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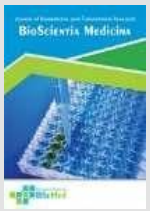

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Profile of Side Effects of Chemotherapy in Non-Small Cell Lung Cancer Patients (NSCLC) Undergoing Chemotherapy at Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: Chemotherapy is one of the treatment options for lung cancer at any stage. Side effects due to chemotherapy are still a problem in the treatment of lung cancer patients. Chemotherapy drugs have different side effects according to their pharmacokinetics and pharmacodynamics. This study aimed to determine the side effects of both hematological and non-hematological chemotherapy in non-small cell lung cancer patients treated at the lung ward of Dr. M. Djamil General Hospital, Padang, Indonesia, from 2017 to 2019. **Methods:** This was a descriptive observational study, a total of 42 study subjects. The study subjects were non-small cell lung cancer patients undergoing first-line chemotherapy. Sociodemographic, clinical, and laboratory data analysis was carried out with the help of SPSS software in a univariate manner. **Results:** The study subjects were mostly male (85.36%), the age range of 40-60 years (66.67%), at risk of exposure from work (45.23%), smokers (59.52%), had a history of pulmonary TB (11.9%), history of COPD (2.38%), history of malignancy of other organs (2.38%) with the most cell type being adenocarcinoma (54.76%). The most common hematological side effects were first-degree anemia (21.43%) and first-degree leukopenia (21.43%). The most non-hematological side effects were first-degree alopecia (90.48%), followed by first-degree nausea and vomiting (78.57%). **Conclusion:** Chemotherapy side effects were found in all regimens given with mild degrees. The side effects obtained were in the form of hematological and non-hematological side effects.

1. Introduction

Lung cancer is the most common malignancy and the main cause of death related to malignancy in the world.[1] The incidence of new cases of lung cancer is based on Global Cancer Statistics data for 2018, namely 2,093,876 cases (11.6%), followed by breast, prostate, and colon cancer.[2] Nearly 85% of is non-small cell lung cancer (NSCLC).[3] Chemotherapy is an option for cancer treatment at an advanced stage by using chemicals (cytostatics) that inhibit the growth of cancer cells. Chemotherapy in NSCLC causes subjective improvement in 75% of patients. Subjective improvement in the NSCLC patient group was around 53.3% of patients, weight gain was 16.7%, and objective responses in the form of reduced tumor size were seen in around 13.3%.[4,5]

Chemotherapy drugs have different side effects according to their pharmacokinetics and pharmacodynamics. All cytostatic drugs have a bone marrow depressant effect.[4,6] Research by Valliappan Muthu et al. in 112 newly diagnosed lung cancer patients who received first-line chemotherapy experienced chemotherapy side effects, as much as 94%. The most common side effect was diarrhea (61.6%). Vomiting and constipation are other

commonly reported side effects. Severe side effects (degrees 3 and 4) were found in 6.9% of patients, while the rest were of low degree. Side effects in the form of anemia were found in almost all patients (73.3%) with each cycle of chemotherapy, and the frequency and severity of anemia continued to increase.[7] This study aims to determine the side effects of chemotherapy, both hematological and non-hematological, in patients with non-small cell lung cancer who are treated at the lung ward of Dr. M. Djamil General Hospital, Padang, Indonesia, for the 2017-2019 period.

2. Methods

This study was a descriptive observational study. This study uses secondary data sourced from the medical records of Dr. M. Djamil General Hospital, Padang, Indonesia. A total of 42 study subjects were included in this study. The inclusion criteria were in the form of non-small cell lung cancer patients undergoing first-line chemotherapy at Dr. M. Djamil General Hospital, Padang, for the 2017-2019 period and had complete medical record data. This study was approved by the medical and health research ethics committee at Dr. M. Djamil General Hospital, Padang, Indonesia.

This study aims to present research subject data, including gender, age, occupation, smoking status, history of the disease (pulmonary TB, COPD), history of malignancy elsewhere, family history of malignancy, cell type, hematological data (Hb, leukocytes, granulocytes, platelets, and bleeding) and non-hematological data (abnormalities in the digestive tract (bilirubin SGOT/SGPT, alcohol, nausea/vomiting, diarrhea), renal (proteinuria, hematuria), lungs, fever, allergies, skin, infections, and pain). Exclusion criteria were cancer patients with double primary. Data analysis was carried out with the help of SPSS version 25 software to present data in a univariately.

