Comparison between the Originator and Me-too Drugs of First-Generation EGFR-TKI in EGFR-Mutant NSCLC Patients: A Retrospective Cohort Study

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Abstract

Introduction: Epidermal Growth Factor Receptor (EGFR) mutation is a crucial biomarker in selecting appropriate therapies for NSCLC patients. Gefitinib, a first-generation EGFR-TKI, is commonly used as initial treatment for EGFR-mutant NSCLC at Dr. Soetomo General Hospital. Gefitinib is available in two variants: Iressa (originator) and Gefitero (me-too drug).

Methods: This analytic observational study was conducted in January 2017 - January 2022, involving NSCLC patients with positive EGFR mutations who received Gefitinib as first-line treatment at Dr. Soetomo General Hospital. Adverse effects, semisubjective responses, objective responses, and PFS were compared among two Gefitinib therapy groups (Iressa, Gefitero) using Fisher's exact test and Mann-Whitney's test.

Results: A total of 65 subjects are characterized by mean age 59,7 years old, with the majority encompassing male subjects (52,3%), with stage IV disease (95,4%), and exon 19 mutation (60,0%). Iressa was the most frequently administered drug (89,2%), followed by Gefitero (10,8%). Skin toxicity was the primary adverse effect across all Gefitinib therapies (50,8%), while weight loss was more prevalent within the Iressa group (48,3%). Stable Disease (SD) was the most frequently reported response therapy (66,2%). The Iressa group had a longer median PFS compared to Gefitero (6 vs 4 months). However, there were no significant differences regarding side effects, weight changes, response therapy, and PFS between the different Gefitinib therapies.

Conclusion: There were no significant differences of therapy responses between the first generation of EGFR TKI originator and their me-too drug.

Keywords: EGFR TKI; gefitinib; me-too drug; NSCLC

1. Introduction

Lung cancer can be classified into two types, namely small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC is the more commonly encountered type of lung cancer, with a frequency of approximately 80-85%, while SCLC accounts for 10-15% [1]. In the case of NSCLC, a driver mutation plays a pivotal role in disease development and can serve as a target for therapy. The most frequently observed driver mutation is EGFR, which stands for epidermal growth factor receptor [2].

Available modalities for managing NSCLC include surgery, radiation, chemotherapy, and targeted therapy. Surgery is the primary treatment for most NSCLC cases, especially stages I-II and resectable stage IIIA after

neoadjuvant chemotherapy. The preferred option is lobectomy, yielding the highest survival rates. Definitive curative radiotherapy can be administered for medically inoperable early-stage (stage I) NSCLC. Chemotherapy can serve as neoadjuvant therapy for early stages or as adjuvant therapy post-surgery. Adjuvant therapy is applicable for stages IIA, IIB, and IIIA NSCLC. Targeted therapy is indicated for patients with stage IV NSCLC and positive EGFR mutations, responsive to EGFR TKIs [3].

Gefitinib is one of the EGFR TKIs administered to NSCLC patients with EGFR mutations. Iressa is the original gefitinib produced by PT AstraZeneca [4]. An originator is the first drug in a drug class to receive regulatory approval [5]. Meanwhile, me-too drugs can be defined as drugs similar to the originator but with differences such as efficacy and safety[5]. Gefitero serves as an example of a gefitinib me-too drug by PT Amarox Pharma Global [6]. Generally, originator drugs tend to be more expensive as companies invest significantly in new drug development, including clinical trials, marketing, and promotion [7]. In contrast, me-too drugs are not required to demonstrate efficacy and safety through clinical trials, as those have already been conducted for the originator drug. Consequently, me-too drugs are priced lower [7]. The transition from Iressa to Gefitero in its availability through healthcare facilities under BPJS is influenced by these pricing differences. Therefore, conducting an analysis of the efficacy and safety differences between the EGFR TKI me-too drug and its originator in NSCLC patients with EGFR mutations is crucial.

