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Original Article

Efficacy of gefitinib versus erlotinib as first-line treatment in EGFR mutant advanced lung adenocarcinoma at RSP. Dr. H. A. Rotinsulu

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Abstract

Background: Gefitinib and erlotinib are superior to chemotherapy in adenocarcinoma with epidermal growth factor receptor (EGFR) mutation patients. Both drugs can be accessed as first-line therapies. However, the determination of the choice of gefitinib or erlotinib is not yet clear.
Aim: To compare the progression-free survival (PFS), overall survival (OS) and time on treatment (TOT) of adenocarcinoma with epidermal growth factor receptor (EGFR) mutation patients who receiving first-line gefitinib versus erlotinib.
Methods: This is a retrospective study used medical record of patients who were treated with first-line gefitinib 250 mg once daily versus erlotinib 150 mg once daily at Dr. H.A. Rotinsulu Lung Hospital from 1st January 2019 to 31th December 2021.
Results: There are 103 patients (74,1%) who received gefitinib and 36 patients (25,9%) who received erlotinib as first-line treatment. Median PFS in gefitinib and erlotinib group was 26 months and 17 months (P=0,184), respectively. Median overall survival time of the gefitinib group was the 46,78 months but in erlotinib group cannot be analysed. Median time-of-treatment was 12 months in gefitinib group and 11 months in erlotinib group (P=0,172). The incidence rate ratio in the TKI group did not show a causal relationship with death due to IRR values of 0,74 and 95% CI IRR of 0,21;3,24. Based on univariate analysis, gender affects PFS (HR1,7;CI95%;1,0-3,4;P=0,049) and TOT (HR1,6;CI95%;1,1-2,6;P=0,020). The data also showed that age affects TOT (HR1,5;CI95%;1,0-2,4;P=0,037).
Conclusion: There was no difference in efficacy between gefitinib and erlotinib in the treatment of pulmonary adenocarcinoma patients with EGFR gene mutations at Dr. H.A. Rotinsulu Lung Hospital.

***Keyword**: EGFR mutations, erlotinib, gefitinib, non-small cell lung cancer.*

Abstrak

Latar belakang: Gefitinib and erlotinib lebih superior dibandingkan kemoterapi pada pasien adenokarsinoma dengan mutasi EGFR. Kedua obat tersebut dapat diberikan sebagai terapi lini pertama, namun dasar penentuan pilihan antara gefitinib atau erlotinib masih belum jelas.
Tujuan: Penelitian ini bertujuan untuk membandingkan *progression-free survival* (PFS), *overall survival* (OS) and *time on treatment* (TOT) antara pasien adenokarsinoma dengan mutasi EGFR yang memperoleh terapi lini-pertama gefitinib dengan yang memperoleh terapi lini pertama erlotinib.
Metode: Penelitian ini merupakan studi retrospektif berdasarkan data rekam medis pasien yang memperoleh gefitinib lini pertama 250 mg sekali sehari dan erlotinib lini pertama 150 mg sekali sehari di Rumah Sakit Paru Dr. H.A. Rotinsulu dari 1 Januari 2019 hingga 31 Desember 2021.
Hasil: Terdapat 103 pasien (74,1%) yang mendapatkan gefitinib dan 36 pasien (25,9%) yang mendapatkan erlotinib sebagai terapi lini pertama. Median PFS pada kelompok gefitinib adalah 26 bulan, sedangkan pada kelompok erlotinib adalah 17 bulan (P=0,184). Median OS pada kelompok gefitinib yaitu 46,78 bulan, namun yang di kelompok erlotinib tidak dapat dianalisis. Median TOT yaitu 12 bulan di kelompok gefitinib, dan 11 bulan di kelompok erlotinib (P=0,172). Rasio rerata insidens pada kelompok TKI tidak menunjukkan hubungan sebab akibat dengan kematian berdasarkan nilai IRR 0,74 dan 95% CI IRR 0,21;3,24. Berdasarkan analisis univariat, jenis kelamin memengaruhi PFS (HR1,7;CI95%;1,0-3,4;P=0,049) dan TOT (HR1,6;CI95%;1,1-2,6;P=0,020). Data juga menunjukkan bahwa usia memengaruhi TOT (HR1,5;CI95%;1,0-2,4;P=0,037).
Kesimpulan: Tidak terdapat perbedaan efikasi yang bermakna antara gefitinib dan erlotinib dalam tata laksana pasien adenokarsinoma paru dengan mutase EGFR di Rumah Sakit Paru Dr. H.A. Rotinsulu.