3. Results

NSCLC patients who underwent first-line chemotherapy for at least two cycles during the study period were mostly male, with 35 patients (85.36%) and seven patients (16.67%) female. The highest age range was 40-60 years with 28 patients (66.67%), followed by more than 60 years with 13 patients (30.95%) and less than 40 years with one patient (2.38%). Patients at risk of exposure from work totaled 19 patients (45.23%), followed by non-exposed from work totaling 18 patients (42.86%) and at risk of exposure from work totaling five patients (11.90%).

The smoking status was smokers totaling 25 patients (59.52%), followed by non-smokers totaling 10 patients (23.80%), and ex-smokers totaling seven patients (16.67%). Patients who had a history of pulmonary TB were five patients (11.9%), a history of COPD was one patient (2.38%), a history of malignancy of other organs one patient (2.38%), and none of the patients had a history of malignancy in the family. The most common type of cell was adenocarcinoma, totaling 23 patients (54.76%), followed by squamous cell carcinoma, totaling 18 patients (42.85%), no large cell carcinoma was found, and other types were found in one patient (2.38%).

The side effects of chemotherapy in patients based on the chemotherapy regimens given are shown in Table 2. The most chemotherapy regimens given to patients were paclitaxel+carboplatin in 31 patients (73.80%), followed by vinorelbine+carboplatin in six patients (14.29%), gemcitabine +carboplatin in three patients (7.14%) and paclitaxel+cisplatin in two patients (4.76%). Chemotherapy side effects in this study were found in all chemotherapy regimens given to patients with mild degrees. Side effects of chemotherapy in patients undergoing chemotherapy based on hematological disorders according to WHO toxicity degrees can be seen in Table 3.

Table 1. Characteristics of lung cancer patients undergoing chemotherapy at Dr. M. Djamil General Hospital, Padang, for the 2017-2019 period.

Characteristics	Frequency	Percentage (%)
Gender		
Male	35	83.33
Female	7	16.67
Age		
< 40 years	1	2.38
≥ 40-60 years	28	66.67
> 60 years	13	30.95
Occupation		
Exposed	19	45.23
Risk exposure	5	11.91
Not exposed	18	42.86
Smoking status		
Not smoke	10	23.81
Smoker	25	59.52
Former smoker	7	16.67
History of pulmonary tuberculosis		
Yes	5	11.90
History of COPD		
Yes	1	2.38
History of malignancy elsewhere		
Yes	1	2.38
Family history of malignancy		
Yes	0	0
Cell type		
Adenocarcinoma	23	54.76
Squamous cell carcinoma	18	42.86
Large cell carcinoma	0	0
No elsewhere	1	2.38

Table 2. Side effects of chemotherapy in lung cancer patients based on the regimen given.

Chemotherapy regimen	Side effects	
	Yes frequency (%)	No frequency (%)
Paclitaxel+Cisplatin	2 (4.76)	0
Paclitaxel+Carboplatin	31 (73.81)	0
Gemsitabine+Carboplatin	3 (7.14)	0
Vinorelbin+Carboplatin	6 (14.29)	0

Table 3. Side effects of chemotherapy in lung cancer patients based on hematological disorders.

Hematology	Degree of toxicity according to the WHO				
	0 frequency (%)	1 frequency (%)	2 frequency (%)	3 frequency (%)	4 frequency (%)
Hemoglobin	30 (71.43)	9 (21.43)	3 (7.14)	0	0
Leukocytes	27 (64.28)	9 (21.43)	1 (2.38)	5 (11.91)	0
Granulocytes	32 (76.19)	2 (4.76)	4 (9.52)	3 (7.15)	1(2.38)
Platelets	42 (100)	0	0	0	0
Bleeding	0	0	0	0	0

First-degree anemia was found in nine patients (21.43%), second-degree in one patient (7.14%), third-degree and fourth anemia were not found. First-degree leukopenia was found in nine patients (21.43%), second-degree was in one patient (2.38%), third-degree was found in five patients (11.90%), and no fourth-degree abnormalities were found. First-degree granulocytopenia was found in two patients (4.76%),

second-degree in four patients (9.52%), third-degree in three patients (7.14%), and fourth-degree in one patient (2.38%). There were no abnormalities in platelet counts and bleeding in the patients in this study.

