Accessed on: http://jkb.ub.ac.id/index.php/jkb/article/view/3171
Jurnal Kedokteran Brawijaya Vol. 32, No. 3, Februari 2023, pp. 165-170
Article History: Received 24 February 2022, Accepted 1 February 2023

Research Article

Survival Rate of Lung Adenocarcinoma Patients Receiving EGFR - Tyrosine Kinase Inhibitor Targeted Therapy

Angka Tahan Hidup Pasien Adenokarsinoma Paru yang Mendapat Terapi Target EGFR – *Tyrosine Kinase Inhibitor*

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ABSTRACT

Globally, lung cancer is by far the leading cause of death by cancer-which contribute to 2.094 million death-with the highest toll from cancer being 1.8 million. Currently, lung cancer therapy has developed from chemotherapy to targeted therapy, such as Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI). This study aimed to assess the survival rate of adenocarcinoma cell lung cancer patients who received EGFR-TKI therapy at the Pulmonary Clinic of Dr. Saiful Anwar General Hospital Malang. This study was a retrospective study using patient medical records between 2017 and 2020. The data were processed and analyzed using the Chi-Square test. The number of samples was 117 patients consisting of 63 patients receiving Gefitinib therapy, 36 patients receiving Afatinib therapy, and 18 patients receiving Erlotinib therapy. There were no significant differences between variables of age, sex, smoking history, stage, and exon mutations with 1-year survival. Gefitinib therapy has a higher average survival time than Afatinib and Erlotinib. However, the 1-year survival rate (YSR) was highest on Afatinib. The Middle Survival (MS) of the three regimens is almost the same, about 300 days. Statistical data showed no relationship between survival and the treatment regimen given (p=0.187). The most common side effect of TKI is skin rash. This research should be carried out with a larger sample to minimize bias.

Keywords: *EGFR-TKI, lung adenocarcinoma, survival rate*

ABSTRAK

Kanker paru menempati peringkat pertama dalam jumlah kasus yaitu 2,094 juta kasus diseluruh dunia dan kematian akibat kanker tertinggi di dunia sebesar 1,8 juta kematian. Sekarang ini terapi kanker paru sudah sangat berkembang dari kemoterapi sampai terapi target terutama *Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor* (EGFR-TKI). Penelitian ini bertujuan untuk menilai angka tahan hidup pasien kanker paru adenokarsinoma yang mendapat terapi EGFR-TKI di Poli Paru RSUD Dr. Saiful Anwar Malang. Penelitian ini merupakan penelitian cohort retrospektif dengan menggunakan rekam medis pasien antara tahun 2017 sampai 2020. Data tersebut diolah dan dianalisis dengan uji Chi-Square dan menggunakan Kaplan meier untuk melihat angka tahan hidup. Besar sampel sebanyak 117 pasien terdiri dari 63 pasien mendapat terapi Gefitinib, 36 pasien mendapat terapi Afatinib, dan 18 pasien mendapat terapi Erlotinib. Tidak didapatkan perbedaan signifikan antar variabel seperti usia, jenis kelamin, riwayat merokok, stadium, dan mutasi exon dengan kesintasan 1 tahun. Gefitinib memiliki rata-rata masa tahan hidup lebih tinggi dibandingkan Afatinib dan Erlotinib. Namun, pada Angka Tahan Hidup (ATH) 1 tahun didapatkan Afatinib tertinggi. Masa Tengah Tahan Hidup (MTTH) ketiga regimen tersebut hampir sama yaitu sekitar 300 hari. Data statistik menunjukkan tidak didapatkan perbedaan antara masa tahan hidup dengan regimen terapi yang diberikan (p=0,187). Efek samping yang paling sering terjadi pada TKI adalah ruam kulit. Penelitian lanjutan sebaiknya dapat dilaksanakan dengan sampel yang lebih besar untuk meminimalkan bias.

Kata Kunci: Adenokarsinoma paru, EGFR-TKI, *survival rate*

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DOI: http://dx.doi.org/10.21776/ub.jkb.2022.032.03.5

INTRODUCTION

One of the malignancy with the highest incidence rate is lung cancer. Globally, lung cancer is the second most common cause of all cancers after non-melanoma skin cancer, which counted to 2.2 million cases in 2017. Lung cancer is also the leading cause of death due to cancer and Disability-Adjusted Life Years (DALYs) among men. Among women, this cancer has also become the second most common cause of death due to cancer and has caused 1.9 million deaths while causing a total of 40.9 million DALYs in both sexes (1). Socioeconomis status and smoking habits are the risk factors for lung cancer. Low- and middle-income countries contribute more than 50% of lung cancer deaths annually (2).

