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THE EFFECT OF PLATINUM-BASED CHEMOTHERAPY IN ADVANCED NON-SMALL CELL CARCINOMA LUNG CANCER (NSCLC) ON CARDIOVASCULAR EVENTS IN ULIN HOSPITAL BANJARMASIN

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Abstract

Chemotherapy for lung cancer can provide many benefits, but it also has side effects that cause side effects of treatment, one of which is in the field of cardiology. This study was conducted to assess the cardiovascular side effects of platinum-based chemotherapy in advanced stage non-small cell lung cancer. This research method uses a retrospective cohort design. Samples diagnosed with advanced stage KPKBSK who underwent first-line platinum-based chemotherapy underwent electrocardiography and echocardiography assessments at the beginning and after the fourth cycle or when cardiovascular disorders occurred to assess the incidence of atrial fibrillation, PAC, ST-T segment changes, prolonged QT, decreased EF and E/A ratio at Ulin Banjarmasin Regional General Hospital in April 2022-April 2023. The results of this study indicate that chemotherapy for lung cancer with hypertension has an effect on decreasing ejection fraction (p-value <0.05, OR: 0.409). In the group of lung cancer with coronary heart disease receiving chemotherapy, the incidence of atrial fibrillation increased (p-value <0.05, OR: 20). Furthermore, cardiovascular events such as atrial fibrillation increased (p-value <0.05, OR: 6.800) and PAC (p-value <0.05, OR: 6.800) in the squamous cell carcinoma and adenocarcinoma lung cancer groups (p-value <0.05, OR: 0.409). There was no decrease in the E/A ratio and prolonged QT with chemotherapy. The conclusion of this study is that there is no effect of platinum-based chemotherapy on cardiovascular events in advanced lung cancer, but administration to groups with comorbid hypertension and coronary heart disease has an effect on increasing cardiovascular events in lung cancer patients at Ulin Banjarmasin Hospital.

Keywords**:** *Lung Cancer, Chemotherapy, Cardiotoxicity, Banjarmasin.*

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INTRODUCTION

Lung cancer is a type of cancer with a high incidence throughout the world. According to the World Health Organization (WHO), around 1.8 million people will die from lung cancer in 2020.(World Health Organization International Agency for Research on Cancer, 2020) Treatment of cancer with platinum-based chemotherapy is the standard chemotherapy treatment for advanced-stage lung cancer,(Pérez-Callejo et al., 2017) using a combination of docetaxel, paclitaxel, pemetrexed, gemcitabine, and etoposide.(Trapani et al., 2020) The side effects of chemotherapy on the cardiovascular system are classified into three groups, such as vascular diseases, structural heart diseases, and heart dysfunction.(Babbar et al., 2020)

Platinum-based chemotherapy can affect blood vessels, leading to heart failure, atrial fibrillation, and myocardial infarction. The use of docetaxel and paclitaxel affects heart conduction, increasing cardiovascular events by 14%, such as atrial fibrillation, myocardial infarction, and bradycardia. (Zaborowska-Szmit et al., 2020).

METHODS

The research population was all patients diagnosed with KPKBSK advanced stage with platinum-based first-line chemotherapy at the Ulin Banjarmasin General Hospital registered in April 2022 – April 2023.

Sampling technique

Samples on research with purposive total sampling techniques, according to criteria:

Inclusion criteria

1. Patients who have complete data such as CT scan thorax contras, histopathological, as well as protocols or resumes of chemotherapy drug administration.
2. Patients whose electrocardiography and echocardiography data prior to starting chemotherapy.
3. Electrocardiography data during evaluation before or after the 4th cycle who experience side effects of chemotherapy.