***Kata kunci**: erlotinib, gefitinib, mutasi EGFR, non-small cell lung cancer.*

Introduction

Cancer is the leading cause of death in the world.[1] Data from WHO in 2020 showed that there were 19.29 million new cases and 9.95 million deaths from cancer. The five most diagnosed cancer areas in 2020 in all sexes were breast (11.7%), pulmonary (11.4%), colorectal (10%), prostate (7.3%), stomach (5.6%).[1]

Among malignant diseases, primary lung cancer is the leading cause of death in the world. Every year there are more than 2.2 million cases of lung cancer in the world that cause the death of more than 1.7 million people. In 2020, the disease is estimated to be deadly around 1.1 million in Asia. Data from Asia landmark 2020, lung cancer caused the deaths of 109,250 people.[1]

Lung cancer is the most common type of cancer in men in Indonesia, and the fifth most common type of cancer in women. Lung cancer is also the leading cause of cancer death in men and second in women.[1] Bukittinggi's consensus in 2005 stipulated that EGFR-TKI could be given as a first-line treatment if patients for various reasons could not or refused chemotherapy.[1] From various research results consensus 19 could no longer be used because the EFGR mutation examination technique had been carried out in Indonesia. And efficacy is influenced from the location of the mutation that occurs.[3.4]

Studies in East Asian populations on erlotinib or gefitinib administration gave good results in cases with positive EGFR gene mutations in exon 19 and 21.[5,6] However, there was no significant difference in the efficacy of erlotinib with gefitinib in patients with EGFR gene mutations.[6] Given the importance of efficacy data on drugs that work as inhibitors on epidermal growth factor inhibitor receptors (EGFR-TKI) in this case the difference in the efficacy of gefitinib with erlotinib in the treatment of pulmonary adenocarcinoma patients with EGFR gene mutations at dr. H. A. Rotinsulu Lung Hospital.

With the access of TKI for lung cancer with EGFR mutation as a first-line therapy for generation 1 and 2 migrant workers. However, the determination of the choice of the 1st generation TKI, gefitinib or erlotinib, is not yet clear. Whether there are differences in the efficacy of gefitinib with erlotinib in the treatment of pulmonary Adenocarcinoma patients with EGFR gene mutations at DR. H. A Rotinsulu Lung Hospital and influencing factors such as patient characteristics and types of mutations.

Material and Methods

The design of this study is descriptive analytic. Secondary data are taken from medical records with retrospective cohort designs. The research site at the poly oncology of Dr. H.A. Rotinsulu Lung Hospital and the research time is from October 1, 2021 to March 31, 2022. The study samples were taken through existing medical record data from all pulmonary Adenocarcinoma patients with EGFR gene mutation of Dr. H. A. Rotinsulu Lung Hospital who received gefitinib or erlotinib treatment as a first line from January 1st, 2019 to December 31th, 2021. Inclusion Criteria: Patients with KPKBSK diagnosis based on cytopathological and histopathological examinations; mutational EGFR test results (+) on exón 19, 21; using TKI > 2 months; have never received other therapies (surgery, radiotherapy, chemotherapy). Exclusion Criteria: Double Primary Cancer Patients.

Results

Research has been conducted at the Dr. H.A. Rotinsulu Lung Hospital on 258 patients with pulmonary adenocarcinoma patients with EGFR gene mutations who received gefitinib or erlotinib treatment as the first line from January 1st, 2019 to December 31th, 2021, and 139 met the inclusion and exclusion criteria. Sample Collection was carried out in a retrospective cohort. Secondary data was taken from medical records.

