Section A-Research paper
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Effectiveness of Carboplatin-Paclitaxel with Cisplatin-Paclitaxel in Patient with Non-Small Cell Lung Cancer in Advance Stage in Riau Province, Indonesia

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Abstract: Effectiveness data is an important parameter that describes the successful work of a drug in daily clinical practice and can provide recommendations to policy makers in hospitals when evaluating or reviewing drugs for hospital formularies. Research on the effectiveness of carboplatin-paclitaxel for advanced Non-Small Cell Lung Cancer (NSCLC) patients is still limited in Indonesia. This study aims to compare the effectiveness of carboplatin-paclitaxel with carboplatin-paclitaxel in patients with advanced NSCLC. This study is an observational retrospective cohort study that observed the medical records of advanced NSCLC patients at the Arifin Achmad Regional General Hospital, Riau Province with a time span of January 2020 to Desember 2021. Effectiveness seen in Progression free Survival (PFS) and Overall Survival (OS) based on the patient's medical record and analyzed using the Kapplan Meier method of survival analysis. A total of 90 samples met the research criteria where 85 patients had used carboplatin-paclitaxel and 5 patients had used cisplatin-paclitaxel. Carboplatin-paclitaxel had a longer PFS (63 days or 2 months) than cisplatin-paclitaxel (8 days or 0 months) with p = 0,098; 95% CI = 0,850-5,376 the same goes for OS events, where carboplatin-paclitaxel had a longer OS (426 days or 14 months) than cisplatin-paclitaxel (148 days or 5 months) with p = 0,226; 95% CI = 0,415-27,685. The Effectiveness of carboplatin-paclitaxel with cisplatin-paclitaxel was not statistically significant. However, when viewed from external parameters (PFS and OS), showed that the effectiveness of carboplatin-paclitaxel was better than cisplatin-paclitaxel as the first- choice therapy in NSCLC patients.

Keywords**: Effectiveness, Carboplatin-paclitaxel, Cisplatin-paclitaxel, Non-Small Cell Lung Cancer**

INTRODUCTION

Cancer is a disease that occurs because of abnormal cells that grow uncontrollably, have the ability to invade and move between cells and tissues (1). Data from Global Burden of Cancer (GLOBOCAN) states that the largest country that contributes to cancer cases is Asia. This is because some countries in the Asian region have large populations such as China, India, and Indonesia (2). Data form Riset Kesehatan Dasar (Riskesdas) in 2018 reported that there was an increase in the prevalence of cancer from 1,4 per 1000 population in 2013 to 1,8 per 1000 population in 2018 (3). Based on prevalence, the most common cancer found in the world is breast cancer (11,7%), lung cancer (11,4%) and colorectal cancer (10%). while in Indonesia, most cancer is breast cancer (16,6%), cervical cancer (9,2%), and lung cancer (8,8%). In term of gender, the most common suffered by men is lung cancer (14,1%), colorectal cancer (11,9%), and liver cancer (9%), while in women is breast cancer (30,8%), cervical cancer (17,2%) and ovarium cancer (7%) (2).

Lung cancer is one of the most common cancers that cause morbidity and mortality in the world. Lung cancer is a non-communicable disease, a type of malignant tumor originating from the epithelium of the respiratory tract, namely the bronchial epithelium or from the lung cancer (primer)(4). Lung cancer is the leading cause of cancer death in the world, which is 18% (1.796.144 populations), in Indonesia lung cancer is also in the first place in cancer deaths, namely 13,2% (2). Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all lung cancer cases, which consist of *non-squamous carcinoma (adenocarcinoma, large-cell carcinoma*, and other cell types) and squamous cell carcinoma. Approximately 80% of NSCLC cases are advanced stage patients (*stage* IIIB/IV) (5)(6).

The first line treatment for advanced NSCLC ia chemotherapy consisting of platinum-based chemotherapy (cisplatin and carboplatin) and non-platinum-based chemotherapy which is a new generation of drugs (*etoposide, gemcitabine, paclitaxel,* dan *vinorelbine*) (7). The goals of chemotherapy in patients with advanced NSCLC is palliative therapy, namely chemotherapy plays a role in reducing existing symptoms (8).

