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Original Article

Prognostic factors in lung cancer patients with lung adenocarcinoma who received chemotherapy and EGFR TKI at H. Adam Malik Hospital Medan

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Abstract

Background: Lung cancer has a poor prognosis compared to other types of cancer because of its low survival rate. The management of lung adenocarcinoma includes a chemotherapy approach and targeted therapy with EGFR-TKI, but the outcome is still not optimal.
Aim: This study aims to determine the prognostic factors in lung cancer patients with lung adenocarcinoma who received chemotherapy and EGFR-TKI at H. Adam Malik Hospital, Medan.
Method: This is an analytic study with a retrospective cohort design conducted at the Oncology Polyclinic, H. Adam Malik Hospital from January 2017 to December 2019. The subjects were all patients with lung adenocarcinoma who received chemotherapy and EGFR-TKI treatment. Demographic and clinical evaluation data of patients were used to assess prognostic factors of adenocarcinoma patients who have been treated.
Results: The median length of life for patients receiving EFGR-TKI was 9 months (95% CI: 6,866 – 11,134 months). The median length of life of subjects receiving chemotherapy was 10 months (95% CI: 8,923 – 11,077 months), median progression-free survival (PFS) of patients receiving chemotherapy was 6 months (95% CI: 4,841 – 7,159 months) and patients receiving EGFR therapy for TKI was 6 months (CI 95%: 4,720 – 7,280 months). A log-rank test showed that there was a significant difference in median PFS between adenocarcinoma patients receiving EGFR TKI and chemotherapy (p = 0.013).
Conclusion: A significant difference was found in the median PFS between patients with lung adenocarcinoma who received EGFR-TKI and chemotherapy.

Keywords: *chemotherapy, EGFR-TKI, lung adenocarcinoma, PFS*

Abstrak

Latar belakang: Kanker paru memiliki prognosis yang buruk dibandingkan jenis kanker lainnya karena tingkat kelangsungan hidup yang rendah. Penatalaksanaan adenokarsinoma paru meliputi pendekatan kemoterapi dan terapi target dengan EGFR-TKI, namun hasilnya masih belum optimal.
Tujuan: Penelitian ini bertujuan untuk mengetahui faktor prognostik pada pasien kanker paru dengan adenokarsinoma paru yang mendapatkan kemoterapi dan EGFR-TKI di Rumah Sakit H. Adam Malik Medan.
Metode: Penelitian ini merupakan penelitian analitik dengan desain kohort retrospektif yang dilakukan di Poliklinik Onkologi RS H. Adam Malik dari Januari 2017 hingga Desember 2019. Subjek penelitian adalah seluruh pasien adenokarsinoma paru yang mendapatkan kemoterapi dan pengobatan EGFR-TKI. Data demografi dan evaluasi klinis pasien digunakan untuk menilai faktor prognostik pasien adenokarsinoma yang telah dirawat.
Hasil: Rata-rata lama hidup pasien yang menerima EFGR-TKI adalah 9 bulan (95% CI: 6.866 – 11.134 bulan). Median lama hidup subyek yang menerima kemoterapi adalah 10 bulan (95% CI: 8,923 – 11,077 bulan), median PFS pasien yang menerima kemoterapi adalah 6 bulan (95% CI: 4,841 – 7,159 bulan) dan pasien yang menerima terapi EGFR untuk TKI adalah 6 bulan (CI 95%: 4.720 – 7.280 bulan). Uji log-rank menunjukkan bahwa ada perbedaan yang signifikan dalam PFS median antara pasien adenokarsinoma yang menerima EGFR TKI dan kemoterapi (p = 0,013).
Kesimpulan: Terdapat perbedaan yang bermakna pada median PFS antara pasien adenokarsinoma paru yang mendapat EGFR-TKI dan kemoterapi.