Lung cancer is a primary lung malignant tumor originating from the airways or bronchial epithelium. The occurrence of cancer is characterized by abnormal, uncontrolled cell growth that damages normal tissue cells. The World Health Organization (WHO) divides lung cancer into two main classes based on pathology and biological characteristics, namely Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). Non-Small Cell Lung Cancer makes up more than 80% of lung cancer cases, and it includes the two main types: non-squamous, including adenocarcinoma and large-cell carcinoma, and squamous cell carcinoma (epidermoid)(3). Adenocarcinoma was the most prevalent histological form of lung tumor, according to data on lung tumor cases at Dr. Saiful Anwar General Hospital Malang in 2016 (46%) (4).

Various therapies given to cancer patients, such as systemic therapy, radiotherapy, and surgery, have not fully yielded good results. Conventional therapeutic agents that work by non-specifically inhibiting cancer cells can cause toxicity to both cancer cells and normal cells. Therapy using specific pathways, which affect cancer growth, can reduce toxicity to normal cells, thus can increase the tolerability (5).

One of the targeted therapies currently developing is Tyrosine Kinase Inhibitor (TKI), which works intracellularly. TKI therapy is divided into EGFR-Inhibitors, VEGFR-Inhibitors, ALK-Inhibitors, and Bcr-Abl Inhibitors according to their receptor targets (6). Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) will compete against Adenosine Triphosphate (ATP) to bind the intracellular domain of EGFR Catalytic Tyrosine Kinase; thus, inhibiting cancer cell proliferation and tumor angiogenesis in large doses. The mutations of EGFR, EGFR polymorphism, and gastric pH affect the success of EGFR-TKI therapy. The three generations of EGFR-TKI are the first generation Gefitinib and Erlotinib, the second generation Afatinib and Dacomitinib, and the third generation Osimertinib (7). In Indonesia, the management of adenocarcinoma cell lung cancer using targeted therapy has been implemented since 2012. Government support is shown from the financing of adenocarcinoma cell lung cancer with positive EGFR mutations using the target therapy drug, Gefitinib, which is fully covered in the insurance package (8). This study was conducted to determine discriptive the effectiveness of EGFR-TKI therapy in adenocarcinoma cell lung cancer patients with positive EGFR mutations by evaluating the survival rate (SR) and side effects of therapy.

METHODS

This study was a retrospective study using medical records of adenocarcinoma cell lung cancer patients with EGFR mutations in January 2017-December 2020 at Dr. Saiful Anwar General Hospital Malang. This study was approved by the ethical clearance board hospital number 400/192/K.3/302/2021. The study inclusion criteria were all adenocarcinoma patients with EGFR mutations and receiving 1st or 2nd generation TKI therapy.The sample size that met the criteria was 117 patients. Data including patient characteristics, namely demographics, risk factors smiking habits, clinical features lung cancer stage and EGFR mutation, and treatment options, were collected. The data were descriptively presented in tables and graphs to see the proportions and comparisons, and the Chi-Square test was performed. SR calculation was assessed since the

Table 1. Characteristics of adenocarcinoma lung cancer patients with EGFR mutations at Dr. Saiful Anwar Hospital Malang in 2017-2020

Characteristics	Gefitinib (63)	Afatinib (36)	Erlotinib (18)	Total (117)	Percetage (%)	Chi Square p-value
Age, (n)						
<40 years	1	0	2	3	2.56%	0.457
40-60 years	32	15	9	56	47.86%	
>60 years	30	21	7	58	49.57%	
Gender, (n)						
Male	27	12	11	50	42.74%	0.608
Female	36	24	7	67	57.26%	
History of Smoking Habit, (n)						
Active smoker	26	12	10	48	41.03%	
Passive smoker	20	13	2	35	29.91%	
Non-smoker	17	11	6	34	29.06%	
Lung Cancer Stage, (n)						
IIIB	0	1	0	1	0.85%	0.192
IVA	35	17	12	64	54.71%	
IVB	28	18	6	52	44.44%	
EGFR mutation, (n)						
Exon 18	1	0	2	3	2.56%	0.660
Exon 19	55	15	8	78	66.67%	
Exon 21	7	21	8	36	30.77%	

EGFR-TKI therapy was initially given until the patient died or the study ended. Survival rate analysis was performed by comparing the EGFR-TKI therapy regimens, i.e., Gefitinib, Afatinib, and Erlotinib, using the Kaplan-Meier curve.