Data analysis

The data obtained will be analyzed using the SPSS 26.0 (Statistical Package for the Social Sciences) program. Subgroup analysis was performed in this study to assess the influence of independent, dependent, and confounding variables when p-value was <0.25 were candidates. Logistic regression analysis was then conducted until significant variables were identified. Results were considered statistically significant if $p < 0.05$.(dr. M.Sopiyudin Dahlan., M.Epid., 2019)

Ethical approval

Ethics permission was obtained with the approval and consideration of the Ethics Commission of the Faculty of Medicine, Lambung Mangkurat University and the Ethics Commission of the Research and Development Agency of ULIN Hospital Banjarmasin.

RESULT AND DISCUSSION

Subject characteristic

Table 1 shows the general data characteristics of this study. The 36 samples taken in this study were described by age, gender, history of smoking, comorbidity, stage, type of histopathology, cycle, and chemotherapy regimen.

Table 1. Characteristics of Sample Research

Variabel	N	(%)
Age		
40-50	8	(22.2)
51-60	14	(38.9)
61-70	13	(36.1)
>70	1	(2.8)
Sex		
Male	25	(69.4)
Female	11	(30.9)
Smokers		
Yes	21	(58.3)
No	15	(41.7)
Hypertention		
Yes	20	(55.6)
No	16	(44.4)
Obesity		
Yes	3	(8.3)
No	33	(91.7)
Diabetes Mellitus		
Yes	1	(2.8)
No	35	(92.2)
Coronary Heart Disease		

Variabel	N	(%)
Yes	6	(16.7)
No	30	(83.2)
Comorbid Combination	6	(16.7)
Stage of Lung Cancer		
Stage III	9	(25.0)
Stage IV	27	(75.0)
Histopatology		
squamous cell carcinoma	18	(50)
Adenokarsinoma	18	(50)
Large sell	0	(0)
Chemotherapy cycle		
Siklus 1	4	(11.1)
Siklus 2	4	(11.1)
Siklus 3	3	(8.3)
Siklus 4	25	(69.4)
Chemotherapy		
Carboplatin-paklitaksel	18	(50)
Carboplatin-docetaksel	3	(8.3)
Carboplatin-pemetrexed	13	(36.1)
Carboplatin-etoposide	0	(0)
Carboplatin-gemsitabin	0	(0)
Cisplatin-paklitaksel	0	(0)
Cisplatin-docetaksel	0	(0)
Cisplatin-pemetrexed	2	(5.6)
Cisplatin-etoposide	0	(0)
Cisplatin-gemsitabin	0	(0)

In this study was within the age range of 51–60 years, with 14(38%). Meanwhile, the gender distribution showed a higher number of male samples compared to female samples, with 25(69.4%) and 11(30.6%), respectively. According to smoking history data, 21(58.3%)

The comorbid data from this study's samples showed that hypertension was the most prevalent, comprising 20 (55%). The most frequently used chemotherapy regimen was a combination of carboplatin-paclitaxel, totaling 18 (50%).

frequency distribution of cardiovascular events

Based on Table 2 of ECG abnormalities obtained after chemotherapy, most were ST-T segment changes of 6 (16.6%) in the carboplatin-pemetrexed regimen, followed by a carboplatin-paclitaxel regimen of 5(13.8%).

Table 2 Frequency distribution of cardiovascular events on electrocardiography before and after chemotherapy

chemotherapy	Pre-chemotherapy ECG n (%)			Post-chemotherapy ECG n (%)				
	AF-VES-PAC	ST-T	P.QT	AF	VES	PAC	ST-T	P.QT
Carboplatin-pemetrexed	0	2 (5,6)	0	0	0	0	6 (16,6)	0
Carboplatin-paklitaksel	0	2 (5,6)	0	2 (5,6)	0	4 (11,2)	5 (14)	2 (5,6)
Carboplatin-docetaksel	0	1 (2,8)	0	1 (2,8)	0	0	1 (2,8)	0
Cisplatin- pemetrexed	0	0	0	0	0	0	2 (5,6)	0

Based on Table 3 of cardiovascular abnormalities detected through echocardiographic examination of fractional ejection decrease in this study, 16 (44.7%)

Table 3. Frequency distribution of cardiovascular events on echocardiography before and after chemotherapy