Kata kunci: *adenokarsinoma paru, EGFR-TKI, kemoterapi, PFS*

Background

Lung cancer is a health problem in the world because of the death rate World Health Organization (WHO) reports that lung cancer is the most common cause of cancer death in 2020, which is 2,206771 cases.[1] The incidence of lung adenocarcinoma is increasing in Asia and North America, especially in women, young people and men who are not smokers. Lung adenocarcinoma in the United States reaches 31%-54% in male lung cancer patients who are non-smokers compared to 25%-33% of male lung cancer patients who smoke. Lung adenocarcinoma accounts for 49%-74% of female lung cancer patients who are non-smokers and 33%-43% of female lung cancer patients who smoke.[2]

Prognostic factor is one of the variables measured related to lung cancer. Prognostic factor is divided into three: Progression Free Survival (PFS), which is referring to survival without disease progression in clinical trials. A progression-free survival measure would compare the number of patients whose disease had progressed with the number whose disease had not progressed. Overall Survival (OS) is the overall survival refers to the fact that the patient does not die from any cause. Thus, in clinical trials, the OS measure will compare the number of patients who have died and the number who have not died. Survival rate in cancer with high malignancy such as lung cancer is 1-year survival and 2-year survival and 3-year survival. The 5-year survival rate for lung cancer patients in the United States reaches 15%, Europe 10% and in half of developing countries only 8.9%.[3]

Methods

This is an analytic study with a retrospective cohort design at the Oncology Polyclinic at H. Adam Malik Hospital Medan from January 2017 to December 2019. The sample was all lung adenocarcinoma patients who received chemotherapy and EGFR treatment for TKI who met the inclusion criteria, namely having proven of lung adenocarcinoma with cytological and histopathological results, who received the first EGFR-TKI targeted therapy from January 2017 to December 2019, received the first chemotherapy from January 2017 to December 2019. The exclusion criteria were having double primary cancer and incomplete medical record data. The total sample required was 96 patients by non-probability sampling with the technique of *consecutive sampling*.

The data that has been collected will be processed using the SPSS (Statistical Package for Social Science) software application. The univariate analysis was carried out to determine the one-year survival rate for each group which was presented in the frequency distribution table.

This analysis was continued by using the Kaplan Meier curve, the difference between drug A (chemotherapy) and drug B (EFGR-TKI) could not be detected if the incident parameter measured was the same between the two groups, the difference between drug A and drug B was only detected when what was measured was Incidence Rate parameters. Group B > Group A, indicating that group B's death was faster than group A. The difference was significant if the p-value < 0.05 was found.

Results

In this study, the surviving patients who received EGFR TKI were 7 subjects (7.3%) with a death rate of 89 subjects from 96 patients and a survival rate of 7.3% with a median length of life 9 months (95% CI: 6,866 – 11,134 months). Overall, for subjects who received EGFR TKI and chemotherapy, the number of subjects who passed away was 7 subjects (4.7%) with 143 deaths from 150 patients. The Kaplan Meier curve shows that the two lines intersect, which means that there is no significant relationship between the type of therapy and ATH in lung adenocarcinoma patients.

Table 1. Median length of life and ATH based on subject characteristics of adenocarcinoma patients receiving EGFR TKI and chemotherapy

Subject Characteristics	n	Events	Median Length of Life		ATH 30 Months		P*
			Month	95% CI	n	%	
Type of Therapy, n (%)							
EGFR TKI	96	89	9	6,866-11,134	7	7.3	0.350
Chemotherapy	54	54	10	8,211-11,789	0	0	
Overall	150	143	10	8,921-11,099	7	4.7	

*Kaplan Meier Curve

Progression Free Survival (Kaplan-Meier) Analysis of Lung Adenocarcinoma Patients receiving EFGR TKI

The median PFS of patients receiving EGFR TKI was 6 months (95% CI: 4,720 – 7,280 months. Variables in the bivariate analysis have p < 0.25. The bivariate analysis revealed that there were four variables that had p < 0.25, namely ethnicity (p = 0.218), history of TB (p = 0.154), performance status score (p = 0.058) and metastasis (p = 0.106). The four variables are candidates for modelling.