RESULTS

Table 1 presents the characteristics of adenocarcinoma cell lung cancer patients with EGFR mutations based on therapy types. The most widely used therapy was Gefitinib (63 patients, 52%) followed by Afatinib (36 patients, 27%) and Erlotinib (18 patients, 21%). Overall, the ratio of men and women was almost the same, but in patients treated with Gefitinib and Afatinib, the proportion of women was more dominant but was the opposite in the Erlotinib therapy. Almost all patients were over 40 years old, but there were patients below 40 years old, namely one patient receiving Gefitinib therapy and two patients receiving Erlotinib therapy. Most patients from all types of therapy had active smoking behavior, while the proportion of passive smokers and non-smokers was almost the same. Most patients were in stage IVA, namely 64 patients (54.71%), and the most mutation was found in exon 19, as many as 78 patients (66.67%)

Table 2 shows the SR of patients with adenocarcinoma cell lung cancer receiving EGFR-TKI therapy. Overall, most patients (55.56% to 83.33%) had below 1-year survival in all types of therapy. Patients with a survival rate higher than one year were found to be the least in the Erlotinib group.

Table 2. Survival rate of adenocarcinoma cell lung cancer patients receiving TKI therapy at Dr. Saiful Anwar Hospital Malang in 2017-2020

TKI Therapy Regimen	Survival Rate, N (%)	
	<1 Year	>1 Year
Gefitinib	35(55.56)	28(44.44)
Afatinib	22(61.11)	14(38.89)
Erlotinib	15(83.33)	3(16.67)

Without differentiating the type of therapy, the side effect of the EGFR-TKI therapy regimen in adenocarcinoma cell lung cancer patients was skin rash, which was found in 34 patients (53.97%). Other side effects were diarrhea in 22 patients (34.92%) and stomatitis in 1 patient (1.59%) (Table 3).

Table 3. Side effects of TKI administration in adenocarcinoma cell lung cancer patients with EGFR mutations at Dr. Saiful Anwar Hospital Malang in 2017-2020

Side Effects	N (%)
Skin Rash	34(53.97)
Stomatitis	1(1.59)
Diarrhea	22(34.92)

In this study, the correlation of survival rate time-based on the time from the first time the therapy regimen was administered until the patient died or the end of the study-of adenocarcinoma cell lung cancer patients receiving EGFR TKI gefitinib therapy with age, sex, smoking history, cancer stage, and exon mutations was analyzed using Chi Square. The analysis resulted In p value of >0.05 which indicated no significant correlation between survival rate and age, gender, smoking history, stage, and exon EGFR Mutations (Table 4).

Table 4. Chi Square analysis of correlation between survival rate and age, gender, smoking history, stage, and exon EGFR mutations

Characteristics	Survival Rate		Total	%	Chi Square p-value
	<1 Years	>1 Years			
Age (n)					1.567*
<40 Years	0	1	1	1.59	
40-60 Years	17	15	32	50.79	
>60 Years	18	12	30	47.62	
Sex (n)					0.263*
Male	14	13	27	42.86	
Female	21	15	36	57.14	
Smoking history (n)					1.353*
Active Smoker	16	10	26	41.27	
Passive Smoker	9	11	20	31.75	
Non-Smoker	10	7	17	26 98	
Stage (n)					1.700*
IVA	22	13	35	55.56	
IVB	13	15	28	44:44	

Table 4. Chi Square analysis of correlation between survival rate and age, gender, smoking history, stage, and exon EGFR mutations

Characteristics	Survival Rate		Total	%	Chi Square p-value
	<1 Years	>1 Years			
EGFR mutation (n)					0.830*
Exon 18	1	0	1	1.59	
Exon 19	30	25	55	87.30	
Exon 21	4	3	7	11.11	

This study also evaluated the median survival (MS), 337 days with one year SR of 44.4%. In patients receiving Afatinib therapy, the MS was 334 days with an SR of 50.0%, while the MS of patients treated with Erlotinib was 180 days with an SR of 16.7%. The overall survival rate for the three EGFR regimens showed that the MS was 313 days with one year SR of 41.9% (Table 5).

