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Survival Rate in Lung Adenocarcinoma with Mutation of the EGFR Gene with Tyrosine Kinase Inhibitor Treatment

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Abstract

BACKGROUND: EGFR mutation is a genetic disorder that is often observed and examined in Non-small cell lung carcinoma. EGFR mutation detection aims to predict sensitivity to EGFR-TKI and acts as first-line therapy. Targeted therapy with EGFR-TKI can increase the survival rate of patients with non-small cell lung cancer compared to chemotherapy.

AIM: This study aims to obtain data on the survival rate of patients with non-small cell lung Carcinoma who received targeted therapy at H. Adam Malik Hospital.

METHODS: This study is a descriptive study with a retrospective cohort design carried out at the Oncology Polyclinic at RSUP H Adam Malik Medan for 5 years, from January 2014 to December 2018. The subjects of this study were all patients with lung cancer type adenocarcinoma who had received therapy with generation 1 or 2 EGFR TKI.

RESULTS: 99 patients were included as subjects of this study. From the study, the most influential factors on lung cancer were gender, age, and smoking addiction. The study consisted of 60.6% male, 92.9% of the respondents aged 40 years and over, 56.5% active, 43.4% passive smokers, and 41.4% of the respondents with severe Brinkman index. The 30-month survival rate of EGFR-TKI (Gefitinib) patients treated with NSCLC Adenocarcinoma (Gefitinib) from 2014 to 2018 at H. Adam Malik Hospital Medan was 6.3% with a median survival of 7 months. The duration of progression-free survival in patients receiving Erlotinib therapy was 6.6 months (6.6 ± 2.51 months), while the length of progression-free survival for patients treated with Gefitinib was 9.1 months (9.1 ± 6.9 months). The results of statistical tests showed that there was no difference in progression-free survival rate between those who received Erlotinib and Gefitinib (p = 0.82).

CONCLUSION: The 30-month survival rate of lung adenocarcinoma patients treated with EGFR-TKI from 2014 to 2018 was 6.1% with a median survival of 7 months. Those who received Erlotinib therapy experienced Progression-Free Survival for 6.6 months and those who received Gefitinib experienced Progression-Free Survival for 9.1 months.

Introduction

Lung cancer is the most common type of cancer in both men and women, with high rates of morbidity and mortality. According to the American Cancer Society in 2019, the prevalence of lung cancer in men was 116,440 and in women 111,710 people with a death rate of up to 147,510 people per year [1]. According to Histopathology, there are two types of lung tumors, namely, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which consisted of two subtypes, namely, adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and unclassified lung carcinoma [2], [3], [4], [5], [6], [7], [8]. Adenocarcinoma has the highest prevalence among all subtypes [9], [10].

Several studies of adenocarcinoma lung cancer showed EGFR mutations such as the study of Syahruddin *et al*., EGFR mutations were around 44.4% of common EGFR mutations (exon 19 deletion mutation, and L858R), and uncommon EGFR mutations (G179X, T790M, and L861Q) at around 57, 1%, and 29% in Indonesia [11].

Although the development of lung tumors has increased in the past 5 years, the patient's survival rate is still very low [1]. In general, the comprehensive management of patients with lung cancer consisted of surgery with complete or partial resection, chemotherapy, radiotherapy, and targeted therapy [12], [13]. To reduce the side effects of conventional therapies such as chemotherapy and radiotherapy, there have been many studies describing molecular-based targeted therapies. Molecular-based targeted therapy in principle will effectively focus on biomarkers that are generally overexpressed and enhance the carcinogenesis properties of a tumor [14], [12], [15], [16], [17], [18], [19], [20].

The overall survival rate of lung adenocarcinoma patients receiving TKI therapy based on research is 31−33 months [21]. The study concluded that the

survival rate of lung adenocarcinoma patients was 21 months; there is no significant difference between exon 19 and 21 mutations [4].

Research Method

Subject

The subjects of this study were 99 patients with non-small cell lung adenocarcinoma with cytologically or histopathologically positive mutations in EGFR of lung adenocarcinoma type at H. Adam Malik Hospital Medan from January 2014 to December 2018.