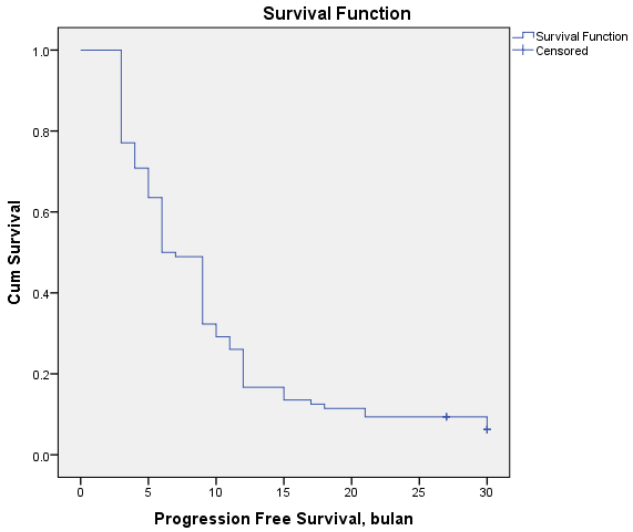

Figure 1. Kaplan Meier PFS curve of lung adenocarcinoma patients receiving EGFR TKI

Progression Free Survival (Kaplan-Meier) Analysis of Lung Adenocarcinoma Patients receiving Chemotherapy

The median PFS of patients receiving chemotherapy was 6 months (95% CI: 4.841 – 7.159 months). From the results of the analysis, there are five variables that have a p-value < 0.25, namely age (p = 0.185), ethnicity (p = 0.236), history of TB (p = 0.183), performance status score (p = 0.030) and metastasis (p =0.093). The five variables are candidates for modelling.

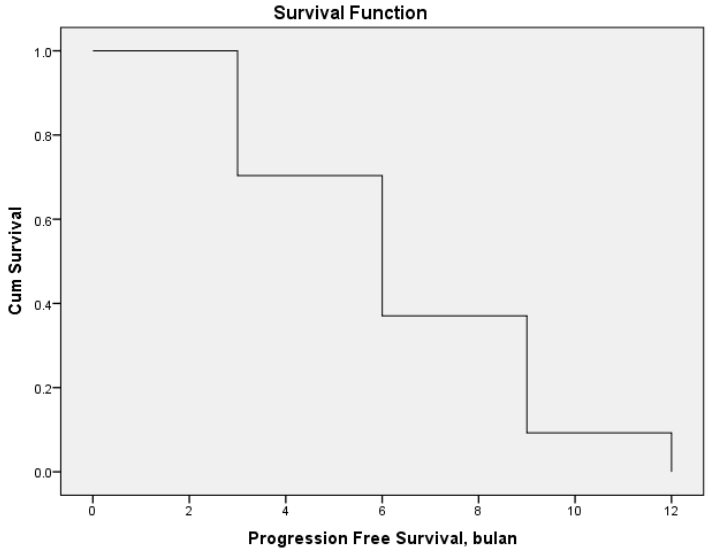

Figure 2. Kaplan Meier PFS curve for lung adenocarcinoma patients receiving chemotherapy

PFS Analysis of Lung Adenocarcinoma Patients receiving EGFR TKI Therapy and Chemotherapy

The median PFS in lung adenocarcinoma patients receiving EGFR TKI therapy was 6 months (95% CI: 4,720 – 7,280 months). Meanwhile, the median PFS of patients receiving chemotherapy was 6 months (95% CI: 4.841 – 7.159 months). The log-rank test showed that there was a significant difference in median PFS between adenocarcinoma patients receiving EGFR TKI and chemotherapy (p = 0.013). The PFS curve of lung adenocarcinoma patients receiving EGFR TKI and chemotherapy can be seen in Figure 3. The Kaplan Meier curve shows that the two lines intersect, which means that there is no significant relationship between the type of therapy and PFS in lung adenocarcinoma patients. The Proportional Hazard assumption is not met, which means that the ratio of PFS by type of therapy is not constant.