2. Methods

This study is an analytical research with a retrospective cohort study design using secondary data from patient medical records. The study sample consists of NSCLC patients with positive EGFR mutations who received first-generation originator EGFR-TKI and me-too drug at Dr. Soetomo General Hospital from January 2017 to January 2022. Inclusion criteria involve patients diagnosed with NSCLC with EGFR mutations, treated at Dr. Soetomo General Hospital, and receiving first-generation originator and me-too EGFR TKI therapy within the period of January 2017 to January 2022. The sample was obtained through total sampling technique, yielding 65 eligible patients. Data required for this study include the usage of first-generation EGFR TKIs, side effects, semi-subjective response, objective response, and patient progression-free survival. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software, and significance was set at $p<0.05$. Normality was assessed using the Shapiro-Wilk test. Data were considered normally distributed if the Shapiro-Wilk test yielded a p-value > 0.05. Fisher's exact test and Kruskal-Wallis test were used for group comparisons. Additionally, post hoc Mann-Whitney tests and descriptive analysis were performed.

The operational definitions of the research variables in this study consist of first-generation originator and me-too EGFR TKIs, age, gender, lung cancer stage, mutation type, side effects, semi-subjective response, objective response, and progression-free survival (PFS). The first-generation originator and me-too EGFR TKIs are Iressa and Gefitero, measured at the beginning of drug usage. Patient age with NSCLC is assessed from medical records in years. Patient gender refers to the gender assigned at birth and is recorded in medical records. Lung cancer stage is determined based on NSCLC staging according to the 8th edition of the IASLC TNM system, as documented in medical records. Patient mutation type is documented in medical records. Side effects encompass undesired effects resulting from the administration of first-generation originator and me-too EGFR TKIs, including skin toxicity, diarrhea, paronychia, and mucositis. The semi-subjective response in this study is the change in weight measured after 3 months of drug usage. Objective response is determined using RECIST criteria measured after 3 months of drug usage, yielding results of Complete Response (CR), Partial Response (PR), Progressive Disease (PD), and Stable Disease (SD). Progression-Free Survival (PFS) is the duration from the initial date of receiving Iressa or Gefitero until the earliest indication of disease progression, including death due to any cause, weight loss, or treatment discontinuation, measured in months. The study protocol has been

approved by the Health Research Ethics Committee of Dr. Soetomo General Hospital with reference number 1048/LOE/301.4.2/IX/2022.

3. Results

This study obtained data from a total of 65 patients who received either Iressa or Gefitero at Dr. Soetomo General Hospital from January 2017 to January 2022. One patient was excluded due to incomplete medical record data, resulting in a final sample of 65 patients who met the inclusion criteria and were included in the study (Table 1).

3.1. Baseline Characteristics

Table 1. Characteristics of the study participants (N=65)

Characteristics	n (%)
Age – years	
Mean±SD	59,7±9,07
Sex	
Male	34 (52,3%)
Female	31 (47,7%)
Lung cancer stage	
III	3 (4,6%)
IV	62 (95,4%)
EGFR mutation	
Exon 18	2 (3,1%)
Exon 19	39 (60,0%)
Exon 21	23 (35,4%)
Exon 18 and exon 21	1 (1,5%)
EGFR TKI	
Iressa	58 (89,2%)
Gefitero	7 (10,8%)

The mean age of the study subjects was 59.7 years with a standard deviation of 9.07. Based on gender, there were 34 male patients (52.3%), outnumbering females. The most commonly encountered lung cancer stage was stage IV, comprising 62 patients (95.4%). The predominant EGFR mutation profile in this study was exon 19 deletion mutation in 39 patients (60.0%), followed by exon 21 mutation in 23 patients (35.4%). The majority of patients used Iressa, totaling 58 individuals (89.2%), while Gefitero was used by 7 patients (10.8%).

