	363,838	2.47%	447,311	3.68%	0.745
9. Drug and comorbidity action cost	1,034,906	7.64%	1,512,475	10,27%	1,159,758	9.55%	0.255
Total Cost of 1–9	13,545,116	100%	14,727,887	100%	12,146,834	100%	0.005*

*Significant value indicators (*p* = 95%).

cost. A supporting clinical examination was conducted at least once in the 2 months to evaluate the clinical condition of each patient.

The comorbidities costs comprised the costs incurred treating patients' comorbidities or complications during cancer treatment. These costs included mutation treatment, radiotherapy (metastases to the brain), and/or bisphosphonate agent administration (metastases to bone). No significant differences were seen in comorbidity-related costs among the three TKI study groups. This result provides evidence contrary to the assumption that comorbidities significantly interfere with total treatment costs.

After statistical analysis with the Kruskal–Wallis test, followed by *post-hoc* testing, the two cost components mentioned previously (i.e., supporting costs and comorbidity-related costs) significantly differed. The supporting costs between the erlotinib and gefitinib groups were not significantly different. Meanwhile, the analysis of the supporting costs of the erlotinib versus afatinib groups and gefitinib versus afatinib groups did significantly differ. The procurement price of the three TKI medicines for NSCLC has remained stable between 2016, for erlotinib and gefitinib, and September 2017, when afatinib was introduced, until 2020.

Cost-effectiveness analysis

In the cost-effectiveness analysis, we compared medication effectiveness and direct medical cost (Table 5). Based on the effectiveness data and average total direct medical cost, the CER and incremental cost-effectiveness ratio (ICER) (Table 6) were calculated.

Table 6 shows that gefitinib provided increased effectiveness over erlotinib; results of *post-hoc* testing of pairwise comparisons towards cost-effectiveness were significantly different ($p = 0.003$) between these groups. Meanwhile, although the total

direct medical cost incurred was also higher for gefitinib compared to erlotinib, these results were not significantly different. The CER value of gefitinib was lower than erlotinib, indicating the higher cost of erlotinib compared to gefitinib as these medications had similar effectiveness. Before calculating the ICER value, we determined the alternative position for treatment between erlotinib and gefitinib using the cost-effectiveness grid, as shown in Figure 3.

The position of erlotinib was the drug with lower effectiveness at a lower cost (Fig. 3). On the other hand, gefitinib had higher effectiveness at a higher cost. Thus, the ICER calculation was required to select between the two drugs. From Figure 3, it can be seen that gefitinib fell into the exchange column I, with higher effectiveness and a higher cost, while erlotinib fell into exchange column A, with lower effectiveness at a lower cost. These results indicated that the ICER calculation between the erlotinib and gefitinib should be conducted. The ICER calculation results showed that treatment alternatives from erlotinib to gefitinib required IDR 295,692.75 for every 1 month increased in PFS achievement. Table 6 shows that the *post-hoc* test results of pairwise comparisons on erlotinib and afatinib on PFS and cost-effectiveness parameters were not significantly different (PFS *p*-value = 0.256; cost *p*-value = 0.179). Thus, it was not necessary to calculate the ICER for the erlotinib and afatinib groups.

The *post-hoc* test results of pairwise comparisons on cost-effectiveness demonstrated a significant difference (*p*-value =0.001) between gefitinib and afatinib. Gefitinib provided better effectiveness than erlotinib; however, the direct total medical cost incurred was also significantly higher.

The CER value of gefitinib therapy was lower than that of afatinib therapy, meaning that the effectiveness of each was similar. A higher cost was required in the afatinib group than the gefitinib group. The position of afatinib was the alternative with lower effectiveness and lower cost. On the other hand, gefitinib had higher effectiveness at higher costs. Thus, ICER calculation was required for further analysis (Fig. 4).

Based on Figure 4, gefitinib fell into Grid I with higher effectiveness and a higher cost, while afatinib fell into Grid A, with lower effectiveness and a lower cost. Therefore, ICER calculation was required to distinguish between the gefitinib and afatinib groups. The results of ICER calculation showed that treatment alternatives from afatinib to gefitinib required IDR 368,721.86 for every 1 month increased in PFS achieved.