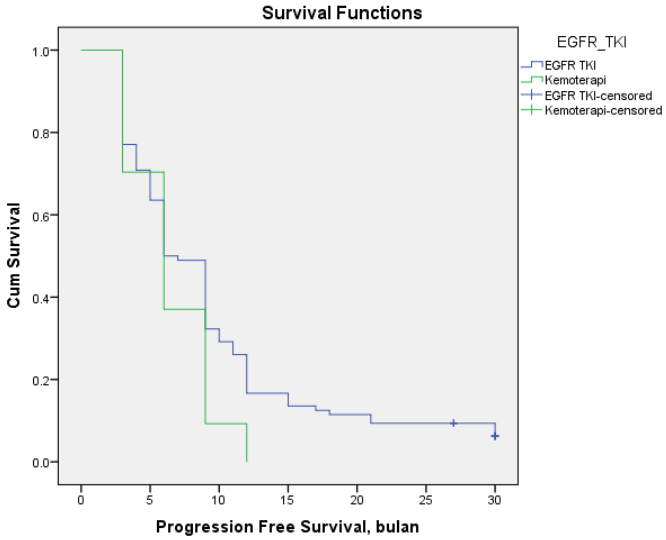

Figure 3. Kaplan Meier's PFS curve for lung adenocarcinoma patients receiving EGFR TKI and chemotherapy

Table 2. Median PFS of adenocarcinoma patients receiving EGFR TKI and chemotherapy

Subject Characteristics	n	PFS median		Mean PFS		p
		Month	95% CI	Month	95% CI	
Type of Therapy, n (%)						
EGFR TKI	96	6	4,720-7,280	9,552	7,995-11,109	0.013
Chemotherapy	54	6	4,841-7,159	6.5	5,727-7,273	

***Kaplan Meier curve**

Discussion

Chemotherapy in Patients with Lung Adenocarcinoma

Chemotherapy agents block the cell cycle and attack rapidly dividing cells. This traditional treatment has low specificity, attacking normal cells as well as cancer cells, and causing significant side effects. The impact of this evolution of LC treatment is reflected in the increase in the 5-year survival rate of patients, which jumped from 10.7% in the early 1970s to 19.8% in the 2010s. The nab-Paclitaxel group also showed higher median OS (12.1 vs 11.2 months) and median PFS (6.3 vs 5.8 months) compared to other groups (p values = 0.271 and 0.214, respectively).[4] Not different from this study, Dong analyzed commonly used third-generation new chemotherapy drugs in combination with a platinum regimen had an overall effect resulting in a significant improvement in survival (HR, 0.79; 95% CI, 0.62-1.00; p = 0.05) and an 11% increase in 5-year survival (67% with chemotherapy vs 56% with observation), however, median survival is only 8-10 months.[5]

EFGR - TKI in Patients with Lung Adenocarcinoma

Anti-EGFR therapy consists of tyrosine kinase inhibitors (TKIs), drugs that target EGFR binding. First-generation drugs bind reversibly to the ATP-binding site of EGFR and inhibit phosphorylation, blocking the signaling pathway associated with EGFR. Second-generation TKI irreversibly blocks EGFR's tyrosine-kinase activity by causing a covalent modification of the protein's catalytic domain. The effectiveness of the first and second-generation TKI depends on the mutation that the EGFR has. Approximately 70% of all EGFR-mutated tumors respond clinically to TKIs, shrinking considerably in response to these drugs. The remaining 30% are intrinsically resistant to TKI drugs (which is referred to as de novo resistance).[4]

Osimertinib (Tagrisso) is a 3rd generation TKI that forms irreversible covalent bonds with EGFR, specifically targeting the T790M mutation. Bartholomew demonstrated a progression-free survival of 9.6 months. Treatment is generally well tolerated. Survival with erlotinib was 6.7 months compared with 4.7 months with placebo.[6,7] Slightly different results from this study, regarding a significantly longer treatment failure time with afatinib compared with gefitinib [median 13.7 months vs. 11.5 months (10.1-13.1)]. However, no significant differences were found in the previously defined del 19 or L858R mutation subgroups.[8]