Table 4 shows the side effects of chemotherapy in patients based on non-hematological disorders. Abnormalities in the digestive tract in the form of abnormalities in bilirubin were found in the first degree in one patient (2.32%), and no abnormalities in the second, third, and fourth degree were found. Abnormalities in SGOT/SGPT were first-degree in four patients (9.52%), second-degree in one patient (2.321%), and no third and fourth-degree abnormalities were found. Oral abnormalities were not found in the patient. Abnormalities in the form of first-degree nausea/vomiting were found in 33 patients (78.57%), and no second, third or fourth-degree abnormalities were found. Diarrhea, renal, pulmonary, allergic, skin, infection, and pain abnormalities were not found in the patient (degree 0). Alopecia was found in first-degree in 38 patients (90.48%), second-degree in four patients (9.52%), and no third and fourth-degree abnormalities were found.

Table 4. Side effects of chemotherapy in lung cancer patients based on non-hematological disorders.

Non-hematological	**Degree of toxicity according to WHO**				
	0 frequency (%)	1 frequency (%)	2 frequency (%)	3 frequency (%)	4 frequency (%)
SGOT/SGPT	37 (88.1)	4 (9.52)	1 (2.38)	0	0
Oral	42 (100)	0	0	0	0
Nausea/Vomiting	9 (21.43)	33 (78.57)	0	0	0
Diarrhea	42 (100)	0	0	0	0
Proteinuria	42 (100)	0	0	0	0
Hematuria	42 (100)	0	0	0	0
Pulmonary	42 (100)	0	0	0	0
Fever	42 (100)	0	0	0	0
Allergies	42 (100)	0	0	0	0
Skin	42 (100)	0	0	0	0
Hair	0	38 (90.48)	4 (9.52)	0	0
Infection	42 (100)	0	0	0	0
Pain	42 (100)	0	0	0	0

4. Discussion

This study shows that 85.36% of patients diagnosed with lung cancer are male. Men who smoke more than women have a higher death rate. The estimated 2018 new cases of lung cancer in the United States are 121,680 in men and 112,350 in women. Lung cancer is the second most common cancer diagnosis after gender, after prostate cancer in men and breast cancer in women. Lung cancer accounts for 14 percent of new cancers in men and 13 percent of new cancers in women in the United States.[1]

The age range for lung cancer in this study was 40-60 years (66.67%). Older age is associated with cancer development due to biological factors such as DNA damage over time and telomere shortening. The median age at diagnosis of lung cancer is 70 years for both men and women. Approximately 53% of cases occur in people aged 55-74 years and 37% in people aged >75 years. The highest incidence of lung cancer was in men, namely 585.9/100,000 aged 85-89 years, while the highest incidence in women was 365.8/100,000 aged 75-79 years.[8] Lung cancer is the leading cause of death in men over 40 years and in women over 59 years.[1]

Lung cancer is also found in young adults. Lung cancer occurs in patients aged <55 years in 10% of cases. Lung cancer studies of the NSCLC type in patients aged 20-46 years have reported that young

lung cancer patients are more likely to be female, have adenocarcinoma histology and are non-smokers. Young patients usually have few co-morbidities, and genetic factors are thought to play a large role in this patient population. Younger patients are more likely to receive more aggressive treatment at all stages of the disease and have increased survival.[9]

Patients who were at risk for lung cancer and were exposed to work in this study totaled 19 patients (45.23%), with the most smoking status being smokers, namely 25 patients (59.52%). The addictive component of tobacco is nicotine, a natural alkaloid that acts as an acetylcholine agonist and binds to the nicotinic acetylcholine receptor (nAChR) in the nervous system. This causes the release of neurotransmitters into the bloodstream, including dopamine, serotonin, norepinephrine, endorphins, and gamma-aminobutyric acid (GABA). Nicotine is not a carcinogen but upregulates nicotinic receptors and produces changes in gene expression that promote tobacco dependence and are associated with the development of lung cancer.[10]

The burning of tobacco produces at least 60 known carcinogens. The most significant carcinogens are polycyclic aromatic hydrocarbons (PAHs), including benzopyrene, nitrates, and tobacco-specific nitrosamines (TSNAs), such as 4-(methylnitrosamino)-1-(13-pyridyl-1-butanone).