The characteristics of the study subjects are broadly summarized in table 1. Includes age, gender, smoking status, stage, EGFR mutations and their types, and Performance Status. The characteristic distribution has proportions that do not differ significantly in the groups of erlotinib and gefitinib, except for smoking characteristics. The proportion of those who used gefitinib was greater in the non-smoking group than in the group that smoked. A total of 139 subjects took part in this study.

Table 1. Characteristics of adenocarcinoma patients who received gefitinib and erlotinib therapy.

Characteristic	*Tyrosine Kinase Inhibitor*		*p-Value*
	Gefitinib (n=103)	*Erlotinib (n=36)*	
Age			
Median (Range)	59 (34-80)	61(39-81)	0.362
≥60 years	51 (49.6)	21 (58.3)	
<60 years	52 (50.4)	15 (41.6)	
Sex			0.219
Male	45 (43.6)	20 (55.5)	
Female	58 (56.4)	16 (44.5)	
Smoking (N=110)			0.03
Yes	17 (16.5)	14 (38.9)	
No	60 (83.5)	19 (61.1)	
Staging			0.361
Stage IIIA and IIIB	16 (15.5)	8 (22.2)	
Stage IVA and IVB	87 (84.5)	28 (77.8)	
Mutation Type of EGFR			0.93
Single	78 (75.7)	27 (0.75)	
Multiple	25 (24.3)	9 (0.25)	
EGFR Mutation			0.042
Exon 19, del	55 (53. 3)	12 (33.3)	
Exon 21; L858R	22 (21.3)	15 (44.7)	
Lain-lain	26 (25.2)	9 (25.0)	
Performance Status			0.997
<2	83 (80.5)	29 (80.5)	
≥2	20 (19.5)	7 (19.5)	

For EGFR mutation type, there are two largest types of mutations found in the subject group, including Exon 19 del and Exon L858R. The types of mutations found in this study are presented in **Image 1**.

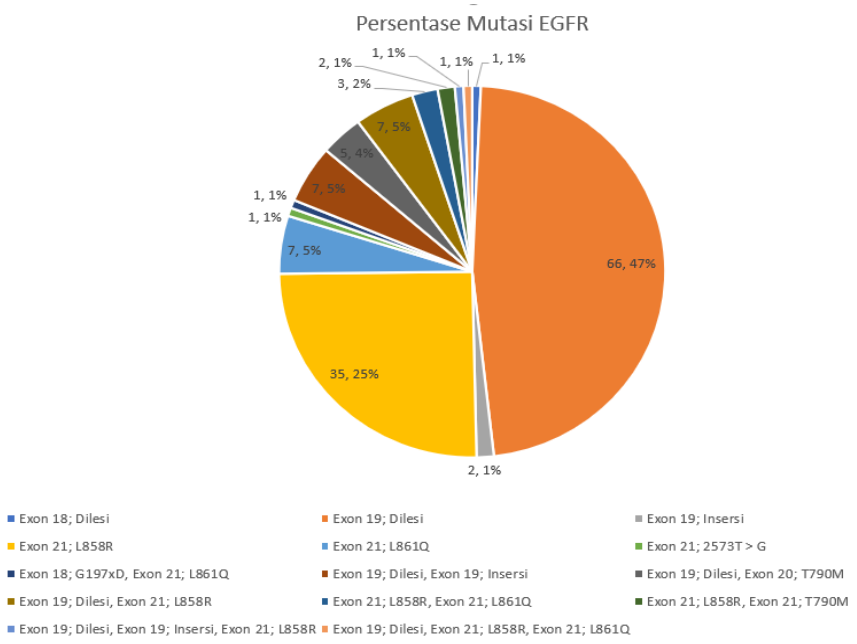

Image 1. Diagram for Type EGFR Mutation

Progression Free Survival

The median PFS group gefitinib 26 months, the erlotinib group 17 months with log rang test p> 0.5.

