Original Article

Hematologic and Non-Hematologic Side Effects in Lung Cancer Patients Post Chemotherapy at Arifin Achmad General Hospital

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Abstract

Background: Lung cancer is the second-highest cause of malignancy in the world, with a prevalence of 11.4% of all types of cancer. The majority of lung cancer patients are diagnosed at an advanced stage; therefore, chemotherapy acts as palliative therapy without curative therapy options. Chemotherapy drugs have various side effects, both hematologic and non-hematologic. Thus, monitoring side effects should be notable to improve the quality of life for patients with lung cancer undergoing chemotherapy.

Method: This research was a descriptive study with a total sampling data collection technique. Samples were collected for 6 months according to the inclusion criteria, and the results were presented in the form of a distribution table.

Results: During August 2023 to January 2024, 29 lung cancer patients met the inclusion criteria at Arifin Achmad General Hospital. Of these 29 patients, 25 (86.21%) were men and 4 (13.79%) were women. The hematologic side effects were observed in 16 (55.17%) patients, while non-hematologic side effects were found in 18 (62.07%) patients. The most common hematologic side effect is anemia, and the most common non-hematologic side effect is gastrointestinal disorders.

Conclusion: The chemotherapy regimen used for lung cancer patients caused both hematologic and non-hematologic side effects. The non-hematologic side effects were more common than the hematologic.

Keywords: hematologic, lung cancer, non-hematologic, side effects

INTRODUCTION

Lung cancer is the world's second-highest cause of cancer, accounting for 11.4% of all cancer cases.[1] Despite advances in diagnostic procedures, surgical techniques, and therapy development, the 5-year survival rate for lung cancer in underdeveloped countries remains at 8.9%. In Indonesia, the majority of lung cancer cases are identified at an advanced stage, significantly reducing survival rates.[2]

The choice of therapy for lung cancer is determined by the illness stage, overall condition, comorbidities, therapeutic goals, and cost-effectiveness. Lung cancer

treatments include surgery, radiation, chemotherapy, and targeted therapy. Chemotherapy is used as a neoadjuvant treatment in the early stages, as an adjuvant following surgery, or as palliative therapy in advanced stages of non-small cell lung cancer (NSCLC) if the patient's overall state is stable, as evidenced by a Karnofsky score greater than 60% or a World Health Organization (WHO) score of 0-2.[3]

Chemotherapy drugs are divided into two types: non-cell cycle dependent alkylating agents (carboplatin, cisplatin) and cell cycle dependent drugs, which include antimetabolites (pemetrexed, gemcitabine), antimicrotubule (paclitaxel, docetaxel, vinorelbine), topoisomerase inhibitors (etoposide, irinotecan), and cytotoxic agents (bleomycin).[4]

The four factors for selecting chemotherapy medications are platinum-based compounds, doubling, objective response rates greater than 15%, and the lack of toxicity greater than grade 3 on the WHO scale. Carboplatin and cisplatin are platinum-based chemotherapy alternatives, although cisplatin has more nephrotoxicity than carboplatin despite their same efficacy levels.[3]

Chemotherapy regimens can cause a variety of side effects, including gastrointestinal disturbances, such as nausea and vomiting with cisplatin, and hematologic changes with carboplatin. The vast majority of lung cancer patients are discovered at an advanced stage, placing chemotherapy a palliative rather than curative treatment. Appropriate monitoring and control of both hematologic and non-hematologic side effects are critical to improving patient quality of life.

To date, no research at Arifin Achmad General Hospital has looked into hematologic and non-hematologic side effects of chemotherapy in lung cancer patients. Thus, the author is motivated to undertake a study about hematologic and non-hematologic side effects of chemotherapy in lung cancer patients.

METHOD

This study used a descriptive research design, concentrating on the careful observation and recording of side effects that chemotherapy-treated lung cancer patients encountered. The research has been approved with the number B/016/UN19.5.1.1.8/UEPKK/2024.

Patients with lung cancer receiving treatment at Arifin Achmad General Hospital between August 2023 and January 2024 were the focus of this study. The sample consisted of lung cancer patients with a confirmed diagnosis through pathology examination. All patients who met the inclusion criteria during this time were included in the trial using a total sampling method.