3.2. Side Effects

Table 2. Side effects of EGFR TKI originator (Iressa) and me-too drug (Gefitero)

Side Effects	Iressa	Gefitero	p-value
Skin toxicity	32 (49.2%)	1 (1.5%)	0.054
Diarrhea	17 (26.2%)	3 (4.6%)	0.667
Oral mucositis	6 (9.2%)	1 (1.5%)	0.568
Paronychia	5 (7.7%)	0 (0%)	1.00

Based on Table 2, the skin toxicity side effect yielded a significance value of p=0.054 (p>0.05). This result indicates the absence of a significant difference between the first-generation originator EGFR TKI drug and the me-too drug concerning skin toxicity. Similarly, the diarrhea side effect demonstrated a significance value of p=0.667 (p>0.05), suggesting no significant difference between the first-generation originator EGFR TKI drug and the me-too drug in relation to diarrhea. The significance value for oral mucositis, at p=0.568 (p>0.05), signifies the lack of a significant difference between the first-generation originator EGFR TKI drug and the me-too drug regarding oral mucositis. Lastly, the significance value for paronychia was determined to be p=1.00 (p>0.05), indicating no significant difference between the first-generation originator EGFR TKI drug and the me-too drug concerning paronychia.

3.3. Subjective Therapy Response

Table 3. Subjective therapy response of EGFR TKI originator (Iressa) and me-too drug (Gefitero)

Weight Changes	Iressa	Gefitero	p-value
Weight loss	28 (48.3%)	2 (28.6%)	
Weight unaffected	25 (43.1%)	2 (28.6%)	0.058
Weight gain	5 (8.6%)	3 (42.9%)	

Based on Table 3, following the Chi-Square test, a significance value of p=0.058 (p>0.05) was obtained. This result indicates the absence of a significant difference between the first-generation originator EGFR TKI drug and the me-too drug concerning weight change.

3.4. Objective Therapy Response

Table 4. Objective therapy response of EGFR TKI originator (Iressa) and me-too drug (Gefitero)

Therapy Response	Total	Iressa	Gefitero	p-value
RECIST outcome				
Complete Response (CR)	1 (1.5%)	1 (1.7%)	0 (0%)	
Partial Response (PR)	7 (10.8%)	6 (10.3%)	1 (14.3%)	0.616
Stable Disease (SD)	43 (66.2%)	39 (67.2%)	4 (57.1%)	
Progressive Disease (PD)	14 (21.5%)	12 (20.7%)	2 (28.6%)	
Objective Response Rate (CR + PR)	8 (12.3%)	7 (12.1%)	1 (14.3%)	1.00
Disease Control Rate (CR + PR + SD)	51 (78.5%)	46 (79.3%)	5 (71.4%)	0.638

Based on Table 4, subsequent to conducting the Fisher Exact Test, a significance value of p=0.616 (p>0.05) was obtained. This result signifies the absence of a significant difference between the first-generation originator EGFR TKI drug and the me-too drug concerning treatment response. Despite achieving a higher Objective Response Rate in the Gefitero group compared to Iressa (14.3% vs. 12.1% respectively), this

difference is not statistically significant (p=1.00). The Disease Control Rate in the Iressa group is higher than in the Gefitero group (79.3% vs. 71.4% respectively); however, this difference is not significant.

3.5. Progression Free Survival

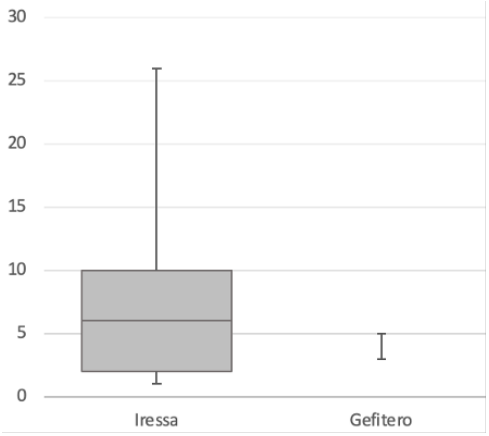

Fig. 1. Comparison between EGFR TKI originator (Iressa) and me-too drug based on progression-free survival

Patients using Iressa exhibited a median Progression-Free Survival (PFS) of 6 months, while the 7 patients using Gefitero had a median PFS of 4 months. The data from both groups were not normally distributed. Subsequently, a Mann Whitney test was performed, yielding a significance value of p>0.05, indicating no significant difference between the first-generation originator EGFR TKI drug and the me-too drug concerning Progression-Free Survival (PFS). Additionally, there was no disparity in the survival curves between the two treatment groups (log rank p=0.7076).