The PFS for both groups at 1 year, 2 years, and 3 years respectively were (80% vs 87%), (53% vs 0%), dan (19% vs 0%), p=0,184.

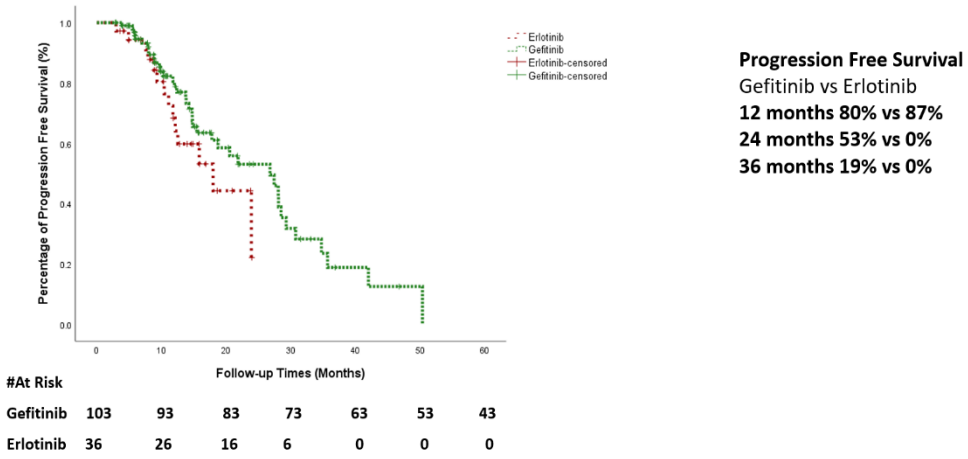

Image 2. Graph of Kaplan-Meier PFS for Gefitinib and Erlotinib

Table 2. Effect Hazard Ratio (HR) of Each Characteristic on PFS

Variable	HR	P (z)	95% CI	
Age	1.6	0.076	0.9	2,8
Sex	1,7	**0.049**	1,0	3.0
Mutase	1,4	0.287	0.7	2,5
TNM	1,5	0,169	0.8	3,0
PS	0,8	0.687	0.4	1,7
TKI	1.5	0.188	0.8	2.9

All characteristic variables with significant values of P (z) > 0.05, except for the sex variable HR 1.7 CI95% 1.0-3.0 p=0.049, which confirmed multivariate analysis of HR 1.9 CI95% 1.0-3.4, p=0.033.

Overall Survival

The overall median survival time (MST) in patients receiving TKI without distinction from gefitinib or erlotinib was 46.78 months with an average incidence of 0.007. View in **Table 3.**

Table 3. Median Survival Time Over-all

	Incidence rate	subject	MST
Total	0.007	139	46.78

The median survival time of the gefitinib group is the same as the overall MST which is 46.78 months. MST in the erlotinib TKI group cannot be analyzed. Incidence rate ratio (IRR) in TKI group 0.74 dan 95% CI IRR 0.21; 3.24.

Table 4. Median Survival Time TKI

Dead	Incidence rate	Subject	MST	IRR	95% CI IRR	
erlotinib	0.009	36	.46.78	0.74	0.21	3.24
gefitinib	0.007	103				

The results of the overall survival analysis in both groups, gefitinib and erlotinib groups at 1 year, 2 years, and 3 years respectively were (96% vs 95%), (91% vs 0%), and (91% vs 05) with significant values p=0.356, shown in **Image 3**