Table 5. Survival rate of adenocarcinoma cell lung cancer patients receiving EGFR-TKI therapy from January 2017 to December 2020

Therapy	MS (day)	1-Year SR	
		N	%
Gefitinib	337	28	44.4
Afatinib	334	18	50.0
Erlotinib	180	3	16.7
Overall	313	49	41.9

The curves in Figure 1 show that the average survival rate of patients treated with Gefitinib was 531 days, patients' SR receiving Afatinib therapy was 456 days, and patients' SR receiving Erlotinib therapy was 270 days.

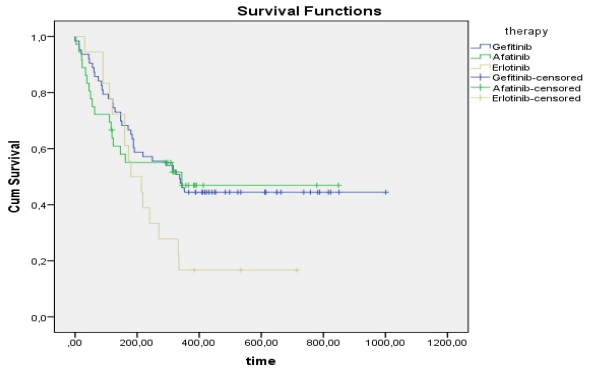

Figure 1. *Survival rate* adenocarsinoma cell lung cancer with TKI therapy Gefitinib, Afatinib and Erlotinib

DISCUSSION

The most common treatment option in this study was Gefitinib (54%). The age range of the patients in this study was from 34 to 84 years old, with an average age of 60.3 years. The number of female subjects was higher than the male. Non-Small Cell Lung Cancer incidence increases with age; 60% occurs in patients aged older than 60 years, and 30% to 40% occurs in patients aged older than 70 years (9). Women had a higher susceptibility to the carcinogenic effects of cigarette smoke, although not in all cases. Compared to men who have never smoked, women who have never smoked have a significantly greater incidence of lung cancer. Environmental exposure, genetics, hormonal factors, and viral infections also have a role in the development of lung cancer in women (10).

Most of the patients in this study were active smokers. Smoking is one of the causes of lung cancer, about 10% to 15% of active smokers develop lung cancer (11). However, in a study by Wakelee-who compared the individual characteristics of smokers and non-smokers with the incidence of lung cancer, it was found that about 10% of lung cancers occur in individuals who have never smoked. Another study found the highest proportion of adenocarcinoma cell lung cancer (53-70%) in individuals who had never smoked (12). This study also found similar proportions of passive smokers compared to the patients who did not smoke, thus, indicating that further study of cancer risk with overall cigarette exposure-whether active or passive-is required.

In this study, almost all patients with adenocarcinoma cell lung cancer were in the advanced stage (IV), while only one patient was found in stage IIIB. This distribution is in line with a study at Washington University involving 6118 patients. According to the study, the percentage of lung cancer cases in stage IV increased significantly between 2000 and 2005, rising from 30%-between 1990 and 1999-to 38%. Based on EGFR mutations, most mutations occurred in exon 19 compared to other exons in this study. Mutations in EGFR are common in exon 19 deletions and L858R substitutions in exon 21, reaching for approximately 90% of EGFR mutations in Non-Small Cell Lung Cancer (13).

Many factors affect survival rates. Characteristics of cancer patients that play a role in patient survival are age, gender, and smoking habit (14). White et al. states that the prognosis of lung cancer depends on age at diagnosis. Increasing age causes the accumulation of carcinogenic substances in the body and genetic damage. In addition, increasing age causes a decrease in immunity, decreases DNA repair, and causes a loss of cell regulation that facilitates carcinogenesis in the body. Each 10-year increment increases the risk of death by 30% (15).