	Pre-chemotherapy EF n (%)			pre-chemotherapy E/A ratio n(%)		Post-chemotherapy EF n (%)		post-chemotherapy E/A ratio n(%)		
	40-50%	51-60%	> 61%	>1	<1	normal	decreased < 10%	decreased > 10%	>1	<1
Carboplatin-pemetrexed	0	2 (5.6)	11(30.8)	7 (19.6)	6 (16.7)	1 (2.8)	6 (16.6)	5 (14)	7 (19.6)	6

	Pre-chemotherapy EF n (%)			pre-chemotherapy E/A ratio n(%)		Post-chemotherapy EF n (%)		post-chemotherapy E/A ratio n(%)		
	40-50%	51-60%	> 61%	>1	<1	normal	decreased < 10%	decreased > 10%	>1	<1
Carboplatin-paklitaksel	1 (2.8)	3 (8.3)	14(39.2)	11 (36.8)	7 (19.6)	6 (16.8)	8 (22.4)	5 (14)	10 (28)	8 (16.7) (22.4)
Carboplatin-docetaksel	0	0	3 (8.3)	2 (5.6)	1(2.8)	2 (5.6)	1 (2.8)	0	1(2.8)	2(5.6)
Cisplatin-pemetrexed	0	1 (2.8)	1 (2.8)	2 (5.6)	0	1 (2.8)	1 (2.8)	0	2 (5.6)	0

Based on Table 4 of cardiovascular abnormalities detected through echocardiographic examination of the E/A ratio in this study as many as 16 (44.7%) of the ratio E / A < 1 from the initial examination prior to chemotherapy is divided by 8 samples (22.4%) with the carboplatin-paclitaxel regimen 6 samples (16.6%) in the carboplatin-docetaksel regime 2 (5.6%).

Table 4. Frequency distribution of cardiovascular events based on clinical and comorbid data

	POST-CHEMOTHERAPY CARDIOVASCULAR EVENTS								
	EF <10%	EF>10%	E/A<1	E/A>1	AF	VES	PAC	ST-T	P.QT
Age									
41-50	3 (8.4)	3 (8.4)	3 (8.3)	5 (14)	0	0	0	5 (14)	1(2.8)
51-60	6(16.8)	4 (11.2)	7 (19.4)	7 (19.4)	3 (8.4)	0	3 (8.4)	2 (5.6)	0
61-70	6 (16.8)	3 (8.4)	6 (16.8)	7 (19.4)	0	0	1 (2.8)	6 (16.8)	1 (2.8)
>70	1 (2.8)	0	0	1 (2.8)	0	0	0	1 (2.8)	0
Stage									
Stage IIIb	4(11.2)	1 (2.8)	4 (11.2)	5 (14)	0	0	1 (2.6)	5 (14)	1 (2.6)
Stage IV	12(33.6)	9 (25.2)	12 (33.3)	15 (41.7)	3 (8.4)	0	3 (8.4)	9 (25.2)	1 (2.6)
Histopathology									
Adenocarsinoma	8 (22.4)	5(14)	7 (19.4)	11(30.6)	0	0	1 (2.8)	10 (28)	0
squamous cell carcinoma	8 (22.4)	5 (14)	9 (25.2)	9 (25.2)	3 (8.4)	0	3 (8.4)	4 (11.2)	2 (5.6)
Large sel	0	0	0	0	0	0	0	0	0
Siklus kemoterapi									
Cycle 1	4(11.2)	0	3 (8.4)	1 (2.8)	0	0	2 (5.6)	1 (2.8)	1 (2.8)
Cycle 2	2 (5.6)	1 (2.8)	1 (2.8)	3 (8.4)	3 (5.6)	0	0	1 (2.8)	0
Cycle 3	1 (2.6)	0	3 (8.4)	0	0	0	1 (2.8)	0	1 (2.8)
Cycle 4	9 (25.2)	9 (25.2)	9 (25.2)	16 (44.4)	1 (2.8)	0	1 (2.8)	0	0
Comorbid									
hypertension	9 (25.2)	8 (22.4)	9 (25.2)	11 (30.6)	1(2.8)	0	3 (8.4)	7(19.6)	2 (5.6)
Diabetes melitus	0	0	0	1 (2.8)	0	0	0	1 (2.8)	0
Obesity	3 (8.4)	0	0	3 (8.4)	0	0	0	2 (5.6)	1 (2.8)
coronary heart disease	4 4(11.2)	3 (5.6)	2 (5.6)	4 (11.2)	3(5.6)	0	1 (2.8)	1 (2.8)	2 (5.6)