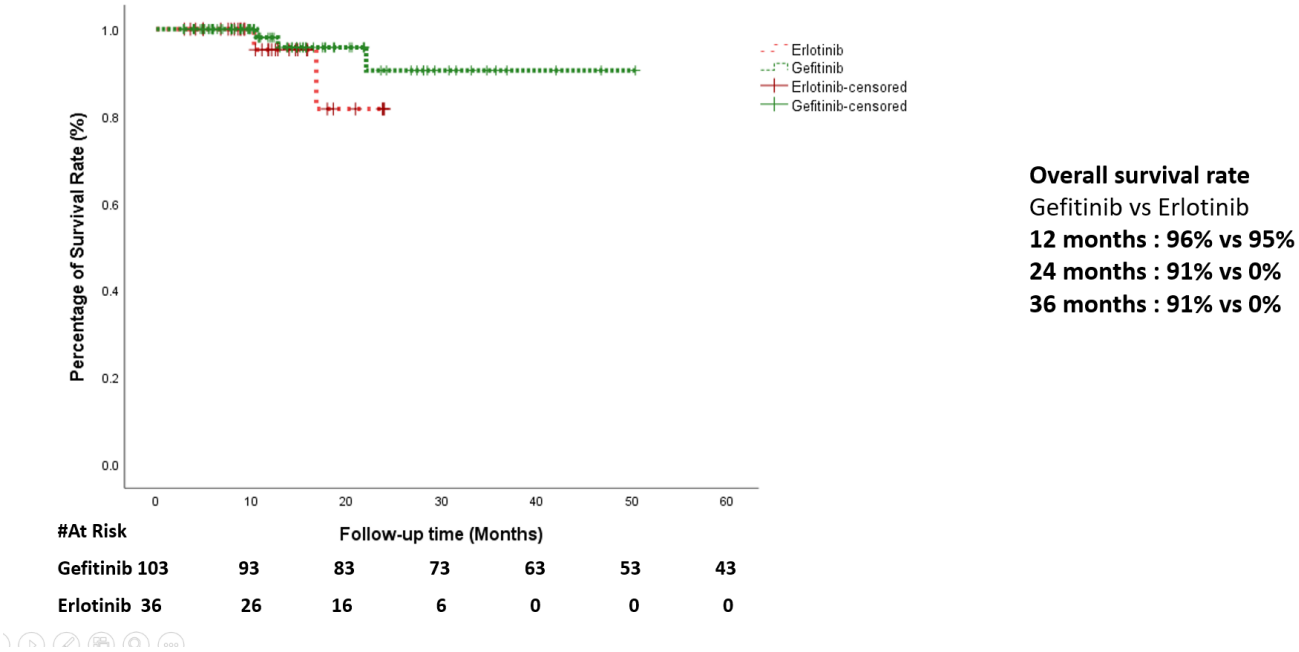

Image 3. Graph of Kaplan-Meier OS for Gefitinib and Erlotinib groups

Hazard Ratio (HR) of each characteristic to the OS with bivariate analysis is shown in table 4.5-3. All characteristic variables with significant values of P (z) > 0.05 and confirmed with a value of 95% CI.

Table 5. Effect Hazard Ratio (HR) Effect of Each Characteristic on OS

Dead	HR	P (z)	95% CI	
Age	0.54	0.27	0.19	1.59
Sex	2.5	0.11	0.81	7.74
Smoking	1.39	0.66	0.35	5.14
Mutation	0.97	0.95	0.32	2.94
TNM	2.29	0.08	0.89	5.91
PS	1.02	0.95	0.52	2.02
TKI	0.66	0.5	0.19	2.2

Time of Treatment

Median TOT of the gefitinib group of 12 months, the 11-month erlotinib group with a log rank test of p> 0.5 The results of the TOT analysis in the two groups of groups at 1 year, 2 years, and 3 years respectively were (98% vs 87%), (53% vs 0%), and (19% vs 0%) p=0.172