DISCUSSION

Results of the current study showed that the majority of patients who obtaining either of the three TKIs were males (55.8%). In accordance with the study of Groot *et al*., the current study demonstrated that the most frequent age group was patients

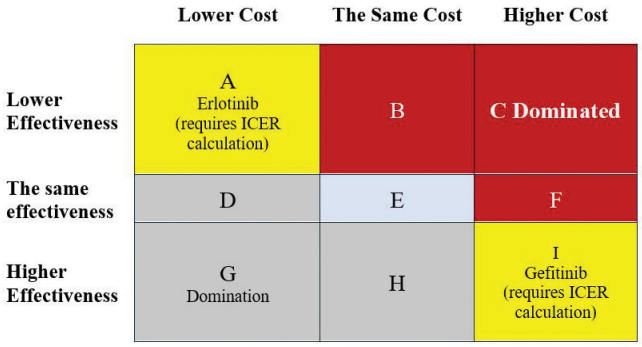

Figure 3. Alternative position of erlotinib and gefitinib treatments (Adapted from Rascati, 2009).

Table 5. Summary of the comparison of treatment effectiveness towards the average monthly direct medical cost.

Treatment effectiveness	Erlotinib (*n* = 50)	Gefitinib (*n* = 62)	Afatinib (*n* = 17)	*p*-value Kruskal-Wallis
Median PFS (month)	8	12	5	0.001*
Direct medical total cost (IDR)	13,545,116	14,727,887	12,146,834	0.005*

*Significant value indicators (*p* = 95%).

Table 6. CER and ICER.

	PFS median (months)	Direct medical cost (IDR)	CER	ICER
Erlotinib versus gefitinib				
Erlotinib (*n* = 50)	8	13,545,116	1,693,139.50	1,182,771 4 = 295,692.75
Gefitinib (*n* = 62)	12	14,727,887	1,227,323.92	
	p-value = 0.003*	*p*-value = 0.236		
Erlotinib versus afatinib				
Erlotinib (*n* = 50)	8	13,545,116	1,693,139.50	
Afatinib (*n* = 17)	5	12,146,834	2,429,366.8	
	p-value = 0.256*	*p*-value = 0.179		
Gefitinib versus afatinib				
Gefitinib (*n* = 62)	12	IDR 14,727,887	1,227,323.92	2581,053 7 = 368,721.86
Afatinib (*n* = 17)	5	IDR 12,146,834	2,429,366.8	
	p-value = 0.001*	*p*-value = 0.005*		

*Significant value indicators, post-hoc using pair comparison Mann–Whitney test (*p* = 95%).

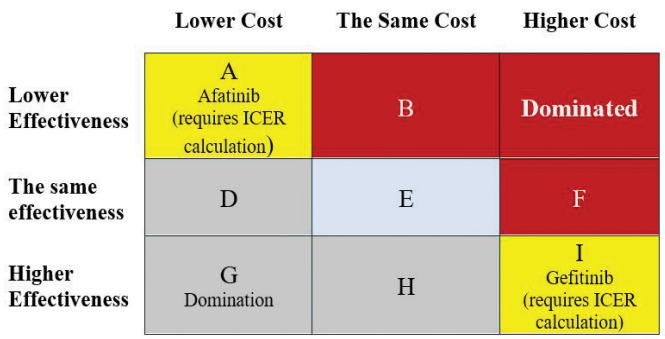

Figure 4. Alternative position of gefitinib and afatinib treatments (Adapted from Rascati, 2009).

55–74 years, accounting for approximately 53% of the patients. Prior studies have shown similar results with most cancer patients 56–65 years of age (Holleman *et al*., 2020; Köhlera and Schuler, 2013).

The current study found that the median PFS between the three TKI groups was slightly different as follows: gefitinib 12 months, erlotinib 8 months, and afatinib 5 months. Patrikus *et al*. conducted similar research in Surabaya and found the PFS for gefitinib and erlotinib to be 9.4 months and 8.7 months, respectively (Tio, 2017). Meanwhile, the study series by Lux-Lung observed that the PFS for afatinib was over 11 months (Deeks and Keating, 2018), which was much lower than the median PFS of 5 months in the current study. The relatively low median PFS in the current study could be due to such issues as the modest sample size and/or difficulty measuring the effectiveness of some patients that discontinued treatment prior to the presence of a progression measurement. Additionally, patients who were still undergoing treatment at the end of December 2019 were not included in the study since they had not reached the progression period.