The inclusion criteria included chemotherapy-treated lung cancer patients with types of adenocarcinoma, squamous cell carcinoma, large cell carcinoma, neuroendocrine carcinoma, and small cell lung cancer who were treated in Arifin Achmad General Hospital between August 2023 and January 2024. The exclusion

criteria were lung cancer patients who did not undergo chemotherapy and those who had previously been sampled during a chemotherapy cycle within the data collection period.

Data was obtained from patient medical records via the Electronic Data Processing (EDP) system at Arifin Achmad General Hospital. The data were presented as frequency distribution tables with percentages. To further analyze, statistical comparisons were performed to evaluate differences in mean values of hematological parameters (hemoglobin, leukocytes, neutrophils, and platelets) based on the chemotherapy regimen used. Data analysis utilized the t-test for comparing two groups to determine statistical significance. Distribution tables will present the findings, allowing for clear visualization and interpretation.

RESULT

According to the data, 29 out of 34 patients met the inclusion criteria. The remaining five patients were excluded because they were not receiving conventional chemotherapy for various reasons.

The oldest patient in the sample was 71 years old, while the youngest was 26. The majority of lung cancer patients receiving chemotherapy were over 40 years old, with a total of 27 (93.10%) patients. On the other hand, there were two patients under the age of forty (6.90%). The average age of lung cancer patients receiving chemotherapy was 55 years. Based on this study, 29 lung cancer patients receiving chemotherapy were divided into 25 males (86.21%) and 4 females (13.79%). Male patients made up the majority of the sample.

The most common type of lung cancer in this study was adenocarcinoma which accounted for 16 patients (55.17%), followed by squamous cell carcinoma which accounted for 13 patients (44.83%). There were no patients with large cell carcinoma, neuroendocrine, or small cell lung cancer.

As indicated by this study, the most commonly used chemotherapy drugs were a combination of carboplatin and paclitaxel, which accounted for 12 patients (41.38%); followed by a combination of pemetrexed and cisplatin, which accounted for 9 patients (31.03%); pemetrexed alone for 5 patients (17.24%); and docetaxel alone for 3 patients (10.34%). First-line treatment included carboplatin and paclitaxel, as well as pemetrexed and cisplatin, while second-line chemotherapy involved pemetrexed or docetaxel alone.

Based on the results of this study, the majority of patients were in the first-line first-cycle of chemotherapy, accounting for 16 patients (55.17%). This was followed by 4 patients (13.79%) who were in the second-line second-cycle; 2 patients (6.90%) each who were in the first-line second-cycle, first-line third-cycle, and second-line first-cycle; as well as 1 patient (3.45%) each who were in the first-line fourth-cycle, first-line fifth-cycle, and second-line third-cycle.

Patients who had already been sampled during previous chemotherapy

cycles were not eligible to be included as samples in the next chemotherapy lines or cycles during the six-month data collection period. The distribution data by chemotherapy line and cycle is shown in Table 1.

Table 1. Distribution of Patients Based on Chemotherapy Line and Cycle (n=29)

Line and Cycle	n	%
Line 1 Cycle 1	16	55.17
Line 1 Cycle 2	2	6.90
Line 1 Cycle 3	2	6.90
Line 1 Cycle 4	1	3.45
Line 1 Cycle 5	1	3.45
Line 1 Cycle 6	0	0.00
Line 2 Cycle 1	2	6.90
Line 2 Cycle 2	4	13.79
Line 2 Cycle 3	1	3.45

According to the research data, 16 patients experienced hematologic side effects. Of these, 15 patients developed anemia and 1 patient had leukopenia. Anemia was observed in 5 patients receiving a combination of carboplatin and paclitaxel, 6 patients with pemetrexed and cisplatin, 1 patient with pemetrexed alone, and 3 patients on docetaxel alone.

Based on WHO toxicity grades, no patients experienced anemia beyond Grade III. The majority of patients, 8 in total, had Grade I anemia. The patient with leukopenia was classified as Grade III. The prevalence of hematologic side effects is presented in Table 2, while the distribution of hematologic side effects by chemotherapy drug is shown in Table 3.

