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Original Article

Overall survival of non-small cell lung cancer treated with systemic therapy: The experience at a regional hospital, Bandar Lampung

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Abstract

Background: The benchmark for the success of cancer treatment is the survival rate. Although the hope for survival is increasing, there are still concerns regarding the cost of treating lung cancer with targeted therapy which is very expensive and has not yet been included in the national formulary for third-generation EGFR-TKI targeted therapy (osemertinib).
Method: Analytic descriptive with retrospective cohort design processed with SPSS 25 with log-rank test and shown with Kaplan Meier product limit curve. Data was taken at Dr. H. Abdul Moeloek Hospital from January 2020 to December 2022.
Results: We analyzed 92 Lung adenocarcinoma who have treated with systemic therapy. Thirty-nine (42.9%) subjects were treated with EGFR-TKI therapy, and 53 (47.1%) subjects were treated with chemotherapy that used paclitaxel-carboplatin regimen. The median survival time of the group treated with EGFR-TKI was 7 months (95% CI: 3.805-10.195) while the chemotherapy group was 5 months (95% CI: 3.788- 6.212) while the overall median survival was 6 months (95% CI: 4.836-7.164). There was no significant difference with the p-value: 0.209.
Conclusion: The median survival rate of two groups was not significantly different.

Keyword: EGFR-TKI, carboplatin-paclitaxel, lung adenocarsinoma, survival rate

Abstrak

Latar Belakang: Tolok ukur keberhasilan pengobatan kanker adalah angka kesintasan hidup. Meskipun harapan untuk bertahan hidup semakin meningkat, masih terdapat kekhawatiran mengenai biaya pengobatan kanker paru dengan terapi target yang sangat mahal. Terapi ini juga belum masuk dalam formularium nasional untuk terapi target generasi ketiga EGFR-TKI (osemertinib)
Metode: Deskriptif analitik dengan desain kohort retrospektif yang diolah dengan SPSS 25 dengan uji log-rank dan disajikan dengan kurva Kaplan Meier. Pengambilan data dilakukan di RSUD Dr. Hj. Abdul Moeloek dari bulan Januari 2020 hingga Desember 2022.
Hasil: Telah dianalisis 92 adenokarsinoma paru yang telah diobati dengan terapi sistemik. Tiga puluh sembilan (42,9%) subjek diterapi dengan EGFR-TKI dan 53 (47,1%) subjek dengan kemoterapi yang menggunakan regimen paclitaxel-carboplatin. Kesintasan hidup rata-rata waktu kelompok yang diobati dengan EGFR-TKI adalah 7 bulan (95% CI: 3.805-10.195) sedangkan kelompok kemoterapi adalah 5 bulan (95% CI: 3.788- 6,212). Median kesintasan hidup keseluruhan adalah 6 bulan (95% CI: 4.836- 7.164). Tidak ada perbedaan yang signifikan dengan nilai-p 0,209.
Kesimpulan: Rerata median kesintasan hidup dari dua kelompok tidak berbeda secara signifikan

***Kata Kunci**: adenokarsinoma paru, angka kesintasan hidup, EGFR-TKI, carboplatin-paclitaxel.*

Background

Regional General Hospital Dr. H. Abdul Moeloek (RSUDAM) is a Type A Referral and Education Hospital in Lampung Province, Sumatra. Data on lung cancer cases at RSUDAM from Fransiska's research results in 2018-2021 found 244 cases with a number of cases man:women around 3:1. Based on the age category, most cases of lung cancer were between 35-65 years old, 173 people (70.9%), and based on the stage of lung cancer, most cases of lung cancer came in stage IV B with a total of 92 people (37.7%), stage IV A 91 people (37.3%), stage III B 38 (15.6%) and stage III A as many as 23 people (9.4%).[1]

Treatment of lung cancer uses multimodality therapy. The choice of therapy is based on histological/ cytological type, stage, condition of the patient, availability of drugs in the hospital and the economic capacity of the patient. Surgery and radiotherapy are local treatments while chemotherapy and targeted therapy are systemic treatments. The management of lung cancer non-small cell carcinoma subtype adenocarcinoma (non-squamous) which has mutations in the epidermal growth factor receptor (EGFR) in exons 19 and 21 can be given treatment with the first generation of EGFR-tyrosine kinase inhibitors (TKI) (gefitinib, erlotinib) or second generation of TKI (afatinib), whereas those with mutations in exon 18, 20, L861Q) will respond well to second and third generation EGFR-TKI (osemertinib). Currently, the era of national health insurance (JKN) is managed by the Social Security Administration Agency(BPJS), the requirement to get EGFR-TKI chemotherapy drugs is to have EGFR examination results which not all patients can carry out.[2]

The benchmark for the success of cancer treatment is the survival rate. Survival in cancers with high malignancy such as lung cancer is 1-year survival, 2-year survival and 3-year survival.[3] Although survival expectations are increasing there are still concerns regarding the cost of treating lung cancer with targeted therapy which is very expensive and has not yet been included in the national formulary for third-generation EGFR-TKI target therapy (osemertinib).

