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Effectiveness of Afatinib and Gefitinib in Non-Small Cell Lung Cancer (NSCLC) Epidermal Growth Factor Receptor (EGFR) Mutations in Indonesia: Observational Studies with Retrospectives

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ABSTRACT

Effectiveness data can describe the results or performance of an intervention (treatment) in daily clinical practice and also provide recommendations to policymakers regarding the need or not of health technology to be implemented into the health care system. Research related to the effectiveness of afatinib and gefitinib is still minimal, especially in Indonesia. This study aims to provide an overview of the effectiveness of afatinib and gefitinib in daily clinical practice (the real world) as first-line therapy. This research is an observational study with a retrospective approach that observes the medical records of NSCLC patients who have EGFR mutations in Dr. Sardjito General Hospital Yogyakarta and Dr. Kariadi General Hospital Semarang, Java Island, Indonesia in the period January 2016 - March 2019. There were 113 patients identified, 27 patients using afatinib, and 86 patients using gefitinib. Afatinib had significantly superior progression-free survival (448 days or 14.7 months; 95% CI = 12-17.4 months; p = 0.002) compared to gefitinib (344 days or 11.3 months; 95% CI = 8, 4-14.3 months), however, overall survival of afatinib is no better than gefitinib (472 days or 15.5 months; 95% CI = 13.8-17.2 months vs 653 days or 21.4 months; 95% CI = 18-24.8 months) with a value of p = 0.302. Afatinib has superior progression-free survival compared to gefitinib, but not overall survival as first-line therapy in NSCLC patients with EGFR mutations.

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INTRODUCTION

Lung cancer is a disease that has a high incidence and death rate in the world. Indonesia, in 2018, the highest lung cancer incidence rate in men is 19.4 per 100,000 population, with an average death rate of 10.9 per 100,000 population (Bray *et al.*, 2018).

Non-Small Cell Lung Cancer is the most common type of lung cancer. About 85% of the NSCLC incidence of lung cancer overall and 80% of NSCLC cases are patients with advanced-stage (Stage IIIB

/ IV) (Chouaid *et al.*, 2014). Epidermal growth factor receptor mutations (EGFR) are often found in advanced NSCLC patients; there are 10-15% of cases in western countries and up to 50% in Asian countries (Shi *et al.*, 2015). First-line therapy used in the treatment of NSCLC with EGFR mutations based on the National Comprehensive Cancer Network (NCCN), namely the tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib (first generation), afatinib (second generation) (Ettinger *et al.*, 2017).

Tyrosine Kinase Inhibitors in the first generation have a mechanism of action that reversibly binds and inhibits EGFR signals, whereas in the second generation it can inhibit the family of erythroblastosis oncogene B (ErbB) which irreversibly inhibits signals from all homo-dimers and heterodimers of the ErbB family receptor (EGFR) / ErbB1, HER2 / ErbB2, ErbB3 and ErbB4) (Chi *et al.*, 2013; Solca *et al.*, 2012). TKIs groups such as gefitinib (first generation) and afatinib (second generation) show a progression Free Survival (PFS) and Overall Survival (OS) that are superior to platinum-based chemotherapy (Liang *et al.*, 2014; Ellis *et al.*, 2015).

One that can affect PFS and OS is patient characteristics such as gender, smoking status, mutation type, and comorbidities. Female sex, never smoking, exon 21 (L858R), and deletion 19 are very responsive to the TKIs group that leads to an increase in PFS, whereas comorbidities can affect OS as first-line therapy (Mitsudomi *et al.*, 2010; Inoue *et al.*, 2013).

Several studies related to the efficacy of afatinib and gefitinib in the Lux-Lung 7 study and meta-analysis, show that afatinib is superior to gefitinib in both PFS and OS, and quality life (Liang *et al.*, 2014; Paz-Ares *et al.*, 2017; Park *et al.*, 2016; Li, 2014; Sari *et al.*, 2019) and research related to effectiveness in daily clinical practice seen retrospectively also shows that PFS TKIs (gefitinib and erlotinib) are superior to other chemotherapy (Xu *et al.*, 2016, 2017), however data regarding the effectiveness of gefitinib and afatinib specifically in daily clinical practice is still limited, especially in Indonesia. The effectiveness data can describe the results or performance of an intervention (treatment) in daily clinical practice or the real world, in contrast to the efficacy data that illustrates the outcome or performance of intervention in ideal conditions. Effectiveness data can also be used to provide recommendations to policymakers about whether or not a health technology is necessary (Drummond *et al.*, 2005). Need to do effectiveness research related to the use of afatinib and gefitinib in NSCLC patients who have EGFR mutations, which aims to provide an overview of the effectiveness of afatinib and gefitinib in daily clinical practice as first-line therapy.