Secondary data of the research subject were collected through medical record data; it was found that the smoking status of the research subject ranges from non-smoker, ex-smoker, and smoker. The Brinkman index takes account of the average number of cigarettes smoked per day and the length of the smoking period in years. There are three categories: Light Brinkman Index (0−199), Medium Brinkman Index (200−599), and Heavy Brinkman Index (600). Besides that, the history of first-generation EGFR-TKI (erlotinib and gefitinib) treatment is also included.

Research Design

This study is a descriptive study with a retrospective cohort design. The subjects of this study were all patients with adenocarcinoma lung cancer who had received EGFR TKI therapy. The data were analyzed using the Kaplan–Meier method.

Research Results

The subjects of this study were 99 patients with non-small cell lung adenocarcinoma with cytologically or histopathologically positive lung adenocarcinoma EGFR mutations at H. Adam Malik Hospital Medan from January 2014 to December 2018 (Table 1). About 60.6% of the patients were male (60 people). The average age of the patients involved in this study was 56.64 years with the youngest being 6 years old and the oldest being 87 years old. In total, 56 subjects (56.6%) were active smokers. The results of the Brinkman Index (BI) examination showed that subjects with the highest BI were 40 extremely heavy smokers (40.4%). Exon 19 deletion mutation was the most common mutation found in this study with a total of 47 people (47.5%). Based on the type of Tyrosine Kinase Inhibitor (TKI) treatment given, the majority of the subjects received Gefitinib (96 subjects; 97%). Whereas, there were three subjects (3%) that received Erlotinib.

Survival analysis (Kaplan-Meier)

Based on the time from diagnosis of lung cancer to the patient's death or the end of the study, the survival rate of non-small cell lung adenocarcinoma patients with mutations was obtained using the Kaplan–Meier method of survival analysis. In this study, six patients lived until the end of the study, with 93 deaths from the 99 patients involved at the beginning of the study (Table 2). The 30-month survival rate was 6.1% with a median length of life of 7 months (95% CI: 5.050 - 8.950 months). Figure 1 presented the survival curve for lung adenocarcinoma patients for 30 months for all patients.

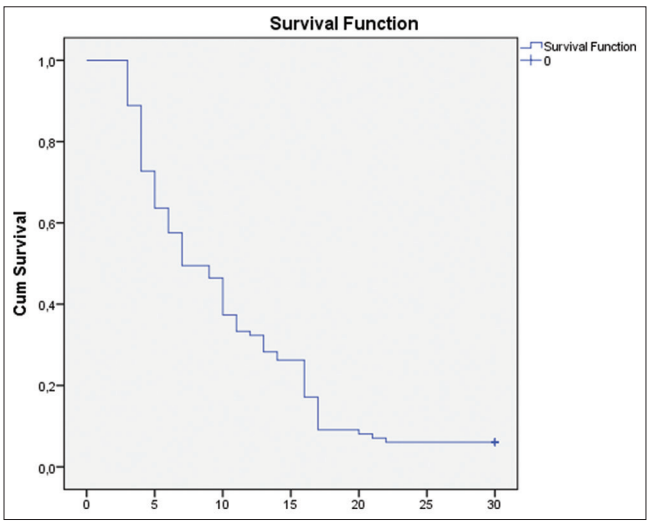

Figure 1. Kaplan Meier 30 Month Survival Curve of Non-Small Cell Lung Adenocarcinoma Patients

The 30-month survival rate of patients with lung adenocarcinoma patients among male subjects was 6.7% with a median survival of 9 months (95% CI: 6.831 to 11.169). The 30-month survival rate of lung adenocarcinoma patients amongst five women patients was 1% with a median survival of 7 months (95% CI: 3.186 to 10.814). The log-rank test showed that there was no significant difference in 30-month survival between male and female subjects (log-rank = 0.635 df = 1 p = 0.426) (Figure 2).

The 30-month survival rate of adenocarcinoma patients with EGFR single mutation is 6.1% with a median survival of 7 months (95% CI: 4.958−9.042). The 30-month survival rate for lung adenocarcinoma patients with combined EFGR mutations is 0% with a median survival of 7 months. The log-rank test showed that there was no significant difference in the 30-month survival based on the EFGR mutation (log-rank = 0.213 df = 1 p = 0.644) (Figure 3).