Table 2. The Prevalence of Hematologic Side Effects (n=29)

Hematologic Side Effects	n	%
Experienced hematologic side effects	16	55.17
No hematologic side effects	13	44.83

Table 3. Distribution of Hematologic Side Effects Based on Chemotherapy Drugs

Chemotherapy Drugs	Hematologic Side Effects	n (based on WHO Grade)	%
Carboplatin and paclitaxel	Anemia	5 (I: 2 patients; II: 3 patients)	17.24
	Leukopenia	III: 1 patient	3.45
	Neutropenia	0	0.00
	Thrombocytopenia	0	0.00
	No side effects	6	20.69
Pemetrexed and cisplatin	Anemia	6 (I: 4 patients; II: 2 patients)	20.69
	Leukopenia	0	0.00
	Neutropenia	0	0.00
	Thrombocytopenia	0	0.00
	No side effects	3	10.34
Pemetrexed	Anemia	I: 1 patient	3.45
	Leukopenia	0	0.00
	Neutropenia	0	0.00
	Thrombocytopenia	0	0.00
	No side effects	4	13.79
Docetaxel	Anemia	3 (I: 1 patient; II: 2 patients)	10.34
	Leukopenia	0	0.00
	Neutropenia	0	0.00
	Thrombocytopenia	0	0.00
	No side effects	0	0.00

Based on the results, about 18 patients experienced non-hematologic side effects, while 11 patients did not experience any non-hematologic side effects. Of the 18 patients, 17 experienced gastrointestinal disorders, 2 had skin disorders, 9 experienced hair loss, and 1 patient had a fever.

Gastrointestinal issues were observed in 8 patients receiving the combination of carboplatin and paclitaxel, 5 patients on the combination of pemetrexed and cisplatin, 3 patients on pemetrexed alone, and 1 patient on docetaxel alone. Skin disorders were caused by the use of carboplatin and paclitaxel, as well as pemetrexed and cisplatin, with 1 patient in each group.

Hair loss occurred in 6 patients receiving carboplatin and paclitaxel, 1 patient on pemetrexed and cisplatin, and 2 patients on pemetrexed alone. Fever was observed in 1 patient receiving carboplatin and paclitaxel. The prevalence of non-hematologic side effects and non-hematologic side effects based on symptoms, and the distribution of non-hematologic side effects based on chemotherapy drugs can be observed in Table 4 and 5, respectively.

Table 4. The Prevalence of Non-Hematologic Side Effects and Non-Hematologic Side Effects Based on Symptoms (n=29)

Non-Hematologic Side Effects	**n**	**%**
Experienced non-hematologic side effects	18	62.07
No non-hematologic side effects	11	37.93
Based on Symptoms		
Gastrointestinal disorders	17	58.62
Shortness of breath	0	0.00
Hematuria	0	0.00
Skin disorders	2	6.90
Hair loss	9	31.03
Fever	1	3.45
Allergies	0	0.00
Pain	0	0.00

Table 5. Distribution of Non-Hematologic Side Effects Based on Chemotherapy Drugs

Chemotherapy Drugs	**Non-Hematologic Side Effects**	**n**	**%**
Carboplatin and paclitaxel	Gastrointestinal disorders	8	27.59
	Skin disorders	1	3.45
	Hair loss	6	20.69
	Fever	1	3.45
Pemetrexed and cisplatin	Gastrointestinal disorders	5	17.24
	Skin disorders	1	3.45
	Hair loss	1	3.45
	Fever	0	0.00
Pemetrexed	Gastrointestinal disorders	3	10.34
	Skin disorders	0	0.00
	Hair loss	2	6.90
	Fever	0	0.00
Docetaxel	Gastrointestinal disorders	1	3.45
	Skin disorders	0	0.00
	Hair loss	0	0.00
	Fever	0	0.00

Table 6. Comparison of Mean Hematologic Parameters Based on Chemotherapy Regimens

Parameter	Carboplatin & Paclitaxel (n=12)	Pemetrexed & Cisplatin (n=9)	P*
Mean Hemoglobin (g/dL)	12.17	10.59	0.17
Mean Leukocytes ($10^3/mm^3$)	8.01	6.89	0.28
Mean Neutrophils (%)	56.40	58.74	0.65
Mean Platelets ($10^3/mm^3$)	321.78	316.51	0.85

Note: *t-test with a significant statistic if P<0.05

Further statistical analysis was conducted to compare the mean values of hemoglobin (Hb), leukocytes, neutrophils, and platelets between the most commonly used chemotherapy regimens (the combination of carboplatin and paclitaxel, also pemetrexed and cisplatin).

The results of the t-test showed no statistically significant difference in the mean hemoglobin value (P=0.17) between the group of patients who received carboplatin and paclitaxel and those who received pemetrexed and cisplatin. Similarly, no statistically significant difference was obtained for the mean values of leukocytes (P=0.28), neutrophils (P=0.65), and platelets (P=0.85) between the two regimens.

