Comparison of the Efficacy of Generation 1 and 2 Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer Patients with EGFR Positive Mutations

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Abstract

Background: The use of TKI generation 1 (Gefitinib, Erlotinib) and Generation 2 (Afatinib) has become the standard therapy for JPIC pulmonary adenocarcinoma type with positive EGFR gene mutations.

Objective: to analyze the comparison of the efficacy of TKI generation 1 and 2 in NSCLC patients with positive EGFR mutations.

Methods: The design of this study used a retrospective in which the participants who received EGFR therapy for TKI generations 1 and 2 were compared its efficacy. Data collected included health-related quality of life (HRQOL), body weight, performance status (PS), Response Evaluation Criteria in Solid Tumors (RECIST) of thoracic CT, Common Terminology Criteria for Adverse Events (CTCAE), progression free survival (PFS) and overall survival (OS). The statistical analysis used was the independent t test, Mann Whitney test, or Kruskal Wallis test with $p < 0.05$.

Results: Most of the participants' quality of life scores did not change before and after therapy, where the EQ5D value was 67.5% (group 1 = 60.6%; Group 2 = 94.1%; p = 0.806). The participant's weight decreased by 49.5% (group 1 = 45.9%; group 2 = 60.0%; p = 0.658) and the participant's PS was stable (group 1 = 29.4%; group 2 = 50.0%; p = 0.014). The RECIST value of the participant was progressive disease 51.0% (p = 0.338). CTCAE differed in stomatitis ($p < 0.001$), paronychia ($p < 0.001$), and diarrhea ($p < 0.001$). There was no significant difference between the first and second groups in the PFS (p = 0.197) and OS (p = 0.740) values.

Conclusion: EGFR therapy for TKI generations 1 and 2 have almost the same efficacy, in which there is no significant difference in the quality of life of the participants.

Keywords: *TKI EGFR, Gefitinib, Erlotinib, Afatinib, NSCLC*

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Introduction

Lung cancer is the leading cause of cancer-related death in men and women in the United States, and the median 5-year worldwide survival rate for lung cancer is 5% [(1)]. Based on 2018 Globocan data, in Indonesia, the proportion of lung cancer is more prevalent by men (68%) and women (32%), where in men lung cancer is the highest number of cancer (19.4%), and ranks the

fifth most (6%) in women, and the third highest in terms of incidence and mortality rates in both genders. Lung cancer is observed to occur at the age of 20-85 years, with the highest proportion at the age of 40-70 years [2].

Lung cancer is divided into 2 broad categories based on histological features: Small Cell Lung Cancer and Non-Small Cell lung cancer (NSCLC), which account for 15% and 85% of lung cancer cases, respectively. Most of the patients with LCCD are diagnosed at an advanced and inoperable stage (stage IIIB or IV). If left untreated, patients with CPD have a median survival of less than 6 months. The initial standard treatment regimen generally consists of a platinum doublet agent and a taxa. In a study of 1,207 patients with advanced CPD, treatment with one of the 4 doublets yielded similar results in terms of radiological response (19%) and overall survival (OS) [3]. One promising treatment strategy for improving survival in advanced JPIC patients involves targeting the epidermal growth factor receptor (EGFR) [4]. Previous studies have shown a correlation between somatic mutations in the EGFR kinase domain and a strong response in advanced JPIC to EGFR tyrosine kinase inhibitor (TKI). This important study opens a new chapter of targeted therapy and a new treatment paradigm in the management of advanced-stage CPD treatment [5].

There are currently several EGFR-TKIs such as gefitinib, erlotinib, afatinib that are approved worldwide for the treatment of advanced JPICR with positive EGFR mutations. Gefitinib and Erlotinib are oral reversible first-generation EGFR-TKIs. Gefitinib and erlotinib act on the ATP binding site to block EGFR-induced signal activation. While afatinib is an oral second generation EGFR-TKI which is irreversible. Afatinib was developed in response to first generation resistance [6, 7].

Several studies comparing the efficacy of Gefitinib, Erlotinib, and Afatinib on mortality and progression-free survival of pulmonary adenocarcinoma patients have shown conflicting results, for example Fujiwara et al conducted a retrospective study comparing the efficacy of Gefitinib, Erlotinib and Afatinib in JPIC patients in Japan [8] and Garcia-Cuevas et al performed a retrospective study comparing the efficacy of Gefitinib, Erlotinib, and Afatinib in patients with CPD patients in Spain [9].