An important parameter to see the success of a drug is seen from the effectiveness of a drug. Effectiveness is the ability of a drug to show improvement in the patient's health after its use. One of the outcome parameters for effectiveness in NSCLC patients is overall survival (OS) where is the time from initial diagnosis to death and progression free survival (PFS) is the time from initial diagnosis of disease to pregression of disease severity, tumor size shrinkage, and brain, lymph mode and other metastases (9).

Research related to the effectiveness of carboplatin-paclitaxel and cisplatin-paclitaxel in patients with advanced NSCLC in daily clinical practice is still limited, especially in Indonesia, in Riau Province. It is necessary to do research on the effectiveness of carboplatin-paclitaxel and cisplatin-paclitaxel in Indonesia, considering the conditions in each country are different both in terms of race and culture, so that researchers are interested in conducting a study with the aim of comparing the effectiveness of carboplatin-paclitaxel with cisplatin-paclitaxel in patients with advanced NSCLC in Riau Province.

Materials and Methods

Subject

This study is an observational retrospective cohort study by looking at the medical records of advanced NSCLC patients using carboplatin-paclitaxel with cisplatin-paclitaxel at the Arifin Achmad Regional General hospital, Riau Province in January 2020-December 2021. The sample in this study is a sample that has met the inclusion criteria and exclusion criteria. The inclusion criteria in this study were patients with advanced NSCLC with first-line chemotherapy, namely carboplatin-paclitaxel or cisplatin-paclitaxel. While the exclusion criteria were patients with incomplete medical record data consisting of medical record number, age, gender, occupation, education, cancer stage, cate of diagnosis, doctor's note, time of last patient visit, and treatment.

Data Analysis

Patient data collection is done by reviewing the patient's medical record to see the effectiveness of treatment therapy and patient characteristics (age, gender, occupation, and education level). The effectiveness measured is Overall Survival (OS), which is the time from initial diagnosis to death and Progression Free Survival (PFS) which is the time from the initial diagnosis of the disease until the development of the disease (pleural/pericardial effusion, brain metastases, and other metastases). Effectiveness amalysis using Kapplan Meier survival analysis method to obtain patient survival.

Results and discussion

A total of 90 NSCLC patients met the inclusion criteria and exclution criteria. The average patient with advanced NSCLC is 51-60 years old (42,2%), This is in line with previous studies, where advanced NSCLC mostly occurred at the age above 51 years and 60 years. This is because the longer a person lives, the more a person is exposed to risk factors and the ability to repair damaged cells will decrease, in addition, increasing age will also result in decreased DNA repair and loss of regulation resulting in carcinogenesis in the body. The incidence of lung cancer is still low in the age range <40 years but will increase until the age of 70 years (10)(11).

Most of the gender are male patients (83,3%), the number of men diagnosed with NSCLC is most likely due to smoking, which is one of the risk factors for lung cancer. Cigarette smoke can cause histological changes in the bronchial epithelium, widespread premalignant lesions (benign lesions), inflammation and damage to almost all central and peripheral airways (12). Based on the work of advanced NSCLC patients, many are categorized as working (76,7%), most advanced stage NSCLC patient education is basic education (64,4%), this can be seen in table 1.

Table.1 Characteristics of Patients with Advanced Stage Non-Small Cell Lung Cancer (NSCLC)

Characteristics of Patients	**Patients with advanced stage Non-Small Cell Lung Cancer**	**Chemotherapy**	
		Carboplatin-Paclitaxel	**Cisplatin-Paclitaxel**
Total, n (%)	90 (100)	85 (94,4)	5 (5,6)
Age			
≤50	22 (24,4)	19 (21,1)	3 (3,3)
51-60	38 (42,2)	37 (41,1)	1 (1,1)

>60	30 (33,3)	29 (32,2)	1 (1,1)
Gender			
Men	75 (83,3)	70 (77,8)	5 (5,6)
Women	15 (16,7)	15 (16,7)	0
Occupation			
Work	69 (76,7)	64 (71,1)	5 (5,6)
Doesn't work	21 (23,3)	21 (23,3)	0
Education			
Basic Education (SD,SMP)	58 (64,4)	53 (58,9)	5 (5,6)
Higher Education (SMA,PT)	32 (35,6)	32 (35,6)	0