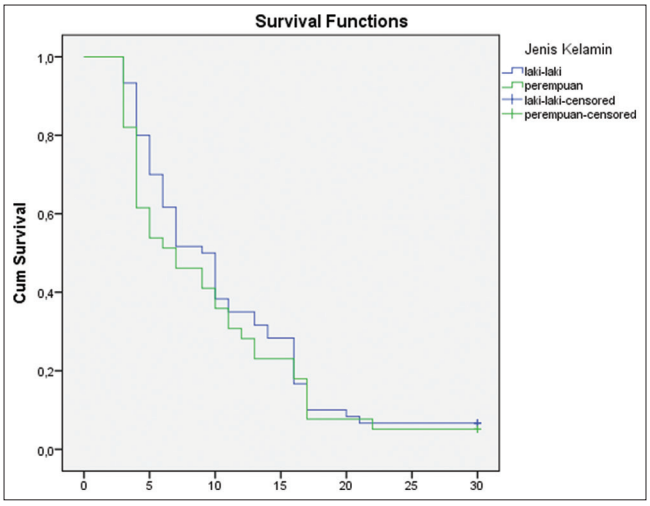

Figure 2. Kaplan Meier 30-Month Survival Curves Non-Small Cell Lung Adenocarcinoma Patients by Gender

The 30-month survival rate of adenocarcinoma patients who received gefitinib treatment is 6.3% with a median survival of 7 months (95% CI: 4.866−9.134). The 30-month survival rate for lung adenocarcinoma patients receiving Erlotinib treatment was 0% with a median survival of 7 months (95% CI: 2.199–11.801). The log-rank test showed that there was no significant difference in the 30-month survival rate based on the type of TKI treatment (log-rank = 0.836 df = 1 p = 0.361) (Figure 4).

The duration of PFS in lung adenocarcinoma patients with Erlotinib therapy was 6.6 months (6.6 ± 2.51 months), while the PFS duration of patients with gefitinib therapy was 9.1 months (9.1 ± 6.9 months). The standard deviation of patients who received gefitinib was greater, but there was considerable variation in the timing of the occurrence of PFS among patients who received gefitinib. The results of statistical tests showed that there was no difference in PFS between patients with erlotinib treatment and those with gefitinib.

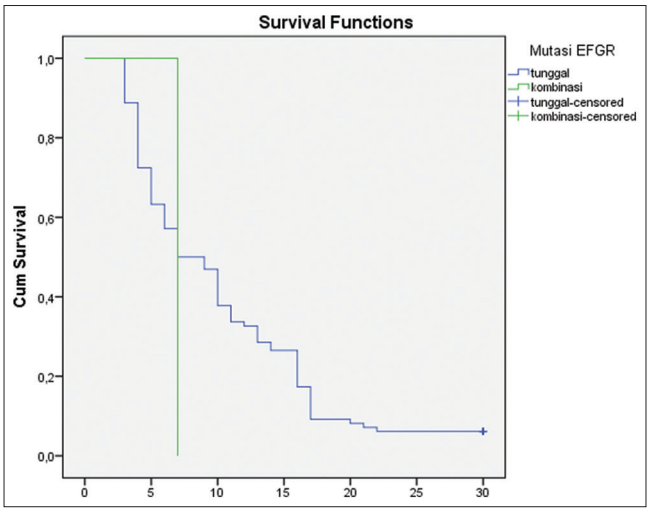

Figure 3. Kaplan Meier 30-Month Survival Curve of Non-Small Cell Lung Adenocarcinoma Patients Based on EGFR Mutations

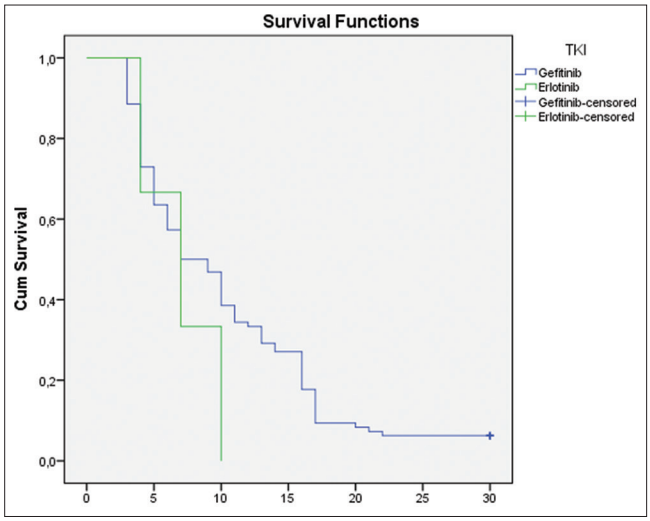

Figure 4. Kaplan Meier 30-Month Survival Curve of Non-Small Cell Lung Adenocarcinoma Patients Based on Type of TKI Treatment