Supriadi Kasum's research at the RSUP Persahabatan for lung cancer cases between 2010 - 2013 concluded that the survival time of non-small cell lung cancer patients of the adenocarcinoma type (non-squamous) treated with EGFR-TKI was slightly longer than first-line chemotherapy (263 days vs. 260 days).[4] Hasan Nyambe's retrospective study at Wahidin Sudirohusodo Hospital Makassar in 2017-2019 survival in non-small cell lung cancer (KPKBSK) patients who received EGFR-TKI had a significantly higher survival rate than those who received first-line chemotherapy (conventional chemotherapy).[5]

Research on survival rates of lung cancer patients at RSUD Dr. Hi. Abdul Moeloek has never done this. This study aims to determine the characteristics and survival rates of lung cancer patients with subtype adenocarcinoma who received EGFR-TKI therapy and who received conventional chemotherapy with carboplatin and paclitaxel. Survival analysis provides great benefits not only for predicting survival chances, but also for better management of lung cancer patients.

Methods

This research is a descriptive-analytic study using a retrospective cohort design. The research sample was obtained from medical record data of patients diagnosed with lung cancer of non-small cell carcinoma of the adenocarcinoma type who received conventional chemotherapy (Carboplatin and paclitaxel) and EGFR-TKI therapy from January 2020 to December 2022 at Dr. H. Abdul Moeloek Bandar Lampung, using the total sampling method (consecutive sampling). The data were processed using the SPSS 25.0 program, then survival analysis was carried out using the Kaplan-Meier product limit method. The log-rank test is used to get the difference between the sub-variables. Significance was determined with a p-value <0.05.

Results

Research subject data from the age variable were grouped into 4 categories, namely age < 45 years, 46 – 60 years, 61 – 75 years and > 75 years. In the group of subjects with EGFR-TKI therapy, the highest number of subjects was in the age range between 46-60 years, with 20 subjects (51.28%), as well as in the group of subjects with carboplatin-paclitaxel therapy with 31 subjects (58.49%). This data is shown in Figure 1.

Table 1. Data on the characteristics of the two groups of research subjects

Variable	Category	EGFR-TKI (N=39)		P-Value*	Chemotherapy with carboplatin-paclitaxel		P-Value**
		n	%		n	%	
Age	Mean	58.08 ± 12.3		0.980	54.11 ± 10.13		0.140
	Median	53.33			56.25		
	(min-max)	(32-84)			(31 – 77)		
Gender	Male	12	30.8	0.581	35	66	0.420
	Female	27	69.2		18	34	
Smoking status	Non- Smokers	26	66.67	0.497	15	28.3	0.450
	Smokers	13	33.33		38	71.7	
Staging	3B	5	12.8	0.577	8	15.1	0.412
	4A	32	82.1		34	64.2	
	4B	2	5.1		11	20.7	
	No data	20	51.3		34	64.2	
EGFR Mutation	Ex 18	1	2.6	0.748	0	0	0.518
	Ex 19 Del	13	33.3		0	0	
	Ex 21	5	12.8		0	0	
	WT	0	0		19	35.8	