MATERIALS AND METHODS

Subject

This study was a retrospective observational study, by looking at the medical records of NSCLC patients with EGFR mutations using afatinib and gefitinib therapy at Dr. Sardjito General Hospital Yogyakarta and Dr. Kariadi General Hospital Semarang, Java, Indonesia in the January 2016 - March 2019 period. The sample in this study was balanced between the two groups based on age, gender, type of mutation, comorbidities, and duration of treatment that had previously fulfilled the inclusion and exclusion criteria. As for the inclusion criteria in this study were patients aged 18 years who were both hospitalized and outpatient who received gefitinib and afatinib as first-line therapy, as well as patients with advanced stages (IIIB / IV), while exclusion criteria were patients whose medical records were incomplete, contraindications to treatment, first-line treatment using platinum-based chemotherapy, as well as patients who used afatinib and gefitinib for less than four weeks.

Data Collection and Analysis

Retrieval of patient data is done by reviewing the patient's medical record to see the effectiveness of treatment therapy and patient characteristics (age, gender, type of mutation, duration of treatment, and comorbidities). The effectiveness measured is Progress Free Survival/PFS (the time from being diagnosed until the development of the severity of the disease or recurrence is clinically proven and imaging or cytology examination of tissue and Overall Survival/OS (the time from being diagnosed to death). Effectiveness was analyzed using the Kaplan Meier test to obtain patient survival, and using the Chi-Square test to see the distribution of patient characteristics data, and Mann-Whitney test, Kruskal-Wallis test, and ANNOVA test to see the effect of patient characteristics on the effectiveness of treatment therapy.

Ethical Considerations

This study has received ethical approval from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Gadjah Mada University Indonesia, with reference number KE/FK/0948/EC/ 2018 and the Health Research Ethics Committee of Dr. Kariadi General Hospital with number 033/E / KEPK -RSDK-2018.

RESULTS AND DISCUSSION

113 NSCLC EGFR mutation patients met the inclusion and exclusion criteria. On average, patients affected by NSCLC EGFR mutations aged 51-60 years (38.9%), all of whom were advanced stage IIIB / IV patients. The most common gender was patients with a female (56.6%), while the male was 43.4%. The most common type of mutation was exon 19 (56.6%), while the least was exon 18 (3.5%). The most common comorbid based on Charlson Comorbidity Index (CCI) is a score of 1 (37.2%) such as peptic ulcer disease, while the least with a score of 2 (28.3%) such as diabetes mellitus, peptic ulcer disease, and hemiplegia. Regarding the duration of treatment, the average length of treatment of patients was highest at the duration of treatment <90 days by 43.4%. There is no significant difference between the characteristics of patients using afatinib and those using gefitinib. This can be seen from Table 1, showing that a significance value > 0.005 for age, gender, mutation, comorbidities, and duration of treatment.

Of 113 patients, there were 86 NSCLC EGFR mutation patients who used gefitinib and 27 patients who used afatinib. The results of the study showed that the Progression of Free Survival (PFS) afatinib was better than gefitinib; this can be seen in Figures 1 and 2. This is consistent with the LUX-Lung 7 phase 2B clinical trial research and a meta-analysis has been found that afatinib has a longer PFS than gefitinib and is significantly (p <0.005) superior to gefitinib (11 months vs. 10.9 months) (Liang *et al.*, 2014) (Park *et al.*, 2016) (Krawczyk *et al.*, 2017; Shen *et al.*, 2017). Afatinib can irreversibly block ErbB more effectively than reversible inhibition of EGFR on gefitinib in the treatment of NSCLC with EGFR mutations. The mechanism of action of afatinib, which is broader and irreversible, can result in better tumor control to prolong the PFS of NSCLC patients with EGFR mutations (Park *et al.*, 2016; Xu *et al.*, 2017). However Overall Survival on afatinib was not so better compared to gefitinib and did not differ significantly (P = 0.302). This can be seen in Tables 2 and 3.