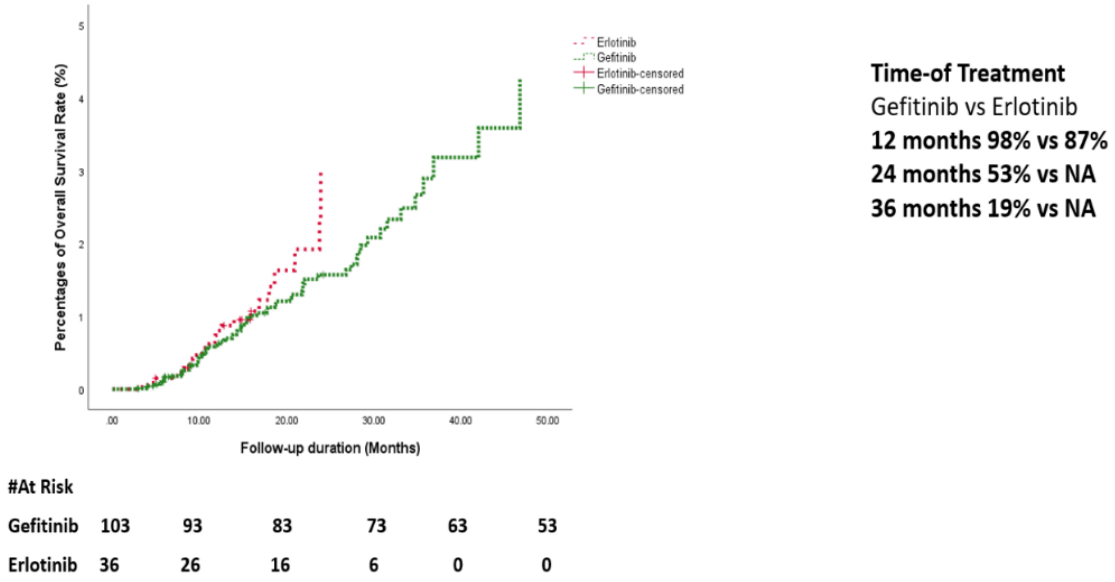

Image 4. Kaplan-Meier chart for TOT for Gefitinib and Erlotinib Groups

Table 6. Effect Hazard Ratio (HR) of Each Characteristic on TOT

Variable	HR	P (z)	95% CI	
Age	1.5	0.037	1.0	2,4
Sex	1,6	0.020	1,0	2,6
Mutation	1,4	0.149	0.8	2,3
TNM	1,3	0,241	0.8	2,3
PS	0,9	0.920	0.5	1,6
TKI	1.4	0.184	0.8	2.2

All characteristic variables have significant values of P(z) > 0.05 and are confirmed with a value of 95% CI, except age and gender. Age < 60 years against >60 years with confirmation of bivariate test (HR 1.7; 95%CI 1.1-2.7; P 0.013), while men against women with confirmation of bivariate tests were significantly meaningful (HR 1.8; 95%CI 1.1-2.8; P 0.012).

Discussion

The median duration of monitoring in the gefitinib and erlotinib groups was 10.5 and 11.4 months. In this study, the PFS median results of the Gefitinib group were 26 months PFS median and in erlotinib 17 months. The PFS for both groups at 1 year, 2 years, and 3 years respectively were (80% vs 87%), (53% vs 0%), and (19% vs 0%). Although gefitinib is higher compared to erlotinib in PFS but its meaning is not statistically meaningful (p=0.184).

Laitupa A at Poli One at RSUD DR. Soetomo Surabaya compared the efficacy of gefitinib with erlotinib, obtaining PFS and OS results in the two groups did not differ significantly.[28] Research of Sutandyo N et al, comparing the efficacy of gefitinib with erlotinib and afatinib obtained PFS results in subjects who received gefitinib and erlotinib were 9 and 13 months, respectively, Log-rank analysis showed that the two groups did not differ significantly p=0.28.[29]

In contrast to the research of Yang JJ et al who got the median results of PFS gefitinib and erlotinib were 10.4 and 13 months.[22] Krawczyj P's research obtained the median PFS in gefitinib and erlotinib was 9 months and 10 months.[34] Studies of Urata Y et al, obtained median PFS at gefitinib 6.5 months and erlotinib 7.5 months and 10 months (HR, 1.125; 95% CI, 0.940- 1.347; HR 1,068; 95% CI, 0.893-1.277).[31] A meta-analysis study conducted by Yang Z et al showed no significant differences in PFS between the gefitinib and erlotinib groups (HR, 1.00; 95% CI, 0.95 to 1.04, p 5 0.89).[21]