In statistical using bivariate and multivariate logistic regression to chemotherapy and cardiovascular events, no significant influence was obtained (p-value >0.05). Evaluating subgroup analysis with a p-value <0.25.

Table 5. Chemotherapy subgroup analysis of cardiovascular events

LOGISTIC REGRESSION ANALYSIS OF SUBGROUPS						
Variabel		**Constant**	**B**	**P-Value**	**OR**	**CI95% Lower-Upper**
AF						
Carboplatin- paklitaksel	coronary heart disease	-3,401	2,996	0,028	20,000	1,374-291,067
	2nd cycle of chemotherapy	-2,930	1,739	0,040	5,690	1,084-29,860

Carboplatin-docetaksel	coronary heart disease	-3,367	1,337	0,045	3,808	1,038-14,100
Carboplatin-pemetrexed	coronary heart disease	-3,367	1,337	0,045	3,808	1,028-14,100
	2nd cycle of chemotherapy	-3,289	1,917	0,017	6,800	1,406-32,877
Cisplatin-pemetrexed	coronary heart disease	-3,434	1,488	0,033	4,429	1,113-17,353
	2nd cycle of chemotherapy	-3,178	1,589	0,026	4,899	1,208-19,870
PAC						
Carboplatin-docetaksel	1st chemotherapy cycle	-3,178	1,589	0,026	4,899	1,208-19-875
Carboplatin-pemetrexed	1st chemotherapy cycle	-3,289	1,917	0,017	6,800	1,406-32,877
Cisplatin-pemetrexed	1st chemotherapy cycle	-3,178	1,589	0,026	4,899	1,208-19,872
Segmen ST-T						
Carboplatin-docetaksel	squamous cell carcinoma	-1,253	0,783	0,046	2,092	1,014-4,316
	Adenocarsinoma	0,215	-0,808	0,043	0,446	0,204-0,976
Karboplatiin-pemetrexed	Adenocarcinoma	0,223	-0,738	0,046	0,478	0,2322-0,987
Cisplatin-pemetrexed	adenocarcinoma	0,223	-0,738	0,046	0,478	0,2322-0,987
Fraksi Ejeksi						
Carboplatin-docetaksel	hypertension	-0,158	0,895	0,036	0,409	0,177-0,944

Based on Table 4, lung cancer with CAD who received carboplatin-paclitaxel, carboplatin-docetaxel, and carboplatin-pemetrexed and cisplatin-pemetrexed chemotherapy regimes obtained a significant influence on the occurrence of AF with a p-value <0.05, the carboplatin-paclitaxel regimen had the highest OR:20. In the analysis of the chemotherapy cycle, of carboplatin-pemetrexed, carboplatin-pemetrexed and cisplatin-pemetrexed chemotherapies that had a significant influence on the occurrence of AF with a p-value <0.05 with the highest OR:6,8.

Discussion

Characteristics of the study subjects

This study was to determine the effect of platinum-based chemotherapy on advanced stage Non-Small Cell Lung Cancer (NSCLC) on cardiovascular events at Ulin Banjarmasin Hospital. In this study, the largest sample was found in the 51-60 year age group, which was 14 people (38%), and the largest gender was male, which was 25 people (69.4%). In accordance with the profile of lung cancer patients in 2006-2011 at Ulin Banjarmasin Hospital, the largest number of lung cancer sufferers were men in the 51-60 year age range, which was 13 (36%), and men in the 61 to 70 year age range, which was 13 (36%). The risk of heart health is also related to age; 86% of new cancers diagnosed in the United States occur in patients over 50 years of age.5 It is known that cancer and cardiovascular disease cause inflammation and oxidative stress. Atherosclerosis, impaired heart muscle regeneration, and metabolic dysregulation are some of the consequences of chronic inflammation. This condition makes cancer patients more susceptible to coronary artery vasospasm, coronary artery disease, cardiomyopathy, and ischemia or heart infarction.