Based on Lux-Lung 7, research that has been done shows that afatinib OS is better than gefitinib, although it is not significantly different (P> 0.2580) (Paz-Ares *et al.*, 2017). The low value of OS afatinib in this study is likely due to patients who have less OS than gefitinib. Besides, overall survival can also be influenced by the chemotherapy used, disease progression, or tumor/cancer progression, and have a better prognosis with radiotherapy (Warth *et al.*, 2012).

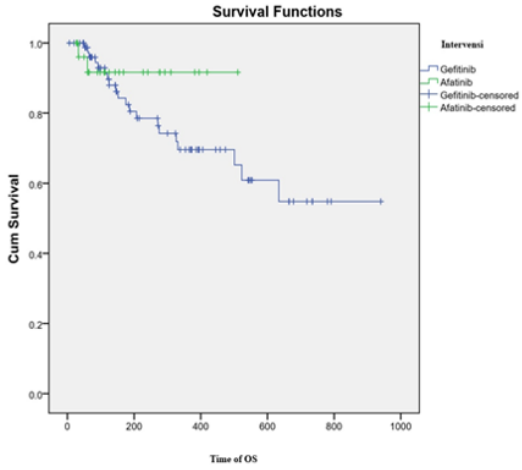

Figure 1: Time of OS

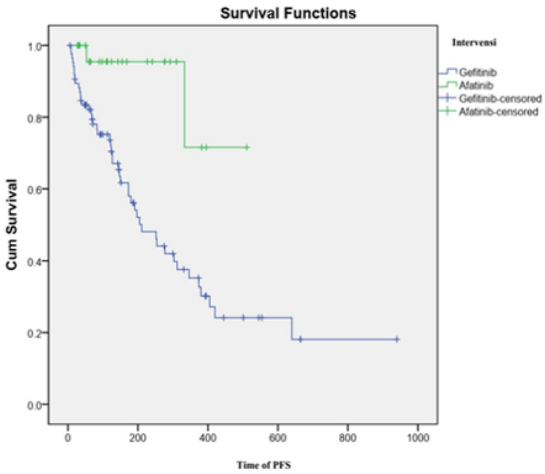

Figure 2: Time of PFS

The progression of free survival in gefitinib and afatinib is not influenced by age, gender, type of mutation, or comorbid, but it is influenced by the duration of treatment. This can be seen in Table 4. This is consistent with research conducted by Otsuka *et al*. There is no correlation between patient characteristics with PFS and OS (Otsuka *et al.*, 2015). Similar to OS in afatinib, it is only affected by the length of treatment. OS patients who get afatinib will be longer than those who get gefitinib, especially in the subpopulation of patients with Deletion 19 and Exon 21 (Park *et al.*, 2016), and gefitinib is also influenced by the length of treatment and comorbidities. Comorbidity has the potential to reduce overall survival, progression-free survival, and mortality compared to patients who do not have comorbidities (Dima *et al.*, 2018; Chiang *et al.*, 2002). This is due to the lack of observation of the early symptoms

Table 1: Patient Characteristics

	Total	Treatment Group		P.Value
		Afatinib	Gefitinib	
Total n (%)	113 (100)	27 (24)	86 (76)	
Age ,n (%)				
< 50 years	25 (22,2)	7 (25,9)	18 (20,9)	0,117
51 - 60 years	44 (38,9)	6 (22,2)	38 (44,2)	
> 60 years	44 (38,9)	14 (51,9)	30 (34,9)	
Gender, n (%)				
Man	49 (43,4)	11 (40,7)	38 (44,2)	0,753
Woman	64 (56,6)	16 (59,3)	48 (55,8)	
Mutation, n (%)				
Exon 18	4 (3,5)	1 (3,7)	3 (3,5)	0,514
Deletion 19	59 (52,2)	16 (59,3)	43 (50)	
Exon 20/T790M	5 (4,4)	0 (0)	5 (5,8)	
Exon 21/L858R	29 (25,7)	8 (29,6)	21 (24,4)	
Others	16 (14,2)	2 (7,4)	14 (16,3)	
Comorbid, n (%)				
1	42 (37,2)	7 (26)	35 (40,7)	0,207
2	32 (28,3)	11 (40,7)	21 (24,4)	
> 2	39 (34,5)	9 (33,3)	30 (34,9)	
Duration of Treatment				
< 90 days	49 (43,4)	14 (51,9)	35 (40,7)	0,204
91 - 180 days	16 (14,2)	3 (11,1)	13 (15,1)	
181 - 270 days	11 (9,7)	6 (22,2)	5 (5,8)	
271 - 360 days	15 (13,2)	2 (7,4)	13 (15,1)	
361 - 450 days	5 (4,4)	1 (3,7)	4 (4,7)	
451 – 540 days	7 (6,2)	1 (3,7)	6 (6,9)	
541 - 630 days	3 (2,7)	0 (0)	3 (3,5)	
631 - 720 days	4 (3,5)	0 (0)	4 (4,7)	
> 721 days	3 (2,7)	0 (0)	3 (3,5)	