There are currently few similar studies in Southeast Asian populations likely to have different characteristics of EGFR mutations compared to populations of East Asia, Europe and America [10]. The use of TKI generation 1 (Gefitinib, Erlotinib) and Generation 2 (Afatinib) has become the standard therapy for NSCLC with positive EGFR gene mutations in Dr. Soetomo General Academic Hospital, Surabaya. Meanwhile, second generation migrant workers began to be used in Dr. Soetomo General Academic Hospital, Surabaya since 2017. So this study was conducted to compare the effectiveness of gefitinib, erlotinib, and afatinib in advanced-stage NSCLC patients with EGFR mutations in the Indonesian population representing the Southeast Asian population.

Methods

Participants in this study were pulmonary adenocarcinoma patients with a positive mutation EGFR test and received targeted therapy for generation 1 or generation 2 TKI who met the participant criteria. Participant inclusion criteria included patients with primary adenocarcinoma in the lung diagnosed with advanced CRCSC with positive EGFR mutations [4, 7, 11] in the period 1 January 2017 to 31 December 2019; EGFR mutation test results are positive for the EGFR mutation exon 18 G719X, exon 18 delE790, exon 19 deletion, exon 21 L858R, and exon 21 L861Q; Get EGFR TKI generation 1 or 2 for at least 3 months; and Have a baseline CT Scan and evaluation of CT Scan based on RECIST Criteria at least once. Meanwhile, the participant exclusion criteria included incomplete data.

The design used was a retrospective design in which the data were used in the period 01 January 2017 to 31 December 2019. The number of participants in this study was 102 participants which were obtained by the total sampling method. The researcher first conducted an ethical approval based on the Declaration of Helsinki in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (1617 / KEPK / XI / 2019). Participants were divided into 2 groups, namely the participant group who received the first generation EGFR-TKI therapy (Gefitinib and Erlotinib) and the group who received the

second generation EGFR-TKI (Afatinib).

The research procedure included collecting data on participants who received the first generation EGFR-TKI consisting of Gefitinib 250 mg, Erlotinib 50-150 mg [12], and EGFR-TKI second generation, namely Afatinib 20-40 mg [10]. Furthermore, the data collected included health-related quality of life (HRQOL), body weight, performance status (PS), Response Evaluation Criteria in Solid Tumors (RECIST) of thoracic CT, side effects, and therapeutic efficacy. HRQOL subjects were measured using the EuroQol EQ-5D questionnaire in Indonesian. This questionnaire consists of 5 simple questions, covering physical symptoms and other functional domains [13]. The EQ-5D questionnaire in Indonesian was declared valid and reliable for measuring HRQOL in lung cancer patients with a value of $\alpha > 0.84$ [14]. The subject's body weight was measured using a calibrated weighing scale in Kg. Subject's PS was measured by the World Health Organization (WHO) scale. Meanwhile, thoracic CT scans were interpreted using RECIST 1.1 [11] and the CT-scan used was Hitachi type RH-6G-E31 series number 12G173J (Hitachi-Aloka Medical, Mitaka, Tokyo, Japan). Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) [15]. The therapeutic efficacy given to the participants was evaluated using progression free survival (PFS) and overall survival (OS) values.

Research results are presented in the form of mean ± standard deviation (SD) or median (minimum - maximum) and percentage (%). In addition, research results are also displayed in the form of figures or tables. The statistical analysis used was the independent t test, Mann Whitney test, or Kruskal Wallis test with $p < 0.05$. Statistical analysis used IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Participant Characteristics

The number of the first group was 76 participants (74.5%) and the second group was 26 participants (25.5%). Most of the participants were female 65 (63.7%) in the first group as many as 48 participants (63.2%) and group 2 as many as 17 participants (65.4%). Most of the participants were in the age range 51 - 65 years, in the first group as many as 37 participants (48.7%) and the second group as many as 15 participants (57.7%). Most of the non-smoker participants (67.6%) of which 49 participants (64.5%) in the first group and 20 participants (76.9%) in the second group were non-smokers (Table 1).