DISCUSSION

The majority of the study samples were over 40 years old, accounting for 27 patients (93.10%), while only 2 patients (6.90%) were under 40. These findings align with a study by Thandra et al in the United States in 2021, which reported that the average age of lung cancer patients is 70, with 55% of patients aged 55-74 and 37% aged over 75.[5,6]

Lung cancer incidence is low in individuals under 40 but increases steadily up to age 70. This is due to carcinogenesis occurring after repeated exposure to mutagens, and advancing age further decreases the cells' ability to repair DNA damage.[5,6]

In this study, 25 patients (86.21%) were male and 4 patients (13.79%) were female. These findings are consistent with GLOBOCAN 2020 data, which indicates that lung cancer is the most common type of cancer among men and the third most common among women.[1,5,7]

A study conducted in 100 hospitals in Jakarta also stated that lung cancer is the most prevalent cancer in men and the fourth most prevalent in women. This is attributed to the fact that men tend to smoke more frequently than women. Smoking is a known risk factor for lung cancer, with its incidence increasing in proportion to the number of cigarettes smoked per day and the number of years spent smoking.[1,5,7]

The most common type of lung cancer in this study was adenocarcinoma (55.17%), followed by squamous cell carcinoma (44.83%). According to the previous studies by Barta et al, adenocarcinoma is the most common type of lung cancer in men and women. Even in America, Canada, Europe, and Japan, the prevalence of adenocarcinoma continues to

increase compared to squamous cell carcinoma.[7]

In this study, the most widely used chemotherapy drugs were a combination of carboplatin and paclitaxel (41.38%) and a combination of pemetrexed and cisplatin (31.03%). This happened because the majority of samples in this study underwent first-line chemotherapy, and patients who had been sampled in previous chemotherapy could not be sampled once again in the next line and cycle of chemotherapy.

The combination of carboplatin and paclitaxel is one of the first-line chemotherapies for NSCLC, while for non-squamous cancer types, a combination of pemetrexed and cisplatin is used. A single dose of docetaxel or a single dose of pemetrexed (non-squamous) is used for second-line chemotherapy with a 21-day cycle.[3,5]

In our study, 16 patients (55.17%) experienced hematologic side effects. Platinum-based chemotherapy drugs (carboplatin and cisplatin) can cause anemia through direct suppression of erythropoietic stem cells in the bone marrow. The results of this study are slightly different from a meta-analysis by Griesinger et al, which stated that the combination using carboplatin causes anemia more often than cisplatin. The use of docetaxel can also cause anemia due to the myelosuppressive effect of inhibited cell division.[8]

The results of our study follow the study of Gubens et al, which explained that docetaxel caused anemia in most patients, with the number of patients experiencing grade 3 or more anemia below 10%. Pemetrexed could also produce anemia, but with a prevalence of <10% in the study from Li et al.[9,10]

The majority of patients experienced anemia grades 1 and 2 on the WHO toxicity scale, so that chemotherapy could still be given. Patients who experienced hematologic side effects were mostly undergoing the first and second cycles of chemotherapy.

This is in accordance with the study by Rosell et al, which clarified that the majority of patients who received carboplatin and paclitaxel encountered anemia grade I and II. The effects of myelosuppression are cumulative throughout the chemotherapy cycle, so anemia will worsen as the chemotherapy cycles continue.[11] Based on research conducted by the European Cancer Anemia Survey (ECAS) in 2004, there was an increased occurrence of anemia throughout chemotherapy cycles, namely about 19.5% in the first cycle to 46.7% in the fifth cycle.[12]

Patients who had leukopenia in this study were included in the WHO scale of grade III. The patient was 59 years old and was undergoing chemotherapy using the first-line of carboplatin and paclitaxel in the third cycle. This corroborates the study of Rosell et al, which revealed that the combination of carboplatin and paclitaxel caused more severe leukopenia, namely grade III and IV, compared to the combination of pemetrexed and cisplatin. Another factor causing leukopenia is the

final stage of lung cancer, so the cancer cells have spread to the hematopoietic system, and the administration of multiple chemotherapies causes bone marrow suppression to become more severe.[11]