Note:
*P-value from Shapiro-wilk
** P-value from Kolmogorof-Smirnof

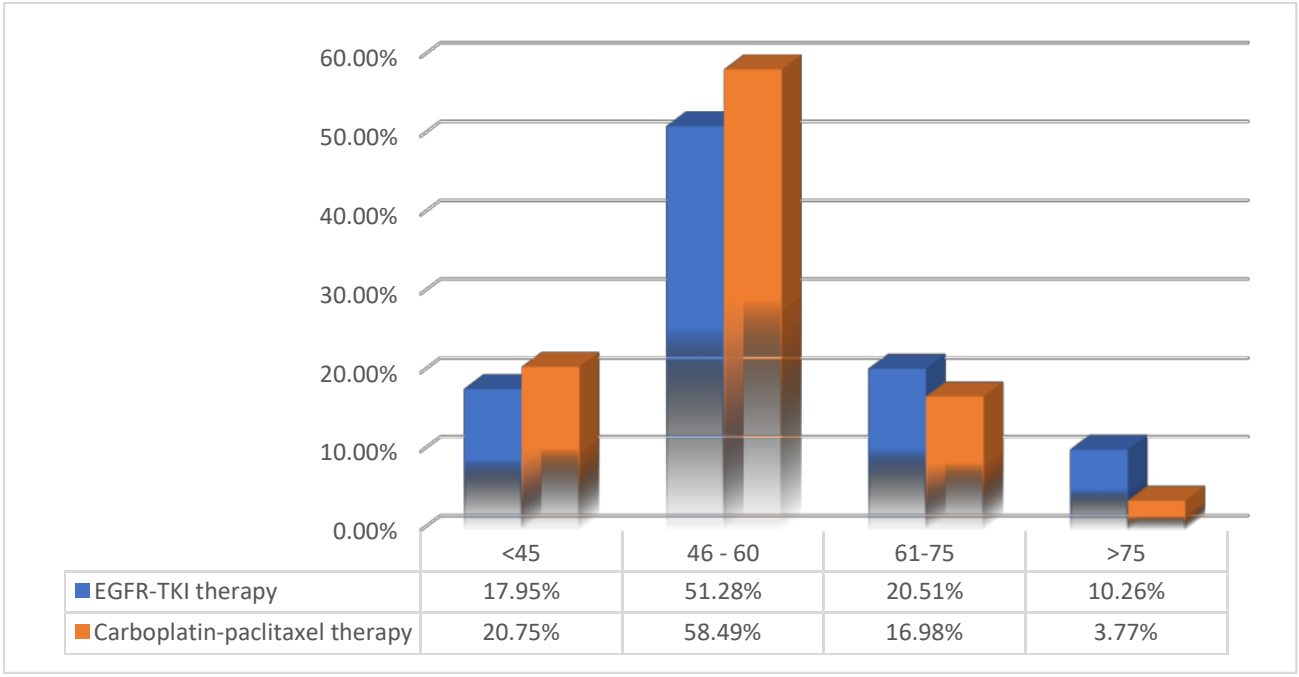

Figure 1. Description of the basic data on the characteristics of research subjects by age group

Survival Rate in The Adenocarcinoma Lung Cancer Group Receiving Systemic Therapy

In the Kaplan Meier chart in Figure 2. it is shown that 50% survival rate in the EGFR-TKI groups 7 months. Whereas in the paclitaxel carboplatin therapy group 50% survival rate was 5 months. Overall, 50% survival rate is 6 months.

The average survival rate in the EGFR-TKI group was 10.50 months with a 95% confidence interval between 7.28 and 13.72. The mean survival rate for the carboplatin-paclitaxel group was 7.81 months with a 95% confidence interval between 5.80 and 9.81. The mean survival rate for the two groups was 8.90 months with a 95% confidence interval between 7.10 and 10.66 and was not significantly different with a p-value > 0.05 (p = 0.209). Data analysis results are shown in Table 2.

Survival Rate in The Adenocarcinoma Lung Cancer Group Receiving Systemic and Influencing Factors

In the table of statistical analysis results with SPSS 25 (table 3) in the EGFR-TKI treatment group with Kaplan Meier the mean survival rate (mean) in women was 11.53 months with a 95% confidence interval between 7.29 to 15.78 (95% CI: 7.29-15.78). The mean survival rate for males was 8.13 months with a 95% confidence interval between 4.66 months and 11.60 (95% CI: 4.66-11.60). Statistically, there is no significant difference in the average survival rate with a value of p = 0.370 for men and women.