Most of the participants had an ECOG score of 1 (54.9%) in the first group as many as 42 participants (55.3%) and in the second group there were 14 participants. The carcinoma tissue sampling method mostly used the fine needle aspiration biopsy (FNAB) technique as many as 70 participants (68.6%), of which 49 participants (64.5%) in the first group and 21 participants (80.8%) in the second group. The samples used for the analysis of anatomic pathology, mostly in the form of lung tissue (74.5%), of which 73.7% from the first group and 76.9% from the second group. The majority of NSCLC types of participants identified adenocarcinoma as much as 99.0% and most of the stage IVA was 63.7% (72.4% in the first group and 38.5% in the second group). The types of mutations obtained were mostly exon 19 deletions as many as 61.8%, which in the first group were 48 participants (63.2%) and the second group were 15 participants (57.7%; table 1).

Therapeutic Response

The large proportion of EQ5D values of participants before and after giving therapy to each group in the fixed category were 56 participants (67.5%), of which 40 participants (60.6%) in the first group and 16 participants (94.1%; $p = 0.806$). A lot of participants' body weight decreased (49.5%), which in the first group were 34 participants (45.9%) and the second group was 15 participants (60.0%; $p = 0.658$). A similar condition was also found in the participant's PS score, where in the first group the score was fixed at 29.4% and the second group was 50.0% ($p = 0.014$). The RECIST value of the most participants after therapy was progressive disease as much as 51.0%, which in the first group was 50% and the second group was 53.8% ($p = 0.338$; table 2).

Side effects

Some of the participants who received EGFR TKI therapy, both gefitinib, erlotinib and afatinib, experienced side effects, including rash, stomatitis,

paronychia, diarrhea, and liver dysfunction. There was a significant difference in side effects of EGFR TKI therapy in group 1 and group 2, especially in stomatitis (p <0.001), paronychia (p <0.001), and diarrhea (p <0.001; table 3).

Progression Free Survival (PFS) and Overall Survival (OS)

The PFS value in the first group was 8.0 (2.0 - 43.0) and the second group was 6.6 (3.0 - 25.0), while the OS score in the first group was 12.5 (5.0 - 39.0) and the second group was 15.0 (4.0 - 28.0). There was no significant difference between the first and second groups in the PFS (p = 0.197) and OS (p = 0.740; table 4).

Table 1. Participant characteristics

Characteristic	EGFR-TKI			Total (n = 102)
	Gefinitib n = 60 (%)	Erlotinib n = 16 (%)	Afatinib n = 26 (%)	
Age				
20 – 35 years	1 (1.7)	1 (6.2)	0 (0.0)	2 (2.0)
36 – 50 years	15 (25.0)	3 (18.8)	9 (34.6)	27 (26.5)
51 – 65 years	28 (46.7)	9 (56.2)	15 (57.7)	52 (51.0)
66 – 80 years	16 (26.6)	3 (18.8)	2 (7.7)	21 (20.5)
Sex				
Male	22 (36.7)	6 (37.5)	9 (34.6)	37 (36.3)
Female	38 (63.3)	10 (62.5)	17 (65.4)	65 (63.7)
Smoking status				
Never smoker	39 (65.0)	10 (62.5)	20 (76.9)	69 (67.6)
Ex-smoker	3 (5.0)	2 (12.5)	3 (11.5)	8 (7.8)
Smoker	17 (28.3)	4 (25.0)	1 (3.9)	22 (21.6)
Passive smoker	1 (1.7)	0 (0.0)	2 (7.7)	3 (3.0)
WHO ECOG				
0	27 (45.0)	3 (18.8)	11 (42.3)	41 (40.2)
1	30 (50.0)	12 (75.0)	14 (53.8)	46 (54.9)
2	2 (3.3)	1 (6.2)	1 (3.9)	4 (3.9)
3	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.0)
Sampling technique				
FOB	6 (10.0)	2 (12.5)	1 (3.9)	9 (8.8)
FNAB	38 (63.3)	11 (68.8)	21 (80.7)	70 (68.6)
Cytology	13 (21.7)	2 (12.5)	2 (7.7)	17 (16.7)
Biopsy	2 (3.3)	0 (0.0)	2 (7.7)	4 (3.9)
FOB & FNAB	0 (0.0)	1 (6.2)	0 (0.0)	1 (1.0)
FNAB & Cytology	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.0)