Putra et al., (2015), stated that lung cancer generally occurs in older samples. This is due to the fact that with increasing age, the air space becomes smaller, the gas exchange of the lung surface decreases, the peripheral airway support tissue becomes less effective, and the surfactant system changes. Changes in cilia and the immune system are also associated with these changes.
Comorbidities in this study were mostly hypertension 20 people (55.6%) and, samples with comorbid diabetes mellitus were 1 sample (2.8%). This condition causes pre-existing myocardial damage from underlying hypertension, leading to endothelial dysfunction, which is a definite cause for the development of heart failure.7,34 In multivariate analysis, there was also a significant association between the development of cardiotoxicity and smoking in combination with previous cardiovascular disease (OR: 2.31, 95% CI, 1.15- 4.60, P = .018). In the study by Ayu (2021) and Riska (2021) it was stated that in the study during the period 2017-2019, 50 patients were diagnosed with adenocarcinoma type KPKBSK at Ulin Banjarmasin Hospital.81,82 Meanwhile, in this study, 18 samples of adenocarcinoma lung cancer (50%) and 18 samples of squamous cell carcinoma (50%) were found. In this study, the most chemotherapy combinations consisted of carboplatin-paclitaxel as many as 18 samples (50%), carboplatin-pemetrexed as many as 13 samples (36.4%), carboplatin-dosetaxel as many as 3 samples (2.8%), and cisplatin-pemetrexed as many as 2

samples (5.6%). The combination of chemotherapy used was in accordance with the Guidelines for Clinical Practice in Oncology (NCCN). In this study, there was insufficient information about the number and duration of cigarettes consumed by the sample, so this study did not use the Brinkman index (IB), which is calculated by multiplying the average number of cigarettes smoked each day by the amount of time spent smoking during a year. Light smokers (0-199), moderate smokers (200-599), and heavy smokers (>600). Lucia (2019), stated that there is a correlation between the Brinkman index and lung cancer cases. In the group of lung cancer patients with a severe Brinkman index of 83.3% and a moderate Brinkman index of 54.3%.77 In this study, 21 people (58.3%) had a history of smoking, and 15 people (41.7%) did not smoke.77 Meanwhile, Hasan et al., (2023) in univariate analysis, smoking combined with previous cardiovascular disease increased the risk of cardiotoxicity (OR: 1.99, 95% CI, 1.0-3.84, P = .041).

Based on the American Heart Association (2021), collected data from nine previous studies in the US to evaluate the risk of smoking and cardiovascular disease. This analysis included data from 106,165 people aged 20 to 79 years. More than 50% of people aged 40 to 59 who smoked had cardiovascular disease and were 1.8 times more likely to die from heart attack, stroke, or heart failure. Young men and women who smoke are twice as likely to experience a fatal cardiovascular event as the first sign of cardiovascular disease than nonsmokers. Smoking is associated with developing cardiovascular disease at a younger age and shortening a person's life by four to five years

.

Distribution of Cardiovascular Events Based on Electrocardiography

In this study, according to table 5.2, cardiovascular events of atrial fibrillation occurred in the use of carboplatin-dosetaxel and carboplatin-paclitaxel chemotherapy, this is in line with the statement on the use of taxane chemotherapy, especially paclitaxel, manifestations of cardiovascular disorders such as arrhythmias, bradycardia, AV block, ventricular tachycardia, heart failure.