Univariate and multivariate analyses for PFS were performed with Cox-proportional hazard regression. When p<0.05, the data is said to be significant statistics. The output of the magnitude of the influence of variables on patient survival is expressed in the form of a hazard ratio (HR) using a 95% confidence interval to assess precision. Variables are made in nominal form, including age, gender, SF, stage, EGFR mutation, and the type of TKI used. PFS univariate analysis showed no significant differences in all six variables, PFS univariate analysis showed that sex affected the PFS of both groups (p=0.049, HR 1.7 CI95% 1.0-3.0). A multivariate analysis confirmed that gender (p=0.033, HR 1.9 CI95% 1.0-3.4) as well as age (p=0.034, HR 1.8 CI95% 1.0-3.3).

The median survival time of the gefitinib group is the same as the overall MST of 46.78 months. MST in the erlotinib TKI group could not be analyzed. The OS at 1 year, 2 years, and 3 years in the gefitinib and erlotinib groups were (96% vs 95%), respectively, (91% vs 0%), and (91% vs 05)." Although there were differences between the two groups in OS, no meaningful differences were obtained between the gefitinib and erlotinib groups with the results of the cox regression analysis obtained a p value of 0.356.

The research conducted by Asami K et al obtained the average OS results of the gefitinib group ranging from 17.5-35.5 months and in the erlotinib group ranging from 19.3-22.7 months.[15] A meta-analysis study conducted by Yang Z et al showed no meaningful differences in the OS between the gefitinib and erlotinib groups (HR, 0.99; 95% CI, 0.93 to 1.06, p 5 0.82; heterogeneity I2 5 42%, p=0.450).[21] Studies of Urata Y et al, obtained median OS in gefitinib 6.5 months and erlotinib 22.8 months and 24.5 months (HR, 1,038; 95% CI, 0.833 - 1.294).[32]

Univariate and multivariate analysis for the OS was performed with *Cox-proportional hazard regression*. When p<0.05, the data is said to be significant statistics. The output of the magnitude of the influence of variables on patient survival is expressed in the form of a *hazard ratio* (HR) using a 95% confidence interval to assess precision. Variables are made in nominal form, including age, gender, SF, stage, EGFR mutation, and the type of TKI used. Univariate analysis of OS did not show any significant differences in the six variables, however, in multivariate analysis age became an important predictor in the OS (p=0.036, HR 15.4 CI95% 1.2-201.2).

Median TOT group gefitinib 12 months, erlotinib group 11 months with log rank test p>0.05. The TOT at 1 year, 2 years, and 3 years in the gefitinib and erlotinib groups respectively were (98% vs 87%), (53% vs 0%), and (19% vs 0%). Although there were differences between the two groups in TOT, no meaningful differences were obtained between the gefitinib and erlotinib groups with the results of the cox regression analysis obtained a p value of 0.172. Research of Urata Y et al, obtained median TOT at gefitinib 5.6 months and erlotinib 5.3 months (HR, 1.032; 95% CI, 0.866 to 1.231).[32]

This study has some unavoidable limitations that can affect the results of the study. Some of these limitations include: this study was carried out with an observational design of a retrospective cohort method taken through secondary data from the medical records of lung cancer patients so that these

data are highly dependent on the medical records. Some patient medical records could not be found or the required patient data were incomplete, for example, recording side effects of therapy targets and records of patient clinical development making it difficult to see or assess the patient's subjective and semisubjective response.

Conclusion

Based on the results of the study, there was no difference in efficacy between gefitinib and erlotinib in the treatment of pulmonary Adenocarcinoma patients with EGFR gene mutations at Dr. H.A. Rotinsulu Lung Hospital.

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