Table 2: Average PFS Afatinib compared to Gefitinib

Intervensi	Total (N)	Event of PF	Mean PFS				Sig
			Estimate	SE	95% Cl		
					Lower Basic	Upper Bound	
Gefenitib	86	46 (53,5)	344,071	45,732	254,358	433,785	0,002
Afanitib	27	2 (7,4)	447,705	41,115	367,19	528,290	

Table 3: Average OS Afatinib compared to Gefitinib

Intervensi	Total (N)	Event of OS n(%)	Mean OS				Sig
			Estimate	SE	95% Cl		
					Lower Basic	Upper Bound	
Gefenitib	86	20 (23,3)	652,508	51,585	551,404	753,613	0,302
Afanitib	27	2 (7,4)	472,2	26,291	420,671	523,729	

Table 4: Patients' Characteristic According to PFS and OS

Characteristic	Progression-Free Survival (PFS)		Overall Survival (OS)	
	Afanitib (n=27) P. Value	Gefinitib (n=86) P. Value	Afanitib (n=27) P. Value	Gefinitib (n=86) P. Value
Characteristic	Progression-Free Survival (PFS)		Overall Survival (OS)	
	Afanitib (n=27) P. Value	Gefinitib (n=86) P. Value	Afanitib (n=27) P. Value	Gefinitib (n=86) P. Value
Age (year) [a,c]	0,365	0,284	0,371	0,520
<50				
51-60				
>60				
Gender [b]	0,294	0,879	0,294	0,636
Man				
Woman				
Mutation [a]	0,098	0,124	0,084	0,350
Exon 18				
Deletion 19				
Exon 20/T790M				
Exon 21/L858R				
Others				
Comorbid [a,c]	0,988	0,111	0,965	0,017
1				
2				
>2				
Duration of Treatment [a]	0,000	0,000	0,000	0,000
<90 Days				
90-180 Days				
181-270 Days				
271-360 Days				
361-450 Days				
451-540 Days				
541-630 Days				
631-720 Days				
>721 Days				

a: Kruskal – Wallis Test
b: Mann – Whitney Test
c: Annova Test

of the disease that can be observed at an early stage, whereas on average in lung cancer patients are often diagnosed at an advanced stage whose treatment is limited so that it impacts on the patient's survival rate (Chiang *et al.*, 2002; Chang *et al.*, 2015). Comorbidity can also disguise the symptoms of cancer, which can cause delays in diagnosis but can also influence the choice of treatment, which indirectly prevents patients from receiving aggressive lung cancer treatment (Iachina *et al.*, 2014) But for the type of mutation and gender, based on previous research, shows that mutations can affect the effectiveness of afatinib and gefitinib. atients with Exon / Del 19 mutations, showed an average afatinib OS better than gefitinib (30.7 months vs. 26.4 months), and in patients with L858R / Exon 21 mutations (25.0 vs 21.2 months), and in patients with female sex are also very responsive to the TKIs group that leads to an increase in PFS (Mitsudomi *et al.*, 2010; Vyas *et al.*, 2017), however, the results of this study do not have the effect of mutations in PFS or OS.

Weaknesses in this study are the limitations in the number of samples so that it might affect generalization. Besides, the effectiveness measured in

the study is coprimary endpoint (PFS and OS) without looking at the secondary endpoint (objective response rate and symptom reduction).

CONCLUSIONS

Afatinib has progression-free survival that is superior to gefitinib, but not to overall survival as first-line therapy in NSCLC patients with EGFR mutations.

Conflict of Interest

The author declares that there is no conflict of interest.

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