Of the 90 NSCLC patients, there were 85 patients who had used carboplatin-paclitaxel and 5 patients who had used cisplatin-paclitaxel. Based on the incidence of PFS from 85 patients who used carboplatin-paclitaxel including 67 patients who experienced an event (disease progression/progress) and 18 patients who did not experience an event (no progress occurred until the last time of the study) or called sensor, while the 5 patients who had used cisplatin-paclitaxel all experienced an event (disease progression/progress). Based on incidence of OS from 85 patients who used carboplatin-paclitaxel, 7 patients experienced an event (died), and 78 patients who did not experience the event (live) or called sensors, while of the 5 patients who used cisplatin-paclitaxel including 1 patient who experienced the event (died) and 4 patients who dis not experience the event (lived) or called sensor, this can be seen in tables 2 and 3.

Table 2. Proportion and Estimated PFS time in NSCLC Patients with Combination Chemotherapy

Chemotherapy	Patient (n)	PFS (n)	Median	Log Rank p-Value	HR (95% Cl)
Carboplatin-Paclitaxel	85	67	63 years (2 months)	0,098	2,137 (0,850-5,376)
Cisplatin-Paclitaxel	5	5	8 years (0 months)		

Table 3. Proportion and Estimated OS time in NSCLC Patients with Combination Chemotherapy

Chemotherapy	Patient (n)	OS (n)	Mean	Log Rank p-Value	HR (95% Cl)
Carboplatin-Paclitaxel	85	7	426 years (14 months)	0,226	3,391 (0,415-27,685
Cisplatin-Paclitaxel	5	1	148 years (5 months)		

Based on tables 2, it can be seen that 50% of the samples who had used carboplatin-paclitaxel experienced PFS on day 63 or month 2, while as many as 50% of samples that had used cisplatin-paclitaxel experienced PFS events on day 8, but statistically the difference in the effect of events between the two drugs was not significantly different (p = 0,098). PFS events that often occur, namely pleural effusion, pleural or pericardial effusion occur due to increased fluid formation and decreased resorption in the pleural cavity due to pleural inflammation due to the presence of cancer cells around the lung organs which causes accumulation in the chest cavity and compression of the lungs (13). For metastases occur due to cancer cells that begin to spread to other tissues through the blood circulation. Metastasis in lung cancer consists of brain metastases, bone metastases, liver metastases, and adrenal gland metastases to the kidneys (14). In table 3, it can be seen that the average incidence of carboplatin-paclitaxel OS occurred on the 426th day or 14th month, while cisplatin-

paclitaxel the average incidence of OS occurred on day 148th or month 5. However, statistically the difference in the effect of events between the two drugs was not dignificantly different (p = 0,226), so from the results of the study it can be seen that the incidence of PFS and OS in these two drug combinations is not significantly different (*p-value* = >0,05).

It can be seen from the Kapplan Meier curve in Figure 1 that it can be seen that the two survival lines intersect each other which occurs between days 100-200. Intersecting survival lines mean that the ratio of the rate of occurrence of PFS does not meet the proportional hazard assumption, which means that the ratio of the rate of occurrence of PFS between carboplatin-paclitaxel and cisplatin-paclitaxel always changes (not constant) over time. In this study, the rate of occurrence of PFS cisplatin-paclitaxel was 2,137 times (HR 2,137; 95% CI 0,850-5,376) faster than carboplatin-paclitaxel, which can be seen in table 2.

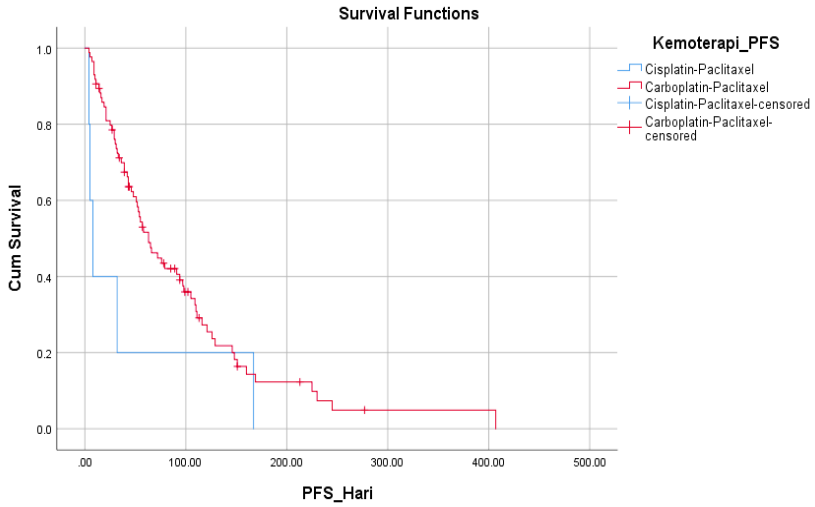

Figure 1. Kapplan Meier PFS Curve Between Carboplatin-Paclitaxel and Cisplatin-Paclitaxel