4. Discussion

In this study, the average age of subjects was 59.7 years with a standard deviation of 9.07. The IPASS study revealed a median subject age of 57 years with an age range of 24 to 84 years [8]. Among the subjects in this study, there were more male participants, totaling 34 individuals (52.3%). In contrast, the NEJ009 study indicated a higher proportion of female subjects at 62.8% [8]. In this study, the most common stage of lung cancer found was stage IV, comprising 62 individuals (95.4%). Stage IV also constituted the majority in the IPASS and NEJ009 studies, at 69.6% and 79.7% respectively [8,9]. In this study, the predominant type of EGFR mutation was exon 19 deletion, observed in 39 individuals (60.0%), followed by exon 21 mutation in 23 individuals (35.4%). A study conducted in Japan identified exon 19 deletion as the most common mutation, accounting for 55.2%, while L858R mutation accounted for 39% [8].

In this study, skin toxicity is one of the most frequently observed side effects in both the Iressa group (55.2%) and the Gefitero group (14.3%). This finding aligns with the IPASS study, where rash was the most common side effect associated with gefitinib use, accounting for 66.2%. Rash induced by gefitinib in lung adenocarcinoma patients can serve as a significant predictive factor for objective response and prognosis [10]. Similarly, in the study by Guan et al., the occurrence of rash due to gefitinib predicted a better progression-free survival (PFS) in EGFR-mutant non-small cell lung cancer patients. However, the degree of rash severity was not linked to improved PFS compared to milder rash severity [11].

Diarrhea is one of the most commonly encountered side effects in both the Iressa group (29.3%) and the Gefitero group (42.9%) in this study. In the IPASS study, a diarrhea side effect was observed in 46.6% of the gefitinib group [8]. A study demonstrated that the ABCG2-15622C/T polymorphism and ABCG2 haplotypes are associated with moderate-to-severe diarrhea in patients receiving gefitinib, indicating susceptibility among certain groups to manifest the drug's toxic effects [12]. EGFR TKIs should be discontinued if diarrhea persists for >48 hours, even with maximum daily loperamide dosing, or at grade 3-4 severity. Re-initiation of EGFR TKIs is only permissible when toxicity levels ≤1.

In this study, oral mucositis was found in 10.3% of the Iressa group and 14.3% of the Gefitero group. A study indicates that the incidence of mucositis with gefitinib administration ranges from 6-17% for all grades and <1% for grade ³3 [13]. In its management, patients with grade 1 mucositis can generally continue EGFR TKI treatment with the same dosage. Patients with grade 2 mucositis may suspend treatment if necessary and are recommended to reduce the dosage. Patients with grade 3 mucositis should discontinue treatment and typically require supportive care. Patients with grade 4 mucositis require evaluation by a dermatology specialist [14].

Paronychia side effects were identified in 5 patients using Iressa in this study. This condition, defined as inflammation in the periungual nail fold, has been widely associated with EGFR TKI drug use. A significant difference in paronychia incidence was found among patient groups receiving different types of EGFR TKIs, with lower incidence observed in the gefitinib recipient group compared to the afatinib or erlotinib groups (9.8% vs. 39.8% vs. 12.8% respectively; $p<0.001$) [15]. A significant difference in paronychia incidence was also noted among patient groups receiving different types of EGFR TKIs, with lower incidence found in the gefitinib recipient group compared to the afatinib or erlotinib groups (9.8% vs. 39.8% vs. 12.8% respectively; $p<0.001$) [15].

A study indicated that the administration of gefitinib can lead to Interstitial Lung Disease (ILD) as a life-threatening side effect [16,17]. Research conducted on the Japanese population revealed an ILD incidence of 5.8% and an ILD-related mortality of 2.3% with gefitinib administration [18]. ILD commonly associated with gefitinib use includes pneumonitis and fatal pneumonitis [18]. However, no significant difference was found between the first-generation originator EGFR-TKI drug and the me-too drug in terms of these side effects. This was also demonstrated by another study, which showed that two biosimilar compounds of gefitinib, namely Iressa and Iretinib, did not result in significant differences in side effects among patients [19].

