Original Article

One Year Survival of Wild-Type Adenocarcinoma Lung Cancer Patients Receiving Chemotherapy at dr. Saiful Anwar Hospital, Malang

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Abstract

Background: Lung cancer is one of the most common malignancies that leads to mortality. In Indonesia, lung cancer ranks first in men and third in women. The most common histological type of lung cancer is adenocarcinoma. Adenocarcinoma lung cancer is divided into 2 types, namely EGFR mutations and no mutations (wild-type). Chemotherapy is the treatment of choice for advanced wild-type adenocarcinoma lung cancer. This study aimed to assess the one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy.

Method: This study used a cross-sectional study design.Data were taken from the medical records of cancer patients at Dr. Saiful Anwar Hospital Malang in 2018-2019. Data were processed and analyzed by chi-square test.

Results: Of the 54 subjects, 24 patients received carboplatin/ pemetrexed (44.4%), 15 patients received carboplatin/paclitaxel (27.8%), 9 patients received carboplatin/gemcitabine (16.7%), 2 patients received pemetrexed (3.7%), and 4 patients received gemcitabine (7.4%). The chemotherapy drug regimen had no correlation with one-year survival (P=0.899).

Conclusion: There wasno significant difference between one-year survival andchemotherapy drug regimens. This study required a larger sample to minimize bias.

Keywords: adenocarcinoma, wild-type, chemotherapy, survival rate

INTRODUCTION

Lung cancer is one of the most common cancers and causes many deaths. Based on cancer profile data from the World Health Organization (WHO), lung cancer in Indonesia ranks first in men, around 21.8% of the 103,100 deaths due to cancer in 2014, while in women it ranks third around 9.1% of the 92,200 deaths along with trachea and bronchial cancer. Smoking is the main cause of lung cancer in Indonesia.[1]

WHO divides lung cancer into 2, non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). The NSCLC accounts for about 80% of lung cancer cases and is divided into 3 subtypes, namely adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[2] Adenocarcinoma is the most common case, accounting for about 40% of all lung cancer cases. Approximately 70% of patientsdiagnosed with lung cancer present with an advanced stage (stage 3 or 4).[3]

Adenocarcinomas are divided into 2 types based on genetic information: adenocarcinomas with mutations such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) rearrangement mutations and adenocarcinomas without mutations.[4] EGFR mutations are common in adenocarcinoma lung cancer and EGFR tyrosine kinase inhibitors (EGFR-TKI) are the first line therapy to improve patients survival.[5] Lung cancers that do not activate the EGFR mutation are called wild-type.[6]

Chemotherapy is a therapeutic option for patients with wild-type adenocarcinoma.[7] The recommended first-line chemotherapy regimen is platinum-based chemotherapy such as cisplatin or carboplatin in combination with taxanes (paclitaxel or docetaxel), antimetabolites (gemcitabine or pemetrexed), or vinca alkaloids (vinorelbine). Second-line chemotherapy regimens such as docetaxel, gemcitabine, paclitaxel, or single agent pemetrexed may be used for advanced patients who failed with platinum-based first-line chemotherapy.[3]

Several studies have shown that in wild-type adenocarcinoma, chemotherapy is more effective than EGFR-TKI. A study conducted by Tomasini et al in 2017 stated that chemotherapy for wild-type adenocarcinoma patients had a survival rate of 8.38 months and a 1-year survival rate of 37.8%, while the survival rate for EGFR-TKI was 4.99 months and the 1-year survival rate was 28%.[5]

Study by Kawaguchi et al in 2014 also verified that chemotherapy had a higher survival rate for wild-type adenocarcinoma, which was 10.1 months compared to 9.0 months for erlotinib. Another trial conducted by Kimura et al in 2016 pointed out that the carboplatin/pemetrexed combination has become the standard for wild-type adenocarcinoma lung cancer because of its good efficacy, controllable toxicity and 12.7 month survival.[8]

Based on the description above, study on one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy has not been widely carried out, especially in Malang. Therefore, this study was conducted to determine the one-year survival rate of wild-type adenocarcinoma lung cancer patients receiving chemotherapy at Dr. Saiful Anwar Hospital Malang.

METHOD

This was an observational cross-sectional study using secondary data taken from medical records at Dr. Saiful Anwar Hospital Malang in 2018-2019. The data obtained were entered in a google form

and put together in Ms. Excel. Data werethen analyzed using chi-square test. This study was approved by the ethical clearance board of Dr. Saiful Anwar General Hospital, Number: 400/192/K.3/302/2021.

RESULTS

This study used data from medical records of wild-type adenocarcinoma lung cancer patients at dr. Saiful Anwar Hospital Malang who received chemotherapy in 2018-2019. There were 54 subjects that met the inclusion and exclusion criteria. The characteristics of the subjects can be seen in Table 1.