In this study, 18 patients experienced non-hematologic side effects. One of the gastrointestinal effects of chemotherapy drugs is hepatotoxicity, which is characterized by an increase in transaminase enzymes. A study from Grigorian et al mentioned that chemotherapy drugs can cause secondary hepatotoxicity. The hepatotoxicity that occurs is mostly idiosyncratic; therefore, it is not dose-dependent and cannot be predicted.[13]

Other gastrointestinal side effects, such as mouth ulcers, nausea, vomiting, and diarrhea, are mostly caused by a combination of carboplatin and paclitaxel. This corroborates the research of Hayashi et al, where chemotherapy caused gastrointestinal cells to proliferate rapidly, resulting in mucosal inflammation, ulceration, and perforation.[14]

Hair loss occurred in 6 persons who received a combination of carboplatin and paclitaxel as chemotherapy, 1 person who received pemetrexed and cisplatin, and 2 people with pemetrexed alone. This follows the research of Wikramanayake et al, where alopecia occurred in 65% of patients undergoing chemotherapy. The main target of chemotherapy drugs is keratinocytes that actively proliferate on the surface of hair follicles, resulting in apoptosis that causes alopecia of the head and body hair, which are mostly in the anagen phase.[15]

Nejat et al stated that the 4 main groups of chemotherapy drugs that often cause alopecia are anti-microtubule (paclitaxel) with the rate of 80%, platinum group (carboplatin or cisplatin) with the rate of 60%, topoisomerase inhibitors with the rate of 60%, and antimetabolites (pemetrexed) with the rate of 10-50%.[15]

Hyperpigmentation due to the use of carboplatin and paclitaxel was experienced by 1 subject, while a combination of pemetrexed and cisplatin in another subject caused it. This is due to a direct toxic effect on melanocytes, so that melanin production increases. Hyperpigmentation in consequence of chemotherapy will disappear several months after the termination of chemotherapy, and this condition does not require further intervention. In addition, carboplatin and cisplatin can cause type 1 hypersensitivity reactions.[16]

Fever occurred in 1 patient who received carboplatin and paclitaxel after the third cycle of first-line chemotherapy. The patient's laboratory results showed leukocyte levels of 0.73 x $10^3/mm^3$ and a neutrophil count of 24.6%. Fever in lung cancer patients can be caused by infection or non-infection.[17]

Routine blood tests, C-reactive protein, and procalcitonin can help establish the cause of fever. After calculation, the absolute neutrophil count (ANC) result was 179.58, so febrile neutropenia could be the cause of the fever in the patient. Febrile neutropenia can be

established if the patient experiences an increase in temperature >38°C and ANC below 500/mm^3.[17]

Although the t-test showed no statistically significant difference in the mean values of hemoglobin, leukocytes, neutrophils, and platelets (Table 6), these findings have important clinical implications. Numerically, the mean hemoglobin value was lower in the pemetrexed & cisplatin group (10.59 g/dL) compared to the carboplatin & paclitaxel group (12.17 g/dL).

This difference, while not statistically significant, aligns with the descriptive findings where 6 patients on the pemetrexed & cisplatin regimen experienced anemia, compared to 5 patients on the carboplatin & paclitaxel regimen. This indicates that, in clinical practice, physicians should be more vigilant about the potential for anemia side effects in patients receiving the pemetrexed & cisplatin regimen.

This study has several limitations to be acknowledged. First, the design was retrospective and it was conducted at a single center, which limits the ability to generalize the findings to a wider patient population. Second, the relatively small sample size (n=29) may have affected the statistical power to detect a significant difference. Therefore, the statistically non-significant results do not completely negate the existence of potential clinical differences.

There is a necessity to conduct future research with a larger sample size and a multi-center design to achieve better statistical power. Furthermore, a prospective study could help collect more accurate and detailed data on side effects and allow for a more in-depth analysis of the relationship between the number of chemotherapy cycles and the severity of side effects.

CONCLUSION

In conclusion, chemotherapy drugs can cause hematologic and non-hematologic side effects. In this study, lung cancer patients undergoing chemotherapy experienced side effects, 55.17% of whom experienced hematologic side effects. The most common hematologic side effect was anemia, while the most common non-hematologic side effect was gastrointestinal disorders. Other non-hematologic side effects found in this study were hair loss, skin disorders, and fever. The statistical analysis showed no significant difference in the mean values of hematologic parameters between the most common chemotherapy regimens. Highlighting the necessity for further research with larger sample sizes to draw more definitive conclusions.

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