In this study, there was no tendency for the survival rate to increase with patient age. This finding might be due to the uneven distribution of patients in this study, in which there is only one young patient. As seen in the statistical analysis of the length of survival, age has no significant relationship with the length of survival. In this study, more females tended to have survival time of less than one year. Research by Kirsh et al. stated that gender is an important factor in determining the survival rate. Overall, women had worse 5-year survival rate than men. This is contrary to the research by Radzikowski *et al.,* that mentions women with lung cancer have a better prognostic factor than men by considering age, histology, the extent of disease, and therapy given (14).

Smoking is acknowledged as one of the causes of lung cancer and is considered as a role in the development of tumors. In this study, patients who were active smokers tended to have a survival rate of less than one year, as well as patients who did not smoke. A study by Nordquist et al. stated that smoking was not an independent predictor of increased survival (16). In this study, smoking history did not significantly correlate with survival rate.

Almost all patients in this study were at an advanced stage (Stage IV), either receiving Gefitinib, Afatinib, or Erlotinib therapy. The test results showed no significant relationship, with a *p*-value of >0.05 (p=1.70). The theoretical facts mention that the factor considered the most influential on survival is disease stage (14). Cancer research in the UK states that the 1-year survival rate for lung cancer patients is highest (88%) in patients with early-stage (Stage I) and the lowest (19%) in patients with stage IV (17).

There was no discernible correlation between the survival rate and the exons that underwent mutations. This might be due to the insufficient number of samples in this study, thus, the patient distribution was uneven. Most mutations occurred in exon 19, and most had a survival rate of less than one year. The research by Krawczyk *et al.,* stated no difference between response rate, progression-free survival (PFS), and overall survival time in EGFR mutations (1,18,19). It contradicts the studies by Castellanos *et al.*, and Krawczyk *et al.,* which states that non-small cell lung carcinoma patients with mutations in exon 19 have longer survival after treatment with Gefitinib or Erlotinib than patients with exon 21 mutation (19,20).

The results showed that patients treated with Gefitinib had almost the same MS (337) as patients treated with Afatinib who had an MS of 334 days with a one-year SR of 50%. In contrast, patients on Erlotinib therapy had the lowest MS (180 days with a one-year SR of 16.7%). In the analysis of patient survival rates, Gefitinib therapy gave a higher survival rate than other EGFR-TKI therapy, 531 days. The

research by Wulandari *et al.,* found that Gefitinib therapy as the first line produced a good objective response, especially in Non-Small Cell Lung Cancer patients who had positive EGFR mutations at Dr. Soetomo Hospital with a median PFS of 8.3 months (95% CI: 6.50-10.2) and median overall survival (OS) of 16 months (95% CI: 11.9-20.2) (21). Research by Sutandyo et al. stated that Gefitinib, Erlotinib, and Afatinib have the same effectiveness in advanced-stage adenocarcinoma cell lung cancer patients with positive EGFR mutations (22). A different finding, however, was found in a study by Sari *et al.,* in which Afatinib therapy gave a longer PFS (448 days or 14.7 months; 95% CI=12–17.4 months; p=0.002) compared to Gefitinib (334 days or 11.3 months; 95% CI=8.4–14.3 months) (23). However, in this study, there was no significant correlation between survival and EGFR-TKI therapy (p=0.187).

The most common side effects of TKI administration found in this study were rash and diarrhea. This is similar to the study by Wulandari *et al.,* in which was stated that the most common side effects in Gefitinib patients were rash in 52 patients (82%) and diarrhea in 29 patients (46%). This is supported by another study which found that the side effect profile of Gefitinib, in general, was frequent skin rashes (85.06%) and diarrhea (54%), and the side effect which often caused death was interstitial lung disease (1.3%) (21).

The weakness of this study is that it is a retrospective study. It was difficult to obtain complete medical record data, thus, not all data is presented. Further study needs to be done to obtain better data. This study identified adenocarcinoma cell lung cancer with the most EGFR mutations occurring in women, aged over 60 years, with a history of active smoking, with advanced stage, and with mutations in exon 19. Patients given Gefitinib have a higher average survival time than those with Erlotinib and Afatinib. Skin rash is the most common side effect in adenocarcinoma cell lung cancer patients receiving TKI therapy. One-year survival did not show significant differences between variables, such as age, gender, smoking history, stage, and exon mutations.

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