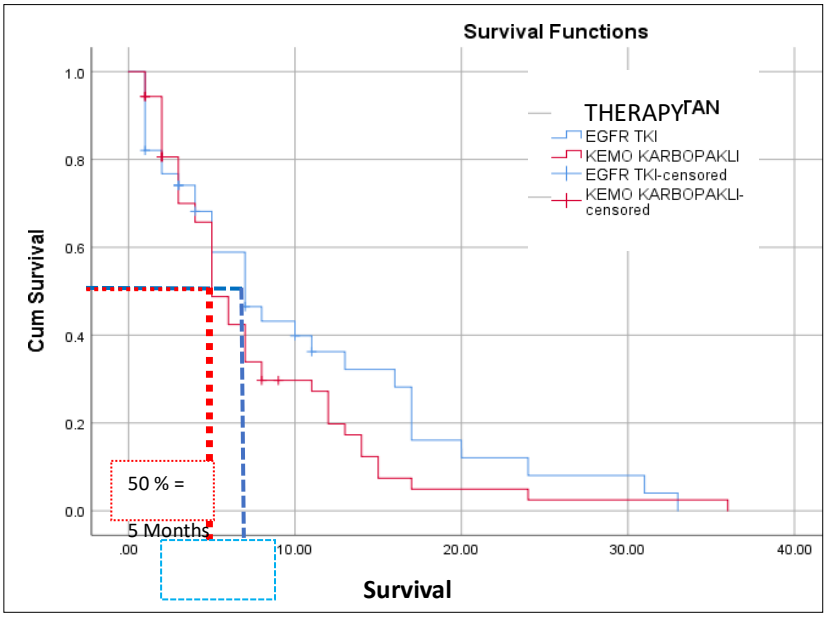

Figure 2. Kaplan Meier curve comparison survival rate EGFR-TKI Group with carboplatin-paclitaxel group of subjects with lung adenocarcinoma

Table 2. Analysis of differences in survival rates between the EGFR-TKI group and the paclitaxel-carboplatin group for subjects with lung adenocarcinoma

Therapy	Mean			Median			P-Value
	Estimate	95% CI		Estimate	95% CI		
		Lower bound	Upper bound		Lower bound	Upper bound	
EGFR-TKI	10.498	7.280	13.715	7.000	3.805	10.195	0.209
Chemotherapy	7.807	5.799	9.814	5.000	3.788	6.212	
Overall	8.875	7.094	10.656	6.000	4.836	7.164	

Table 3. The survival rate of the EGFR-TKI treatment group is based on independent variables

Variable	Catagory	Mean			Median			P-value
		Estimate	95% CI		Estimate	95% CI		
			Lower bound	Upper bound		Lower bound	Upper bound	
Age	<45	14.518	8.011	21.025	17.000	8.530	25.470	0.195
	46-60	12.049	6.215	17.883	7.000	4.389	9.611	
	61-75	6.375	2.545	10.205	7.000	2.199	11.801	
	> 75	5.750	0.000	13.715	1.000	-	-	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Gender	Male	8.130	4.656	11.604	7.000	.386	13.614	0.370
	Female	11.533	7.285	15.782	7.000	3.532	10.468	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Smoking status	Non smokers	12.419	7.980	16.858	7.000	3.664	10.336	0.088
	Smokers	7.000	3.764	10.236	7.000	000	14.105	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Staging	3B	16.000	6.066	25.934	11.000	0.000	23.413	0.614
	4A	9.803	6.279	13.326	7.000	4.545	9.455	
	4B	10.000	10.000	10.000	10.000			
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Mutation status	No Data	9.022	5.154	12.889	7.000	4.951	9.049	0.046
	Wild Type	-	-	-	-	-	-	
	Exon 18	1.000	1.000	1.000	1.000	-	-	
	Exon 19 Del	15.194	7.938	22.450	13.000	8.221	17.779	
	Exon 21	7.133	.223	14.044	5.000	1.681	8.319	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	

The survival rate in the EGFR-TKI group based on the age group was 14.52 months at the longest in the age group <45 years with a 95% confidence interval between 8.01 and 21.03 (95% CI = 8.01-21.03). The mean longer survival rate in this therapy group was also found in the non-smoking group, the 3B stage group and the exon 19 Del mutation status group. There was a significant difference in mutation status with p = 0.046.

The results of the analysis in Table 4.3 show that the Exon 19 Del mutation status has an average survival rate of 15.20 months (95% CI 7.938 – 22.450). However, the average survival rate based on age, sex, smoking status, staging and mutation status in the EGFR-TKI treatment group was not significantly different with an average of 10.50 months with a 95% confidence interval between 7.28 and 13.72.

Survival Rate in The Adenocarcinoma Lung Cancer Group Receiving Carboplatin-Paclitaxel Therapy

In the carboplatin – paclitaxel therapy group, the results of survival rate analysis using the Kaplan Meier test mean survival rate was 11.21 months with a 95% confidence interval between 7.03 and 15.39 (95% CI 7.029 – 15.388) based on independent variable factors, age group < 45 years. There was no significant difference in the mean survival rate in this group based on age, sex, smoking status, staging or mutation status with an average of 7.84 months, with a 95% confidence interval between 5.84 and 9.84 (95% CI 5.840 – 9.836). The results of the analysis of survival rates in the carboplatin – paclitaxel group are presented in Table 4.