In the Iressa group, the most common observation was weight loss, whereas in the Gefitero group, weight gain was the most prevalent. Nevertheless, no significant difference was found between the first-generation originator EGFR TKI drug and the me-too drug concerning changes in weight. Among EGFR-mutant non-small cell lung cancer patients, those with weight loss exhibited shorter progression-free survival (PFS) compared to those without weight loss [20]. Furthermore, additional evidence suggests that weight loss increases the likelihood of patients manifesting progressive disease tendencies [21].

Objective response in this study was measured after 3 months of drug use using the Response Evaluation Criteria for Solid Tumors (RECIST), which categorizes CT scan results into four response types: Complete Response (CR), Partial Response (PR), Progressive Disease (PD), and Stable Disease (SD). In the Iressa group, 1 patient (1.7%) achieved CR, 6 patients (10.3%) achieved PR, 39 patients (67.2%) had SD, and 12 patients (20.7%) had PD. In the Gefitero group, 1 patient (14.3%) achieved PR, 4 patients (57.1%) had SD, and 2 patients (28.6%) had PD. In this study, no significant difference was found between the first-generation originator EGFR TKI drug and the me-too drug in terms of treatment response based on RECIST. The WJOG5108L study showed different results, with PR being the most frequent treatment response (49.5%),

followed by SD (24.2%), PD (21.5%), and CR (0.5%) [22]). Although the Gefitero's overall Objective Response Rate (ORR) was higher than Iressa's in this study, the difference was not statistically significant. The overall ORR for the gefitinib group in this study was 12.3%. The IPASS study found that the ORR in the EGFR mutation-positive group receiving gefitinib was higher compared to the carboplatin-paclitaxel group, with rates of 43.3% vs. 32.2% respectively [8].

Progression-free survival (PFS) in this research refers to the duration from the initial date of starting Iressa or Gefitero until the earliest sign of disease progression, which could be death due to any cause, weight loss, or treatment discontinuation. In this study, no difference was observed between the first-generation originator EGFR TKI drug and the me-too drug concerning PFS. Patients receiving Iressa exhibited a better PFS compared to Gefitero. Iressa patients demonstrated a higher median PFS than Gefitero patients (6 months vs. 4 months, respectively). These figures are relatively lower compared to the IPASS and WJTOG3405 studies, which reported median PFS from gefitinib use at 9.5 and 9.2 months, respectively [8,23]. A study on the East Asian population indicated that EGFR mutation-positive patients receiving gefitinib had longer PFS than those receiving carboplatin-paclitaxel, and age was the only clinical factor influencing PFS outcomes [8].

Limitations in this study include the extensive variation in medical record keeping, which hindered effective data extraction, a relatively small sample size that couldn't fully represent the true variability within the population, and the use of weight measurement instruments that were inaccurately and inconsistently calibrated.

5. Conclusion

There were no significant differences observed in terms of side effects, changes in weight, treatment response according to RECIST criteria, or progression-free survival (PFS) between the first-generation originator EGFR TKI drug Iressa and the me-too drug Gefitero.

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Appendix A. Lung cancer stage classification

Classification of lung cancer staging based on the tumor, node, metastasis classification of American Cancer Society.

Table A.1 Lung cancer stage classification

Stage AJCC	Stage classification		
	T	N	M
Occult cancer	Tx	N0	M0
0	Tis	N0	M0
IA1	T1mi/T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a/T1b/T1c/T2a/T2b	N1	M0
	T3	N0	M0
IIIA	T2a/T2b	N2	M0
	T3	N1	M0
	T4	N0/N1	M0
IIIB	T1a/T1b/T1c/T2a/T2b	N3	M0
	T3/T4	N2	M0
IIIC	T3/T4	N3	M0
IVA	All T	All N	M1a/M1b
IVB	All T	All N	M1c