Cardiovascular disorders such as ST-T segment changes increased with carboplatin-pemetrexed chemotherapy. Before chemotherapy there were 2 samples (5.6%) and after chemotherapy 6 samples (16.6%). The results of this study are in accordance with the statement of Quan X et al., (2022), the combination of pemetrexed and carboplatin contributes to the occurrence of sinus arrhythmia due to abnormal blood perfusion and lack of oxygen which results in secondary thrombosis.41 The chemotherapy regimen used in this study attacks the vascular endothelium which clinically causes heart disorders such as coronary artery vasospasm.30

Distribution of Cardiovascular Events based on Echocardiography

In this study, 16 samples (44.7%) experienced a decrease in ejection fraction of less than 10%, and 10 samples (28%) experienced a decrease in ejection fraction of more than 10%. In carboplatin-dosetaxel chemotherapy, one sample (2.8%) experienced a decrease in ejection fraction of more than 10%. In this study, echocardiography examination involving the E/A ratio showed that in two samples of carboplatin-docetaxel chemotherapy, the number of cases of decreased E/A ratio increased to 2 samples (5.6%). The distribution in this study is in accordance with the statement that docetaxel may play a direct role in myocardial damage, carboplatin-docetaxel chemotherapy also experienced a decrease in ejection fraction. In a study of ten patients given docetaxel, and can cause left ventricular diastolic dysfunction and increased serum BNP concentrations without changing systolic function.

Distribution of cardiovascular events to risk factors

This study found that people who most often experience cardiovascular disease are those aged 51 to 60 years. There was a decrease in ejection fraction of 10 samples (28%), followed by the occurrence of AF of 3 samples (8.4%). This incident increased with age by about 10%. These results are consistent with previous studies that have shown that cancer is a major risk factor for AF. Other contributing factors include age-related cardiovascular risk, with 86% of new cancers diagnosed in the United States occurring in patients over the age of 50. 5,71. Inflammation and oxidative stress are known to be caused by cancer and cardiovascular disease. Atherosclerosis, impaired myocardial regeneration, and metabolic dysregulation are some of the consequences of chronic inflammation. These conditions make cancer patients more susceptible to coronary artery vasospasm, coronary artery disease, cardiomyopathy, and ischemia or myocardial infarction. 29,30

In previous studies by Julia Kravchenko et al., (2015), comorbidities studied included hypertension (57.7%-61.8%), hyperlipidemia (40.0%-46.2%), and coronary heart disease and myocardial infarction (30.0%), ischemic heart disease (30.4%-36.8%), and cardiac arrhythmias (25.6%-30.9%). Most comorbidities were associated with decreased survival. Heart failure in the early stages of chemotherapy was also reported to decrease overall survival.72 In line with this study hypertension was a major risk factor, with a decrease in ejection fraction of less than 10% in 9 samples (25.2%) and more than 10% in 8 samples

(22.4%). In addition, there were ST-T segment ECG changes in 7 samples (19.6%). The findings of this study indicate that pre-existing myocardial damage is the main cause of endothelial dysfunction, which causes heart failure. Other risk factors that increase the risk of heart failure are hypertension, as well as emphysema and chronic bronchitis.

One sample from this study who had diabetes mellitus and contributed to cardiovascular events with ST-T segment changes of 1 sample (2.8%). As stated, diabetes mellitus has also been associated with chemotherapy-induced cardiotoxicity in several studies. In the case of diabetes mellitus, insulin resistance and hyperinsulinemia can increase the risk of atherosclerosis and myocardial infarction.35,36 More than 70% of KPKBSK lung cancer patients have at least one comorbid disease before chemotherapy. According to previous studies, comorbidity with other malignancies decreases lung cancer survival. In this study, 36 samples, including 3 samples (8.4%) with obesity comorbidity, experienced a decrease in ejection fraction of more than 10%. This indicates that the obese group is susceptible to cardiotoxicity. In multivariate analysis, obesity increased the risk of cardiotoxicity events by 3.02%. The risk of heart failure increased by 11% with every 1 kg/m2 increase.