Tobacco smoke has a vapor phase and a particulate phase which produce 1,015 and 1,017 free radicals per gram, respectively.[11] The mechanism of carcinogenesis from tobacco is by forming additional DNA by carcinogens and their metabolites and causing damage due to free radicals.[10]

Occupational exposure plays an important role in the etiology of lung cancer, and the risk of lung cancer is increased among workers in a number of industries and occupations. Two studies have reported that the estimated proportion of lung cancer cases attributable to agency work in England was 14.5% overall and 12.5% in men in France. The most important occupational lung carcinogens were reported to be asbestos, silica, radon, heavy metals, and polycyclic aromatic hydrocarbons.[12]

Patients who had a history of pulmonary TB in the study were 11.9%. Chang et al.'s research on pulmonary TB, which is associated with the risk of lung cancer in Korea, found that the incidence of lung cancer in patients with a history of pulmonary TB was 177.6/100,000 people per year, much higher than in people without a history of pulmonary TB, namely 31.2/100,000 people per year.[13]

Chronic inflammation and fibrosis due to TB can cause genetic mutations. Lung parenchyma tissue is involved in TB disease and lung cancer, and persistent cough in lung cancer, vascular morphological variations, lymphocytosis processes, and the generation of immune system mediators, such as interleukins, are all factors that lead to the hypothesis of a role for TB in lung cancer. Several reports indicate that induction of necrosis and apoptosis or TB reactivation, especially in patients with immunodeficiency, can result in increased IL-17 and TNFα, which will decrease P53 activity or increased Bcl2 expression, decrease BaxT and cause inhibition of caspase 3 expression due to decreased expression. Mitochondrial cytochrome oxidase.[14]

A history of COPD was found in 2.38% of this study. Song et al.'s study of cancer development in COPD patients showed a higher incidence of lung cancer per 100,000 people per year in people who smoked and had COPD (216 in people not with COPD and never smoked, 757 in COPD who had never smoked, 271 in non-COPD former smokers and 1266 in COPD ex-smokers, 394 in non-COPD but smokers and 1560 in COPD and smokers). Multivariate analysis showed that COPD, regardless of smoking status, contributed to the development of lung cancer, colorectal cancer, and liver cancer.[15]

COPD and lung cancer are major health problems worldwide. Lung cancer and COPD share the same basic predisposition, namely an underlying genetic predisposition, telomere shortening, mitochondrial dysfunction, or premature aging. The body's defense mechanisms in the form of antioxidants such as superoxide dismutase, anti-protease, and DNA repair

mechanisms are found in most smokers. Failed defense mechanisms lead to cancer if mutations occur or COPD if damage to cells and proteins becomes too great. COPD may be a driving factor for lung cancer by increasing oxidative stress and the resulting DNA damage, chronic exposure to proinflammatory cytokines, repression of DNA repair mechanisms, and increased cell proliferation.[16]

A history of malignancy in other organs was found in 2.38% of patients, and there were no patients with a family history of malignancy in this study. A positive family history of lung cancer is associated with a 1.7-fold increased risk of developing lung cancer. Several studies have shown that the risk of lung cancer increases two to four times in people with a family history of lung cancer.[10]

The most common cell types found in this study were adenocarcinomas, namely 23 patients (54.76%). These results are consistent with the results of Tsukazan's study, which also found adenocarcinoma as the most pathological type of lung cancer (44.4%), followed by squamous cell carcinoma (40.6%). Yuliandra et al. also found that the most common cell type in their research on hematological toxicity due to chemotherapy in lung cancer patients was adenocarcinoma, which was 77.30%. These findings are in line with global trends in most of the world. The higher incidence of adenocarcinoma is often related to the risk factors.[17]

Side effects of chemotherapy in this study were found in all regimens given to patients in the form of mild hematological and non-hematological side effects. The chemotherapy regimens in this study were paclitaxel+cisplatin (4.76%), paclitaxel+ carboplatin (73.80%), gemcitabine+carboplatin (7.14%), and vinorelbine + carboplatin (14.29%).

Schiller et al.'s study in 1,155 patients compared combinations of four chemotherapy regimens in advanced LCCCC lung cancer, namely cisplatin + paclitaxel, cisplatin + gemcitabine, cisplatin + docetaxel, and carboplatin + paclitaxel, obtained *survival rate* almost the sameTreatment with cisplatin+gemcitabine was associated with a significantly longer time to disease progression than treatment with cisplatin+paclitaxel but was more likely to cause severe renal toxicity (9% for cisplatin+gemcitabine and 3% for cisplatin+paclitaxel).[18]

Anticancer drugs not only work on cancer cells but also on normal cells that grow fast, causing toxicity that needs special treatment. Drug toxicity is divided into hematological and non-hematological toxicity, which is assessed 2-3 days before the next chemotherapy. The toxicity of chemotherapy drugs varies depending on several factors, namely differences in chemotherapy protocols, chemotherapy drug doses, and genetic predisposition.[19]