Table 4. Survival rate in the carboplatin-paclitaxel group based on independent variables

Variable	Catagory	Mean			Median			P-value
		Estimate	95% CI		Estimate	95% CI		
			Lower bound	Upper bound		Lower bound	Upper bound	
Age	<45	11.208	7.029	15.388	14.000	0.000	31.344	0.084
	46-60	6.661	4.722	8.599	5.000	3.270	6.730	
	61-75	9.111	2.248	15.975	5.000	4.026	5.974	
	> 75	3.500	2.520	4.480	3.000	-	-	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Gender	Male	7.981	5.276	10.686	5.000	.3.788	6.212	0.978
	Female	7.500	4.971	10.029	7.000	3.245	10.755	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Smoking status	Non smokers	8.000	5.375	10.625	7.000	4.273	9.727	0.738
	Smokers	7.888	5.188	10.588	5.000	3.577	6.423	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Staging	3B	9.375	3.894	14.856	6.000	.3.228	8.772	0.245
	4A	6.818	4.147	9.490	5.000	4.136	5.864	
	4B	9.515	6.151	12.880	12.000	6.477	17.523	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Mutation Status	No Data	7.805	5.310	10.301	6.000	4.180	7.820	0.668
	Wild Type	7.820	4.964	10.676	5.000	2.720	7.280	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	

Discussion

Data on the characteristics of study subjects in the EGFR-TKI therapy group found that subjects with lung adenocarcinoma cancer were more common in women, and non-smokers, mean age of 58.08 ± 12.3. The age group between 45-65 years has the most lung cancer in both groups. The most common EGFR status mutations occurred in Exon 19 Del 13 (33.3%). In this study, 20 subjects received EGFR-TKI therapy but their mutation status was not recorded in the subjects' medical records. This result is different from the results of Novita's research at Adam Malik Hospital, data from 1 January 2014 - 31 December 2016 that the highestnumber of cases of EGFR mutations were exon 21.[6] The results of the same data as this study were obtained from Hendra Taufik's research on tissue biopsies and plasma ctDNA in several hospitals in Medan from April 2018 – February 2019 the highest number of Exon 19 Del mutationsfrom the two examinations.[7]

Based on gender, the smoking status of the results of this study differed from Novita's research from data on the characteristics of subjects with EGFR mutation lung adenocarcinoma at Adam Malik Hospital, males and more smokers. Based on the age group, the youngest subject was 32 years old and the oldest was 84 years old, in contrast to the results of Novita's study, there were no data obtained at ages <40 years.[6]

Lung adenocarcinoma subjects in the carboplatin – paclitaxel therapy group were mostly male and smoked according to the results of a study by MAW Wicaksono et al at Dr. Kariadi General Hospital Semarang 2014-2016.[8] The same study by Ungky AS et al at dr. Saiful Anwar Hospital Malang 2018-2019 in cases of wild-type lung adenocarcinoma were more common in men and smokers with a survival rate of 5.01 months (153 days).[9]

The mean survival rate for the EGFR-TKI treatment group for women (11.53 months) was longer than that for men (8.13 months) but was not statistically significantly different. Overall, the survival rate for men and women was 10.50 months longer than the paclitaxel carboplatin chemotherapy group, which was 7.81 months, but was not statistically significantly different. These results are different from the studies of Tomasini et al. in 2017 (8.38 months vs. 4.99 months) and Kawaguchi et al. in 2014 in Japan which stated that the survival rate (survival rate) of chemotherapy in adenocarcinoma Wild type was 10.1 months compared to 9 months in EGFR-TKI (erlotinib).[10,11]

This research was conducted during the Covid 19 pandemic where activity restrictions were imposed so that several research subjects were constrained in visiting the hospital.Comorbid factors in research subjects were not documented.

Conclusion

1. Gender, age, smoking status and staging showed no significant difference in the results of the survival rate analysis of the two groups. The status of the Exon 19 Del mutation had the longest survival rate and was statistically significantly different with p=0.046.
2. Overall, the average survival rate in the EGFR-TKI group was 10.50 months.
3. Overall, the average survival rate in the carboplatin – paclitaxel group was 7.84 months.
4. The median survival rate in the EGFR-TKI group for 7 months with a 95% confidence interval was between 3.81 and 10.20, while in the carboplatin-paclitaxel group for 5 months with a 95% confidence interval between 3.79 and 6,21. The overall median survival rate of the two groups was 6 months, with a p = 0.209 indicating that there was no significant difference between the two groups.

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