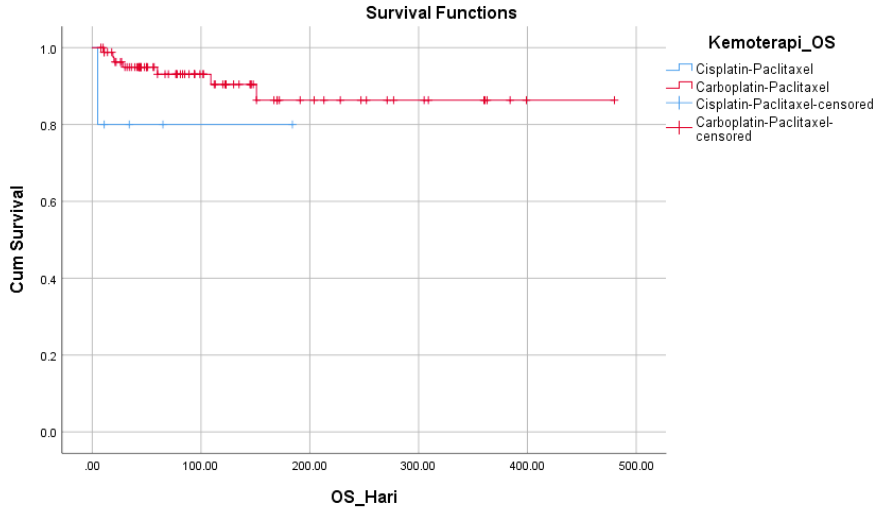

Figure 2. Kapplan Meier OS Curve Between Carboplatin-Paclitaxel and Cisplatin-Paclitaxel

The Kapplan Meier curve in figure 2 shows that the survival lines between carboplatin-paclitaxel and cisplatin-paclitaxel do not intersect each other, which means that the OS curve satisfies the proportional hazard assumption wjere the ratio of the rate of occurrence between these two drugs is constant at all times. In this study, the cisplatin-paclitaxel group had a risk of death at any time 3,391 times (HR 3,391; 95% CI 0,415-27,685) faster than carboplatin-paclitaxel, which can be seen in table 3. It can be seen from the CI value shows that 95% of the sample data already represents the population with a population value range of 0,415-27,685. The range of this population value exceeds 1, meaning that the rate of occurrence of OS from a population point of view between carboplatin-paclitaxel and cisplatin-paclitaxel is not significantly different. This is also the same as the p-value, so it can be interpreted that the p-value and CI on OS events produce consistent conclutions. In addition, the fairly wide CI range is probably due to the small number of samples with large data variations (15)(16).

The results showed that the Progression Free Survival (PFS) and Overall Survival (OS) of carboplatin-paclitaxel were better than cisplatin-paclitaxel. This could be because the toxicity and side effects of carboplatin-paclitaxel are more tolerable than cisplatin-paclitaxel (17)(18)(19). Several studies in other countries also showed that the OS and PFS values of carboplatin-paclitaxel (11,3 months and 5,03 months) were longer than the PS and PFS values of cisplatin-paclitaxel (8,5 months and 4,1 months). This difference in the timing of the occurrence of PFS occurs because of the different drug response in each individual due to racial and genetic differences which is called pharmacogenetics (20)(21).

Conclusions

The effectiveness of carboplatin-paclitaxel showed better results than cisplatin-paclitaxel as the first-line therapy in NSCLC patients, but there was no significant (PFS = p-value 0,098; OS = p-value 0,226) effectiveness between carboplatin-paclitaxel and cisplatin-paclitaxel.

Conflicts of Interest

The authors declare no conflict of interest.

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