In contrast to the present study, the ARCHER study, the PFS of the dacomitinib group was statistically prolonged compared with the gefitinib group (14.7 versus 9.2 months by independent review).[2] In 2009, the first large randomized controlled study, IPASS, showed that gefitinib significantly prolongs PFS in lung cancer patients with EGFR mutations associated with carboplatin-paclitaxel. The FLAURA study showed that regardless of the detected T790M mutation, the PFS of the first-line treatment group with osimertinib was 18.9 months, whereas the median PFS of the first-line standard treatment of first-generation EGFR-TKI was only 10.2 months, and patients with osimertinib had high safety. Therefore, first-line use of osimertinib may have a longer FPS than switching to osimertinib after first-generation EGFR-TKI resistance.[5]

Administration of the targeted drug osimertinib to NSCLC patients with epidermal growth factor receptor (EGFR) mutation T790M, showed a significantly longer mean duration of progression-free survival (PFS) with osimertinib compared with platinum-pemetrexed (10.1 vs 4.4 months; HR: 0.30).[5] For all patients with EGFR-activating mutations, the mean OS was 17.5 months, and Cox analysis showed that adeno-carcinoma (Hazard Ratio 5.650), recurrent disease (Hazard Ratio 1.976), or treatment with EGFR-TKI (Hazard Ratio 2.525) was associated with an increase in OS.[9]

Patients taking gefitinib had a significantly prolonged PFS (median, 10.8 vs. 5.4 months) and a higher response rate (74% vs. 31%).[10] Both PFS (median, 13.1 vs. 4.6 months) and ORR (83% vs. 36%) were better in the erlotinib group. The ENSURE phase III trial confirmed these results in patients with EGFR mutation-positive NSCLC from China, Malaysia, and the Philippines. In a European EGFR-mutated population, the effectiveness of erlotinib was demonstrated in the EURTAC study (European Tarceva versus Chemo-therapy). First-line erlotinib increased ORR (64% vs. 18%) and a longer PFS (median, 9.7 vs. 5.2 months) compared with chemotherapy.[10]

The primary endpoint PFS was longer for patients receiving afatinib (median, 11.1 vs 6.9 months) and higher response rates were observed with afatinib (56% vs 23%). PFS was statistically increased with afatinib (median, 11 vs 10.9 months), as well as treatment failure time (median, 13.7 vs 11.5 months) and ORR was higher with afatinib. Adverse events grade 3 or higher in patients receiving afatinib were diarrhea (13%), rash/acne (9%) and fatigue (6%). A recent analysis reported a median overall survival of 27.9 months in patients who had received afatinib compared with 24.5 months in patients taking gefitinib.[10] Among mono-therapy patients, PFS was significantly lower in the poor prognosis group (exons 4 and 6) compared to the good prognostic group.[11]

Exon 19 deletions were identified in 52 patients in the afatinib group and 326 patients in the erlotinib group, and exon 21 mutations were found in 35 and 268 patients, respectively. The median time to next treatment (TTNT) was similar between these treatment groups for both mutations; the median TNNT was 12.6 months (95% CI 9.0-17.5) with afatinib and 14.0 months (95% CI 12.4-15.3) with erlotinib for patients with exons 19, and 11 deletions, 2 months (95% CI 8.7–16.2) and 12.1 months (95% CI 10.6–14.2), respectively, for patients who had the exon 21 mutation. Median OS appeared numerically longer in patients whose tumors harbored an exon 21 mutation treated with erlotinib (19.9 months, 95% CI 17.3-24.2) vs. afatinib (16.2 months, 95% CI 11.0 -26.1), but this difference was not statistically significant. In patients with exon

19 deletion, median OS was similar between the treatment groups: 23.0 months (95% CI 18.1–not achieved) with afatinib and 24.6 months (95% CI 23.2–29.0) with erlotinib.[12]

Comparison of TKI EFGR Therapy and Chemotherapy in Patients with Lung Adenocarcinoma