Discussion

In this study, 99 patients with lung adenocarcinoma cancer consisted of mostly males (60 patients), 6 % of the subjects with an average age of 56.64 years. There were 56 active smokers (56.6%) with a severe Brinkman Index (>600) in 40 patients with an average of 40.45. According to research, the most common types of adenocarcinoma and smokers with a heavy Brinkman index were mostly found in clove cigarettes smokers [22], [9], [23], [24], [25].

EGFR-TKI treatment in this study predominantly consisted of 96 Gefitinib patients (97.7 %). Due to the

Table 1: Characteristics of research subjects

Characteristics	n = 99
Gender, n (%)	
Male	60 (60.6)
Female	39 (39.4)
Age, years old	
Average (SD)	56.64 (12.57)
Min–max	6–87
<40 years old, n (%)	8 (8.1)
Gender, n (%)	
Male	60 (60.6)
Female	39 (39.4)
Age, years old	
Average (SD)	56.64 (12.57)
Min–max	6–87
<40 years old, n (%)	8 (8.1)
40–60 years old, n (%)	53 (53.5)
>60 years old, n (%)	38 (38.4)
Smoking habit, n (%)	
Smoker	56 (56.6)
Non-smoker	43 (43.4)
Brinkman Index	
Light Smoker	37 (37.4)
Medium Smoker	21 (21.2)
Heavy Smoker	41 (41.4)
EFGR Mutation, n (%)	
Single Mutation	
Exon 18 G7198	2 (2)
Exon 18 G719A	3 (3)
Exon 18 G719A/C	2 (2)
Exon 18 G719S	4 (4)
Exon 19 Deletion	51 (51.5)
Exon 21 L858R	27 (27.3)
Exon 21 L861Q	9 (9.1)
Combined Mutation	
Exon 19 Deletion and Exon 21 L858R	1 (1)
Tyrosine Kinase Inhibitor, n (%)	
Erlotinib	3 (3)
Gefitinib	96 (97)

Table 2: Median duration of survival and survival rate according to subjects' characteristics

Characteristics	Median Survival		30-month Survival Rate	
	Month	95% CI	N	%
Gender				
Male	9	6,831−11,169	4	6,7
Female	7	3,186−10,814	2	5,1
Age				
<40 yo, n (%)	5	3,658−6,342	0	0
40−60 yo, n (%)	10	7,443−112,557	5	9,4
>60 yo, n (%)	7	3,375−10,625	1	2,6
Smoking habit, n (%)				
Smoker	7	4,905−9,095	3	5,4
Non-smoker	7	1,860−12,140	3	7
Brinkman Index				
Light	7	6,024−7,976	2	5,4
Medium	10	7,460−12,540	1	4,8
Heavy	25	4,873−13,127	3	7,5
EFGR Mutation, n (%)				
Single Mutation	7	4,958−9,042	6	6,1
Combined Mutation	7		0	0
TKI, n (%)				
Gefitinib	7	4,866−9,134	6	6,3
Erlotinib	7	2,199−11,801	0	0

fact that, it was easier to assess EFGR mutations with gefitinib treatment in H. Adam Malik General Hospital at that period. Hence, the usage of erlotinib was still very rare. In contrast to the study by Kasum Supriya in 2014 at *Persahabatan* Hospital whereby the administration of EGFR-TKI did not take account of EFGR mutations beforehand [26]. While in this study, all patients were required to provide the results of EGFR mutations before administration of EGF-TKI. This is in accordance with the NCCN guidelines that all NSCLC patients who will receive EGFR-TKI therapy must be examined for mutations [26]. The EGFR mutation detected in all of the subjects were mutations in Exon 19 Deletion with a total of 47 patients (47.5%).