Based on the cost component analysis among the treatment groups, medication cost significantly contributed to the total direct medical cost (accounting for greater than 70% of all costs). Furthermore, the prices of the three TKIs were the same at the time of the study. The government determined the prices of the medications and the information was displayed on the electronic catalog organized by the National Public Procurement Agency.

Several determinants may result in total cost differences, including the frequency of visits to different hospitals, which affects administrative costs and doctor service fees. For example, some patients came to the hospital with a single registration. Those patients underwent a supporting examination in addition to receiving TKI drugs. However, other patients came only for doctor consultation and medicine and, subsequently, had their supporting test on another day.

The current study also identified and calculated the cost related to TKI side effects, mainly skin toxicity and indigestion; these predominant side effects have been proven in various clinical trials and studies (Aw *et al*., 2018; Sheen *et al*., 2015). The patients experiencing side effects were limited to those who experienced side effects mainly involving gastrointestinal disturbances, diarrhea, and skin toxicity (Aw *et al*., 2018; Köhler and Schuler, 2013; Reguart *et al*., 2014; Sheen *et al*., 2015).

Accommodation cost was incurred due to inpatient care and also affected total cost. Some reasons for patient hospitalization included experiencing severe side effects and symptoms of comorbidities or may be due to the cancer condition itself. The different clinical needs of patients caused the cost of the investigation to be different. Inpatient and outpatient status differences led to differences in the cost of accommodation and treatment. Lastly, additional costs may be incurred due to comorbidities, as well as the complexity of cancer itself (mutation state).

Although the outcome for PFS was not significantly different between the gefitinib and afatinib groups, the difference in PFS outcome was quite large compared to other studies. A meta-analysis in China by Liu *et al*. (2016) obtained average PFS outcomes for gefitinib, erlotinib, and icotinib of 5.48, 5.15, and 5.81 months, respectively (the difference between erlotinib and gefitinib was less than 1 month). The meta-analysis revealed that effectiveness outcomes were similar among the erlotinib, gefitinib, and icotinib groups (Liu *et al*., 2017).

A cost-effectiveness analysis by Holleman *et al*. (a study in 2018) found the cost of gefitinib and erlotinib to be €65,889 and €64,035, respectively, with average QALY achievements of 1.36 and 1.39, respectively. Hence, the obtained ICUR was €61.800/QALY from erlotinib over gefitinib (Holleman *et al*., 2020). A cost-effectiveness analysis conducted in Thailand by Limwattananon (2018) concluded the ICER of gefitinib over erlotinib to be $46,783/QALY. ICER of afatinib versus erlotinib incurred an additional cost of €27,058/QALY and €41,504/QALY (Limwattananon *et al*., 2018). Cost-utility analysis (CUA) might serve as another alternative for assessing treatment effectiveness. Evaluation using CUA requires the calculation of QALYs. This study can be expanded further by complementing CEA with CUA.

The nature of the retrospective approach in this study revealed some limitations. This study used secondary data sources (i.e., patients' medical records) and data period for 3 years. Therefore, it was challenging to determine the cause of treatment discontinuation. Thus, potential patients' records should be excluded. Furthermore, the total number of patients from each therapeutic group was less balanced, particularly in the afatinib group (17 people) due to some patients who were still in the therapy period and did not reach a PFS endpoint during the study period. A prospective study may offer benefits concerning the completeness of data collected; however, this approach would require a lengthy observational time.

CONCLUSION

The average monthly total direct medical cost per NSCLC patient with EGFR (+) mutation receiving afatinib was lower than that of patients receiving erlotinib or gefitinib. The treatment of NSCLC EGFR (+) patients using gefitinib was more effective at increasing PFS compared to erlotinib and afatinib. The cost-effectiveness analysis showed that the CER of gefitinib was lower than either erlotinib or afatinib, underlining that the most cost-effective medicine was gefitinib. A prospective cost-utility pharmacoeconomic study regarding the use of erlotinib, gefitinib, and afatinib on NSCLC EGFR (+) mutation patients should be considered. Further cost-effectiveness analyses involving more patients, particularly in the afatinib treatment group, should also be conducted.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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