The AURA phase III study found that osimertinib improved PFS by 5.7 months and disease control rate (DCR) by 19% when compared to standard chemotherapy for NSCLC. The FLAURA phase III study compared osimertinib with first-generation TKI and found a statistical improvement in PFS, which extended from 10.2 to 18.9 months. The FLAURA trial established Osimertinib as the standard of care at the forefront, while impressive results over Crizotinib have been shown, with PFS 18.9 months vs. 10.2 months, HR 0.46; 95% confidence interval (CI), 0.37 to 0.57; p < 0.001); in follow-up at 3 years, 79 of the 279 patients (28%) in the Osimertinib arm and 26 of 277 (9%) in the Crizotinib were alive.[4]

EGFR-TKI was associated with shorter PFS compared with cytotoxic chemotherapy (HR: 1.41; 95% CI: 1.10–1.81). A lower objective response rate (RR) was also noted with TKI compared to chemotherapy (7.2% versus 16.8%, respectively). Likewise, in the Chan et al study, PFS was significantly prolonged with gefitinib compared with chemotherapy [HR 0.48 (95% CI, 0.36-0.64); P<0.001]. In contrast, patients with wild-type EGFR fare better with chemotherapy [HR 2.85; (95% CI, 2.05-3.98); P<0.001]. Overall PFS was not significantly different but after reviewing gefitinib-treated patients, the activating EGFR mutation predicted a superior overall response rate (ORR) (84.6% vs. 25.9%, P<0.001) and a significantly longer PFS. (HR 0.377; 95% CI, 0, 21-0.67; P<0.001).[6] The median PFS of chemotherapy in patients with the exon 21 L858R point mutation was 1 month longer than that of the exon 19 deletion. In the fusion results of the LUX-Lung-3 and 6 studies, differences in OS were noted in patients with tumours with exon 19 deletion, but not in patients with the exon 21 L858R point mutation, although there was no significant difference in OS between exons 19 and 21 in the LUX-Lung 7 study.[8]

Gefitinib was not inferior concerning OS with a median of 7.6 months with gefitinib and 8.0 months with docetaxel, HR 1.02 (95% CI, 0.905-1.150). Further trials with second-line gefitinib and erlotinib demonstrated superior response rates, PFS, and quality of life without significant differences in OS compared with chemotherapy.[6]

In the study of Yang et al., patients receiving combination therapy had a significantly longer PFS than patients receiving monotherapy (19.1 months vs. 14.2 months, P=0.018, HR=0.598 95%CI, 0.391-0.914). Compared with patients with an EGFR of 19del, patients with an EGFR of 21L858R tended to have a shorter PFS in the monotherapy group (12.5 months vs. 15.7 months, P=0.133), whereas they benefited more from combination therapy (19del: 19.0 months vs 15.7 months, P = 0.234, HR = 0.709; 21L858R: 19.3 months vs. 12.5 months, P = 0.046, HR = 0.516).[11]

Prolonged PFS relative to chemotherapy was also demonstrated with afatinib in the LUX-Lung 3 trial (HR 0.47 [95% CI 0.34–0.65], p < 0.001; mean PFS 13.6 months vs. 6.9 months, respectively). However, OS did not differ significantly between treatment groups in the ENSURE study (median OS: erlotinib 26.3 months vs chemotherapy 25.5 months), or in the individual LUX Lung-3 or Lung-6 studies when comparing afatinib with chemotherapy. Similar results were seen in an exploratory subgroup analysis of patients diagnosed with advanced EGFR Mut+ NSCLC after May 2013 (n = 744), following FDA approval for afatinib. The median OS with erlotinib (n = 461) was 23.1 months (95% CI 20.4–25.5), compared with 20.7 months (95% CI 16.2–35.1) with afatinib (n = 87) and 19.3 months (95% CI 17.0–26.2) with chemotherapy (n = 115).[12]

Conclusion

There was a significant difference in median PFS between patients with lung adenocarcinoma who received EGFR TKI and chemotherapy.

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