Table 1. Characteristics of wild-type adenocarcinoma lung cancer patients receiving chemotherapy at dr. Saiful Anwar Hospital Malang in 2018-2019

Characteristic	N	%
Gender		
Male	37	68.52
Female	17	31.48
Age		
≤60 years	35	64.81
≥60 years	19	35.19
History of smoking		
Active smoker	34	62.96
Passive smoker	4	7.41
Non-smoker	12	22.22
No data	4	7.41
Drug regimen		
Carboplatin/pemetrexed	24	44.44
Carboplatin/paclitaxel	15	27.78
Carboplatin/gemcitabine	9	16.67
Pemetrexed	2	3.70
Gemcitabine	4	7.41

Based on the history of smoking, we obtained the one year survival. There were 3 subjects survived more than a year among those who had a history of being an active smoker, while 31 subjects survived only less than 1 year. Among the non-smoker patients, there were 2 subjects who survived more than 1 year, and 10 subjects survived less than a year. For patients who were passive smokers and not recorded in the data, none of them could survive more than 1 year.

Table 2. Correlationofone-year survival to gender, age, smoking history, and drug regimen

Characteristic	N	P
Gender		
Male	37	0.667*
Female	17	
Age		
≤60 years	35	0.813*
≥60 years	19	
History of smoking		
Active smoker	34	
Passive smoker	4	0.658*
Non-smoker	12	
No data	4	
Drug regimen		
Carboplatin/pemetrexed	24	
Carboplatin/paclitaxel	15	
Carboplatin/gemcitabine	9	0.899*
Pemetrexed	2	
Gemcitabine	4	

Note: *P>0.05 indicates that there is no significant difference between variables, while P<0.05 indicates a significant difference between variables.

In terms of the drug regimen given, one year survival was also observed in patients. Among those who received carboplatin/pemetrexed combination, only 3 out of 24 patients survived more than 1 year, while the same survival rate was observed in only 1 from 15 patients received carboplatin/paclitaxel combination and also in only 1 out of 9 patients who received the combination of carboplatin/ gemcitabine. No patients who received

pemetrexed or gemcitabine as a single agent could survive more than 1 year.

In this study, the analysis was carried out by Chi-Square test using the SPSS version 25 which assessed the correlations between one year survival to gender, age, smoking history and drug regimens. The results were shown in Table 2.

There were no significant differences between gender and one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy (P=0.667). The similar result was also found in age (P=0.813), smoking history (P=0.658), and drug regimen (P=0.899).

This study also performed an analysis using the Kaplan-Meier curve to assess the one-year survival of wild-type adenocarcinoma lung cancer patients who received chemotherapy. One year survival in patients who received carboplatin/pemetrexed was 12.5% with a median of 207 days. In patients who obtained carboplatin/paclitaxel it was 6.7% with a mean of 153 days while inthose received carboplatin/gemcitabine it was 11.1% with a mean of 198 days.

Table 3. One-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy in 2018-2019

Therapy	Mean (days)	One-year survival (%)
Carboplatin/pemetrexed	207	12.5
Carboplatin/paclitaxel	153	6.7
Carboplatin/gemcitabine	198	11.1
Pemetrexed	12	0
Gemcitabine	48	0

In this study, patients receiving single-agent pemetrexed and gemcitabine chemotherapy had a one-year survival of 0% because none of these patients survived more than 1 year with a median survival of 12 days for pemetrexed and 48 days for gemcitabine. Table 3 represents the summary while Figure 1 exhibits the *Kaplan-Meier* curve.

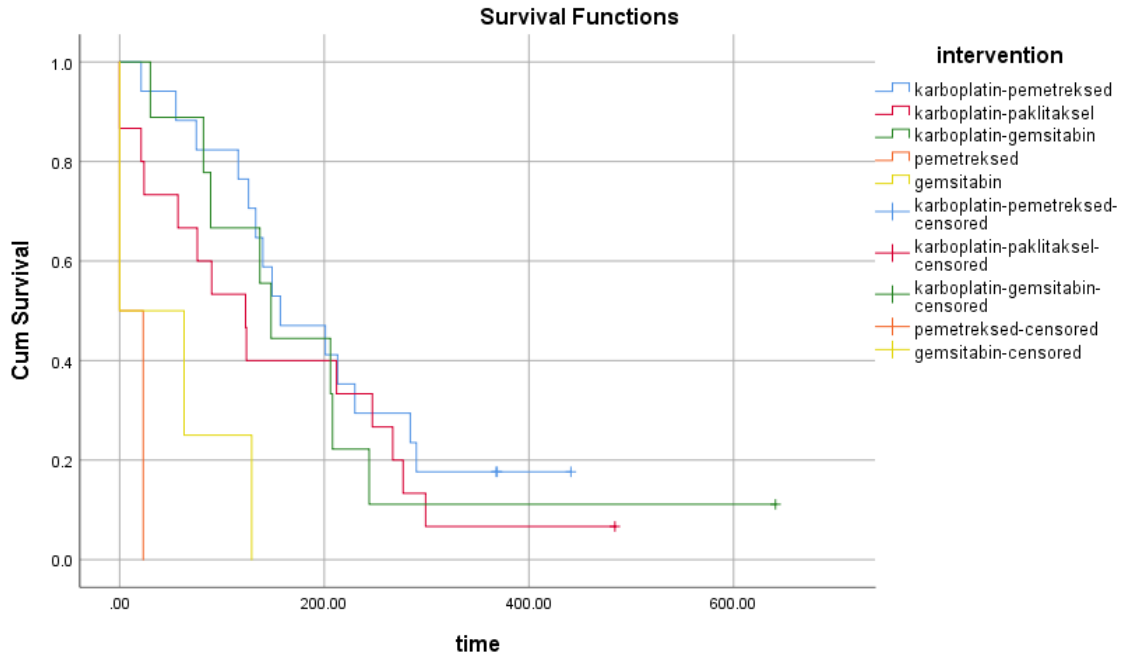

Figure 1. Kaplan-Meier curve comparison of one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy at dr. Saiful Anwar Hospital Malang in 2018-2019.