A total of four samples with coronary heart disease comorbidity also showed a decrease in ejection fraction of less than 10% (11.2%), the incidence of AF was four samples (11.2%), PAC was one sample (2.8%), and prolonged QT was two samples (5.6%). Because they have the same risk factors, heart disease and cancer are are the two leading causes of death in the United States. This is especially true for older people with heart disease and cancer. In addition, cardiovascular complications can arise as a result of cancer therapy, such as radiation or chemotherapy.

The effect of chemotherapy on KPKBSK lung cancer on cardiovascular events Dermitzakis et al., (2016) stated that there was a significant effect of paclitaxel and carboplatin chemotherapy on sympathetic and parasympathetic cardiac nerve disorders. The results of this study between chemotherapy and cardiovascular events did not find a significant effect according to Kanar et al., (2021) that there was no significant effect of paclitaxel and carboplatin chemotherapy on cardiotoxicity in lung cancer patients. The results of the study were not significant because they did not involve risk factors to be tested. As we know that risk factors in lung cancer patients can be a significant causal factor in cardiovascular events. In this study, although there was no relationship and effect of chemotherapy on cardiovascular events, the frequency of cardiovascular events due to carboplatin-paclitaxel mostly caused a decrease in ejection fraction of 8 samples (22.4%), ECG changes with findings of ST-T segment changes in 5 samples (14%), PAC in 4 samples (11.2%), atrial fibrillation and prolonged QT in 2 samples (5.6%), in accordance with the theory that this regimen attacks the vascular endothelium which clinically causes heart disorders such as coronary artery vasospasm.

One of the most dangerous side effects of chemotherapy is cardiotoxicity. Kanar et al., (2021) stated that cardiotoxicity appears within two to four weeks after treatment. Reversible arrhythmias, acute coronary syndrome, pericarditis, and LV systolic dysfunction are signs of cardiotoxicity. Then, in the current study, paclitaxel chemotherapy can cause congestive heart failure at 5-15% of conventional doses. Although chemotherapy improves survival in cancer patients, this regimen can cause cardiotoxicity in some patients. Platinum-based chemotherapy can be discontinued due to increased risk of cardiotoxicity and mortality. For patient prognosis, early detection of chemotherapy cardiotoxicity is very important.

Subgroup Analysis of Effect of Chemotherapy on Lung Cancer with KPKBSK on Cardiovascular Events

Chemotherapy is a treatment for advanced lung cancer, which improves survival and reduces the rate of cancer recurrence, however, cardiovascular events can reduce the positive effects of treatment. Considering the risk factors that may influence cardiovascular disorders in lung cancer receiving chemotherapy. The relationship between cardiovascular risk factors and chemotherapy use is a major issue in terms of increasing the risk of myocardial damage, with or without a specific histological pattern.24 The results of other clinical studies show that this event is usually seen when pemetrexed is used in combination with other cytotoxic drugs, one of which is the platinum-based group, and occurs in patients previously diagnosed with cardiovascular disease risk factors. Serious cardiovascular events such as myocardial infarction, peripheral edema, arrhythmias, and ischemic stroke are rare.

Based on table 5.20, tests were carried out on the independent variables, dependent variables and confounder variables obtained in lung cancer suffering from CHD receiving carboplatin-paclitaxel, carboplatin docetaxel and carboplatin-pemetrexed chemotherapy and, cisplatin-pemetrexed had an effect on the incidence of AF with an OR of 20 times increasing atrial fibrillation. The results of this study are in accordance with those mentioned in other studies that the incidence of atrial fibrillation is higher in the use of taxanes and gemcitabine chemotherapy which can cause an increase in the incidence of atrial fibrillation and myocardial ischemia. The

use of cisplatin chemotherapy increases the incidence of cardiotoxicity in the elderly, especially heart failure, and causes thromboembolism while pemetrexed chemotherapy increases the incidence of myocardial infarction if combined chemotherapy.