The survival rate is defined as the period a patient survives from diagnosis until the patient dies or when the study ends. Various factors affect survival rates. The main factors that determine the prognosis of lung cancer are disease staging [28]. The characteristics of cancer patients also play a role in patient survival, including age, gender, display status, smoking status, Brinkman index, type of mutation EGFR, and EGFR-TKI types [7]. The median survival period in this study was 7 months (5050 – 8950 months). The results of the study showed no significant difference in 30-month survival rate between male and female (log-rank = 0.635 df = 1 p = 0.426). Therefore, there was no significant difference between males and females in the 30-month survival of EGFR-TKI.

Based on age, there was no significant difference in 30-month survival rate (log-rank = 1.931 df = 2 p = 0.381). Therefore, the survival of adenocarcinoma patients who received EGFR-TKI did not differ significantly for patients between 30 and 87 years old. However, the median 30-month survival rate in patients below 40 years old is 5 months, while at the age of 40–60 years old the median is 10 months.

Based on smoking habits, this study showed that there was no significant difference in the 30-month survival rate (log rank = 0.182 df = 1 p = 0.670). However, if we examine more thoroughly than the data, there is a difference of 2 months. The data show that the median survival rate for active smokers is 5 months while the median for passive smokers is 7 months. Thus, patients with adenocarcinoma who received EGFR-TKI with passive smoking habits had a longer life of about 2 months compared to active smokers.

This study does not only observe the characteristics of the effect of smoking habit on patients with lung adenocarcinoma EGFR mutations but also considers the number of cigarettes by using the Brinkman index. According to the results of data analysis, there was no significant difference in the 30-month survival rate based on the Brinkman Index (log-rank = 0.415 df = 3 p = 0.937). This is because patients with moderate Brinkman Index have a median survival rate of 10 months. While patients with severe Brinkman Index scores, the median survival rate is 9 months.

Researchers observed the difference between the first generation (gefitinib) and the second generation (erlotinib) EGFR-TKI targeted therapy in a study involving 99 patients with adenocarcinoma EGFR mutation. There was no significant difference in 30-month survival rate based on the type of TKI treatment (log rank = 0.836 df = 1 p = 0.361). Both EGFR-TKI treatments resulted in a similar median length of survival rate at 7 months.

In accordance with the NCCN Guidelines, non-squamous NSCLC patients who will receive EGFR-TKI as first-line treatment must be examined and proven to have EGFR mutations first [27]. The 99 adenocarcinoma patients who were included in this study had a variant of the EGFR mutation type, with the most common mutation being Exon 19 Deletion [28]. However, after data processing, this study showed that there was no significant difference in the 30-month survival rate based on the EFGR mutation (log rank = 0.213 df = 1 p = 0.644). More precisely, there was no difference in median length of life in patients with single or combined EGFR mutations, which were both at 7 months of EGFR-TKI treatment.

In this study, the PFS of lung adenocarcinoma patients who received therapy with Erlotinib was 6.6 months (6.6 ± 2.51 months), while the PFS of patients who received Gefitinib therapy was 9.1 months (9.1 ± 6.9 months). In a 2017 study, it was found that the average PFS in the exon 19 gene mutation group was 9.05 months, which was greater than exon 21 average PFS of 6.76 months [2].

Limitations of the study

The inevitable obstacle faced by the researchers due to the retrospective method of the research design from the medical records of lung cancer patients between 2016 and 2018. As a result, the data depended heavily on the completeness of

the medical records. However, some medical records were not found. In addition, because this study aims to determine the survival rate of patients receiving first-line EGFR-TKI therapy, the researchers had difficulty finding samples, especially the EGFR-TKI (Gefitinib/Erlotinib) sample. The EGFR-TKI that was often used at that time was gefitinib because it was included in the BPJS Health insurance, while we received an extremely small amount of erlotinib therapy in this study. As a result, gefitinib dominated the sample for EGFR-TKI therapy.

Conclusion

PFS of lung cancer patients who received erlotinib therapy was 6.6 months (6.6 ± 2.51), while PFS of lung cancer patients who received gefitinib therapy was 9.1 months (9.1 ± 6.9).

The 30-month survival rate of lung adenocarcinoma patients treated with EGFR-TKI (Gefitinib) in the 2014−2018 period at H. Adam Malik Hospital Medan was 6.1% with a median survival of 7 months.

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