DISCUSSION

The data used in this study pointed out that there were 54 medical records in Dr. Saiful Anwar Hospital Malang for wild-type adenocarcinoma lung cancer patients who received chemotherapy in 2018-2019. Adenocarcinoma lung cancer can affect both male and female patients. In this study it was found that more cases occurred in male patients. This is in accordance with a study in Indonesia which stated that adenocarcinoma lung cancer was more common in men than women.[9] Reinforced by data from WHO, cases that occurred in Indonesia on 2014 consisted of 25,322 cases in men and 9,374 cases in women.[1]

Study conducted by Wicaksono et al in 2020 concluded that males and smokers were more at risk of developing wild-type adenocarcinoma lung cancer.[10] This study also obtained more patients with a history of active smoking. Based on the age, most of the subjects this study were less than 60 years old, similar to the study from Soetandyo et al in 2020.[9] However, the opposite was observed in the study of Laily et al in 2020 which obtained that more lung cancer patients were the age of more than 50 years.[11]

Based on the chemotherapy drug regimen, 48 patients were given the combination of chemotherapy and 6 patients received single-agent chemotherapy. Combination chemotherapy is the mainstay of therapy whereas single agent chemotherapy is directed to patients who are elderly or have less than 2 appearances.[12] In our study, the carboplatin/pemetrexed combination was the most widely used. This was based on the guidelines which stated that carboplatin/pemetrexed was the main choice of first-line therapy for wild-type adenocarcinoma lung cancer because it had good efficacy and lower side effects.[13]

In this study, there were more male subjects and subjects with a history of active smoking developed wild-type adenocarcinoma lung cancer. In general, lung cancer tends to occur in men because more men smoke.[14] Previous studies on both adenocarcinoma lung cancer with EGFR mutations and wild-type adenocarcinoma have shown better outcomes in women than in men.[15]

Similar results were obtained in this study, the percentage of female patients who survived more than 1 year was greater than that of men. The study of Tseng et al in 2017 also revealed that active smokers had poorer survival among adenocarcinoma lung cancer patients with both EGFR mutations and wild type. This study also expressed similar results based on history of smoking: the percentage of patients who did not smoke had a one-year survival greater than the active smokers and passive smokers. Although between men and women, the smoking history did not produce a significant difference.[15]

Elderly patients had poorer survival than younger patients.[16] This was because elderly patients tended to experience changes in physiological conditions and decreased immunity, such as slowed and reduced cilia which might facilitate

infection, and also hypertrophy of the mucus glands and dilated bronchi.[17] However, this study observed the opposite result in elderly patients who had a greater one-year survival than younger patients, although there was no significant difference in the results.

Based on the chemotherapy drug regimen, carboplatin/pemetrexed had the highest survival at 12.5% with a median of 207 days, followed by carboplatin/ gemcitabine with 11.1% and a mean of 198 days. Furthermore, carboplatin/paclitaxel had a one-year survival of 6.7% with a mean of 153 days, whereas the single agents, each pemetrexed and gemcitabine had a 1-year survival of 0%. The selected platinum-based regimen used carboplatin only. Carboplatin is an option when the side effects of cisplatin are intolerable. Carboplatin causes side effects of hematotoxicity, while cisplatin can cause nausea, vomiting, neutropenia, anemia, thrombocytopenia, peripheral neuropathy, and tinnitus.[18]

Previous studies have shown that carboplatin/pemetrexed had good efficacy, controlled toxicity and survival of 12.7 months so that this combination could be a standard therapy in wild-type adenocarcinoma lung cancer.[8] A study by Joerger et al in 2009 stated that there was no significant difference between carboplatin/pemetrexed and carboplatin/ gemcitabine. Both combinations also had side effects of neutropenia and thrombocytopenia. Moreover, there were grade 3 and 4 haematological toxicity in carboplatin/gemcitabine.[19]

Our study obtained the identical results which did not observe a significant difference between chemotherapy drug regimens on one-year survival. This was due to no further research on the side effects of each drug was conducted in this study and the sample distribution was uneven (from all data, there were only 5 patients who survived more than 1 year).

CONCLUSION

In this study, the incidence of wild-type adenocarcinoma lung cancer was most common in men, age less than 60 years, and had history of active smoking. Most of the patients received carboplatin/ pemetrexed combination chemotherapy. One-year survival did not show significant differences between variables such as gender, age, smoking history, and chemotherapy drug regimen.

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