The side effects of chemotherapy in patients undergoing chemotherapy based on hematological disorders according to WHO toxicity degrees in this study were anemia, leukopenia, and granulocytopenia. The most common hematological abnormalities are first-degree anemia and first-degree leukopenia. There were no abnormalities in platelet counts and bleeding in the patients in this study. Heffingeret al.'s study on 120 NSCLC patients found side effects of degree 3 or 4 chemotherapy occurring in 50.2% of patients. Hematological side effects (febrile neutropenia, infection, thrombocytopenia, and anemia) were most common, accounting for 48% of all degrees of severe toxicity.[20]

Kristensen et al.'s study of 766 NSCLC patients found that 177 patients (23%) experienced severe hematological toxicity during the first cycle of chemotherapy. Fatigue and nausea/vomiting were significantly worse in patients with severe hematological toxicity compared with patients with non-severe hematological toxicity.[21] The results of this study were almost the same as those of Yuliandra et al. It was also found that first-degree anemia was the most common hematological side effect, namely in 30% of patients, followed by leukopenia and thrombocytopenia.[17]

Chemotherapy affects not only cell cancer but also cell normal, which actively splits like marrow bone. Cells progenitor, which produces granulocyte,

erythrocyte, and thrombocyte in circulation peripheral destroyed. A cell that is not yet ripe in the marrow bone and a cell that is newly ripe are destroyed in 7-14 days after chemotherapy, on the moment which the same cells mature in the marrow bone are released into in blood edge. It needs 8-12 days for cells in the marrow bone to become ripe. Toxicity hematology average, occur 2-5 week after chemotherapy. Chemotherapy-based platinum has a side effect that is real and myelosuppressive. Anemia caused by chemotherapy cisplatin is characteristic temporary, but deficiency of erythropoietin is caused by damage to the tubule kidney.[22]

Drug-induced neutropenia is caused by decreased production or increased destruction of neutrophils. Decreased production is often a consequence of chemotherapy drugs that suppress bone marrow myeloid progenitor cells. Chemotherapy drug-induced neutropenia has a very high incidence in oncology patients.[23]

Non-hematological side effects were also found in this study. The most common non-hematological abnormalities were first-degree nausea/vomiting (78.57%) and first-degree alopecia (90.48%). The results of this study are almost the same as the research of Elisna et al., which found non-hematological toxicity in advanced NSCLC patients on the cisplatin+etoposide regimen, the most experienced patients were alopecia (100%) and gastrointestinal toxicity, namely nausea, vomiting (100%). The alopecia that occurred reached third-degree, while first-degree gastrointestinal complaints were in four patients (11.4%) and second-degree in 29 patients (82.9%), and third-degree there were two patients (5.7%). The average non-hematological toxicity in the form of alopecia occurs in the 2nd week after chemotherapy is carried out. Gastrointestinal toxicity in the form of nausea and vomiting occurs in the first week to the 8th week and usually occurs in the first week.[22]

Factors that influence the occurrence of post-chemotherapy nausea and vomiting include the dose of drugs used, age, gender, and history of alcohol consumption. The mechanism of nausea and vomiting after administration of chemotherapy drugs occurs due to stimulation of the vomiting center (medulla oblongata), namely stimulation of the chemotherapy trigger (CTZ), which is the main chemosensory organ for nausea and vomiting. Chemotherapy drugs stimulate neurotransmitter receptors, releasing neurotransmitters (dopamine, serotonin) that activate the CTZ and send impulses to the vomiting center.[24]

It is hypothesized that chemotherapy-induced alopecia is the result of direct toxicity to the highly proliferative keratinocyte matrix, as well as the follicular pigmentation system being very sensitive to poisons, and some chemotherapy drugs can cause rapid apoptosis.[25]

Other non-hematological disorders include first-degree bilirubin abnormalities (2.32%), first-degree SGOT/SGPT abnormalities (9.52%), and second-degree (2.32%). Ying et al. conducted a study on NSCLC patients, which correlated bilirubin levels with the response to platinum-based chemotherapy, and found that increased bilirubin levels were associated with a poor response to chemotherapy. Several chemotherapy drugs can cause increased liver function, including antimetabolites, alkylating agents, antitumor antibiotics, taksan, vinca alkaloids, platinum agents, topoisomerase inhibitors, and tyrosine kinase inhibitors. Close monitoring of liver function is essential when starting chemotherapy.[26]

5. Conclusion

Side effects of chemotherapy were found in all regimens given with mild degrees. The side effects obtained were in the form of hematological and non-hematological side effects.

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