In the incidence of AF, three chemotherapy combinations were found, namely carboplatin-docetaxel, carboplatin-pemetrexed, and cisplatin-pemetrexed which had a significant effect on the incidence of AF since the second cycle of chemotherapy. While in the incidence of PAC, of the four chemotherapy combinations, only carboplatin-docetaxel, carboplatin-pemetrexed, and cisplatin-pemetrexed had a significant effect with a p-value <0.05 with the highest OR in carboplatin-pemetrexed chemotherapy which had an effect on increasing the incidence of PAC since the first cycle of chemotherapy by 6.8 times. Cardiovascular events can occur early or late in chemotherapy and can include problems ranging from myocardial dysfunction to irreversible heart failure cannot be cured. Acute or subacute cardiotoxicity can occur at any time from the start of treatment to two weeks after completion of therapy, and can be indicated by various types of arrhythmias, prolonged QT and acute coronary syndrome.30 In adenocarcinoma lung cancer types receiving carboplatin-dosetaxel, carboplatin-pemetrexed, and cisplatin-pemetrexed chemotherapy which have a significant effect on the ST-T segment with a p-value <0.05. Cancer therapy can induce myocardial damage due to an imbalance in the myocardial repair process with various mechanisms that cause heart failure or inhibition of ion channels or tyrosine kinase signaling pathways that can cause arrhythmias with or without QT prolongation, atherosclerosis, pulmonary thromboembolism, and hypertension. In the study, it can be seen in table 5.20 in patients with hypertension with lung cancer receiving docetaxel chemotherapy, a significant effect was obtained p-value <0.05 with an OR of 0.409 times causing a decrease in ejection fraction. This is in accordance with the statement that docetaxel has a direct effect on cardiomyoblasts, increasing oxidative and endoplasmic reticulum stress resulting in cell death. This suggests that docetaxel may play a direct role in myocardial damage. In a study of 10 patients receiving docetaxel, routine monitoring of diastolic and systolic cardiac function and measurement of serum cardiac neurohormone concentrations one day before, one day after, and three weeks after docetaxel administration, found that docetaxel can cause left ventricular diastolic dysfunction.

In 36 samples, risk factors before chemotherapy showed an increase in cardiovascular events such as atrial fibrillation, PAC, ST-T segment changes, and decreased ejection fraction. In addition, different types of lung cancer and the number of chemotherapy cycles also increased the risk of cardiovascular events. Vascular heart disease, structural heart disease, and cardiac dysfunction are three groups of side effects of chemotherapy on the heart.6 The effects of platinum-based chemotherapy can change blood vessels, causing heart failure, atrial fibrillation, and myocardial infarction. The use of paclitaxel and doxetaxel improves cardiac conduction, which increases the number of cardiovascular events such as atrial fibrillation, myocardial infarction, and bradycardia by 14%.7 In this study, patients under 60 years of age who had hypertension and coronary heart disease as comorbidities were given carboplatin and paclitaxel chemotherapy with a total score of 4 with moderate risk. After one cycle of chemotherapy, they experienced a decrease in ejection fraction and atrial fibrillation. In another case, a 49-year-old female patient who had diabetes mellitus and hypertension and received carboplatin-pemetrexed chemotherapy with a score of 5 with high risk after the 4th cycle of chemotherapy. A decrease in ejection fraction and changes in the ST-T segment were found. Cardiac function assessment using chemotherapy risk scores if> 6 very high risk, 5-6 high risk, 3-4 moderate risk and 1-2 low risk as shown in figure 2.6.10 In accordance with the fact that patients who have more than three of these risk factors have been associated with a risk of cardiotoxic side effects that are five to six times greater than patients who do not have any risk factors. However, the absence of all risk factors can cause myocardial infarction.

CONCLUSION

There was no effect on the administration of platinum-based chemotherapy on cardiovascular events in advanced-stage lung cancer, but administration in groups that had comorbid hypertension and coronary heart disease had an effect on increasing cardiovascular events in lung cancer patients at Ulin Banjarmasin Hospital.

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