***Cont.*. Table 1. Participant characteristics**

Samples of anatomic pathology				
Lung parenchym	45 (75.0)	11 (68.8)	20 (76.9)	76 (74.4)
Pleural effusion	13 (21.7)	2 (12.5)	2 (7.7)	17 (16.7)
Cervical lymph nodes	0 (0.0)	1 (6.2)	0 (0.0)	1 (1.0)
Metastases	1 (1.7)	2 (12.5)	4 (15.4)	7 (6.9))
Lung and pleural effusion	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.0)
Types of anatomic pathology				
Adenocarcinoma	60 (100.0)	15 (93.8)	26 (100.0)	101 (99.0)
Adenosquamous	0 (0.0)	1 (6.2)	0 (0.0)	1 (1.0)
Lung cancer stage				
III A	3 (5.0)	0 (0.0)	0 (0.0)	3 (3.0)
III B	3 (5.0)	0 (0.0)	2 (7.7)	5 (4.9)
III C	1 (1.7)	3 (18.8)	0 (0.0)	4 (3.9)
IV A	45 (75.0)	10 (62.5)	10 (38.5)	65 (63.7)
IV B	8 (13.3)	3 (18.8)	14 (53.8)	25 (24.5)
EGFR mutation				
Exon 19 deletion	36 (60.0)	12 (75.0)	15 (57.6)	63 (61.8)
Exon 21 L858R	21 (35.0)	3 (18.8)	8 (30.8)	32 (31.4)
Exon 18	1 (1.7)	1 (6.2)	2 (7.7)	4 (3.9)
Exon T790M	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.0)
Double Mutation	1 (1.7)	0 (0.0)	1 (3.9)	2 (2.0)

Table 2. Differences in treatment response between types of EGFR TKI

Treatment Response	EGFR-TKI			p
	Gefinitib	Erlotinib	Afatinib	
PS Score (n = 102)				
Decrease	24 (40.0)	5 (31.3)	2 (7.7)	
Constant	21 (35.0)	9 (56.2)	13 (50.0)	0.014*
Increase	15 (25.0)	2 (12.5)	11 (42.3)	
Body weight (n = 99)				
Decrease	28 (47.5)	6 (40.0)	15 (60.0)	
Constant	10 (16.9)	2 (13.3)	0 (0.0)	0.658
Increase	21 (35.6)	7 (46.7)	10 (40.0)	
EQ5D (n = 83)				
Decrease	12 (22.6)	1 (7.7)	1 (5.9)	
Constant	30 (56.6)	10 (76.9)	16 (94.1)	0.806
Increase	11 (20.8)	2 (15.4)	0 (0.0)	

Cont... **Table 2. Differences in treatment response between types of EGFR TKI**

Last Complaint (n = 101)				
No complaints	5 (8.5)	1 (6.3)	5 (19.2)	
Dyspnea	16 (27.1)	4 (25.0)	3 (11.5)	
Hemoptysis	5 (8.5)	0 (0.0)	1 (3.8)	
Chest pain	15 (25.4)	3 (18.8)	5 (11.5)	
Chronic Cough	4 (6.8)	4 (25.0)	3 (11.5)	
Weight loss	0 (0.0)	2 (12.5)	0 (0.0)	
Headache	5 (8.5)	0 (0.0)	2 (7.7)	0.248
Seizures	1 (1.7)	0 (0.0)	0 (0.0)	
Hemiparese	2 (3.4)	0 (0.0)	0 (0.0)	
Bone pain	2 (3.4)	2 (12.5)	3 (11.5)	
Weak	2 (3.4)	0 (0.0)	2 (7.7)	
It's hard to stand	1 (1.7)	0 (0.0)	1 (3.8)	
Chest pain, chronic cough	0 (0.0)	0 (0.0)	1 (3.8)	
Chronic cough, weight loss	1 (1.7)	0 (0.0)	0 (0.0)	
RECIST (n = 102)				
Progressive Disease	32 (53.3)	6 (37.5%)	14 (53.8)	
Stable Disease	21 (35.0)	7 (43.8%)	12 (46.2)	0.338
Partial Response	7 (11.7)	3 (18.8%)	0 (0.0)	

Table 3. The difference in side effects between types of EGFR TKI

Treatment Response	EGFR-TKI			p
	Gefinitib	Erlotinib	Afatinib	
Skin Rash				
Stage 0	7 (11.7)	1 (6.3)	6 (23.1)	
Stage 1	47 (78.3)	13 (81.3)	19 (73.1)	0.169
Stage 2	6 (10.0)	2 (12.5)	1 (3.8)	
Stomatitis				
Stage 0	56 (93.3)	13 (81.3)	10 (38.5)	
Stage 1	4 (6.7)	3 (18.8)	15 (57.7)	< 0.001
Stage 2	0 (0.0)	0 (0.0)	1 (3.8)	
Paronychia				
Stage 0	54 (90.0)	12 (75.0)	13 (50.0)	
Stage 1	5 (8.3)	4 (25.0)	10 (38.5)	< 0.001
Stage 2	1 (1.7)	0 (0.0)	3 (11.5)	
Diarrhea				
Stage 0	39 (68.4)	11 (68.8)	5 (19.2)	
Stage 1	17 (29.8)	5 (31.3)	16 (61.5)	< 0.001
Stage 2	1 (1.8)	0 (0.0)	4 (15.4)	
Stage 3	0 (0.0)	0 (0.0)	1 (3.8)	
Liver Dysfunction				
Stage 0	60 (100.0)	16 (100.0)	25 (96.2)	0.412
Stage 1	0 (0.0)	0 (0.0)	1 (3.8)	

Table 4. The difference between PFS and OS between Generation 1 and Generation 2 TKI

EGFR TKI	Median (min – maks)	p
PFS Generation 1 (n = 61) Generation 2 (n = 20)	 8.0 (2.0 – 43.0) 6.6 (3.0 – 25.0)	0.197
OS Generation 1 (n = 60) Generation 2 (n = 14)	 12.5 (5.0 – 39.0) 15.0 (4.0 – 28.0)	0.740

Discussion

Most of the KPKBSK cases with EGFR mutations were women who were not smokers [8, 16]. In addition, the risk of developing lung cancer increases with age although it does not rule out that it can occur at a young age, after being over the age of 40 the risk of suffering from lung cancer increases every year [17]. Adenocarcinoma is a type of lung cancer that is most found in the Asian region where most of it is diagnosed at stage IV [2, 8, 16]. Based on previous studies, it was found that exon 19 mutations were the most mutations in Asia followed by exon 21 L858R in the second position [2]. As many as 80% of mutations in lung cancer involve exon 19 which is often found around the catalytic site of the receptor and exon 21 L858R which is in the tyrosine kinase activation loop [18]. The diagnosis of adenocarcinoma was based on the results of hispatological examination using the FNAB method in which adenocarcinoma often grows in peripheral areas [19].

HRQOL assessments, including patient-reported outcome (PRO), include a major secondary end-point in many NSCLC-related studies [13, 20] in addition to response rate and survival. This assessment represents an overall evaluation of the patient's health and quality of life and reflects a subjective response to therapy. In this study, the Indonesian language EuroQol EQ-5D was used and the EuroQol EQ-5D questionnaire was the most widely used and available in various languages. Most of the patients in both groups showed a stable EQ-5D score so that there was no difference in HRQOL between the two groups. These conditions may be influenced by several factors such as work, education, marital status, and other comorbid diseases [21, 22]. Based on previous studies by Yang et al, it was found that the Quality of Life (QoL) score using the EQ5D score and the WHO QoL - Brief questionnaires in patients who received Afatinib therapy was lower than in the Gefitinib group but not significantly different in the Gefitinib group compared with the Erlotinib group. The reason why the QoL score for afatinib was lower than for gefitinib about 10 months after treatment remains unclear [21].

In a meta-analysis study by Yang et al found Gefitinib to be generally preferred over the other two agents, given its safety profile as the first-line treatment of patients with JPIC with EGFR mutation positive [23]. Likewise, in Krawczyk et al's study, there was a slight increase in PFS in the afatinib group (18 months) compared to two reversible EGFR-TKI (10 months) although this was not statistically significant (HR = 1.243; 95% CI, 0.648–2,382. ; P = 0.533). However, due to the small sample size (n = 16) of the afatinib-treated group, we cannot make definite conclusions about the differences observed in PFS [16]. In a retrospective study by Fujiwara et al demonstrated the comparable clinical efficacy of gefitinib, erlotinib, and afatinib in Japanese patients with NSCLC [8].

Conclusion

The most common type of lung cancer today is adenocarcinoma which affects women and nonsmokers in Asian populations. There were no significant differences in changes in EQ5D scores, changes in body weight, PS, RECIST, side effects, and therapeutic efficacy in patients receiving first and second-generation TKI EGFR therapy.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical approval: We conducted an ethical approval based on the Declaration of Helsinki at Dr. Soetomo General Academic Hospital Surabaya, Indonesia (1617 / KEPK / XI / 2019).

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