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Brief Research Communications

Hematologic Toxicities of Chemotherapy in Lung Cancer Patients: A Retrospective Study in Dr. M. Djamil Hospital Padang, Indonesia

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Abstract
The use of chemotherapeutic agents in the management of cancer is often followed by a range of toxicities to various organ systems. A retrospective study on the hematologic toxicities of chemotherapy in lung cancer patients has been carried out. The study was conducted by a cross-sectional method from medical records of four-year data in 2010–2014 at Dr. M. Djamil Hospital Padang, West Sumatra, Indonesia. Data from medical records of patients diagnosed with lung cancer and underwent chemotherapy, not suffering from primary hematologic diseases, and with normal kidney and liver function prior to chemotherapy were studied. A number of 22 medical records of lung cancer patients which met the criteria with a total of 40 chemotherapy cycles were observed. The study revealed that a combination of carboplatin-paclitaxel was the most common chemotherapy used for the patients (72.7%). The hematologic toxicities comprised anemia, leukopenia, and thrombocytopenia with the severity ranging from grade 1–3. Carboplatin-paclitaxel was the only combination that caused these three toxicities, and the only combination to cause thrombocytopenia as well. Anemia was the major hematologic toxicity experienced by more than half of the patients. The study concludes that there is a reasonably high incidence of hematologic toxicities from chemotherapy among lung cancer patients.

Keywords: Anemia, chemotherapy, hematologic toxicity, leukopenia, lung cancer, thrombocytopenia

Toksisitas Hematologis Akibat Kemoterapi pada Pasien Kanker Paru: Studi Retrospektif di RSUP Dr. M. Djamil Padang

Abstrak
Penggunaan obat kemoterapi dalam pengobatan kanker sering disertai dengan toksisitas pada beberapa sistem organ. Kajian retrospektif terhadap toksisitas hematologis akibat kemoterapi pada pasien kanker paru sudah dilaksanakan. Studi ini dilaksanakan dengan metode *cross-sectional* dari data rekam tahun 2010–2014 di RSUP Dr. M. Djamil Padang, Sumatera Barat. Data pasien yang didiagnosis menderita kanker paru yang menjalani kemoterapi, tidak menderita penyakit hematologis dan gangguan hematopoiesis, serta memiliki fungsi ginjal dan hati yang normal dimasukkan ke dalam kajian. Sejumlah 22 pasien memenuhi kriteria dengan jumlah siklus kemoterapi sebanyak 40. Hasil kajian ini mengungkap bahwa kombinasi karboplatin-paklitaksel merupakan kemoterapi yang paling banyak digunakan (72,2%). Toksisitas hematologis yang terjadi meliputi anemia, leukopenia, dan trombositopenia dengan tingkat keparahan 1–3. Karboplatin-paklitaksel merupakan satu-satunya kombinasi kemoterapi yang menyebabkan ketiga toksisitas hematologis tersebut, sekaligus juga merupakan satu-satunya kombinasi yang menimbulkan trombositopenia. Anemia merupakan toksisitas hematologis yang paling banyak terjadi meliputi lebih dari separuh pasien. Penelitian ini menyimpulkan bahwa terdapat toksisitas hematologis yang cukup tinggi akibat kemoterapi pada pasien kanker paru.

Kata kunci: Anemia, kanker paru, kemoterapi, leukopenia, toksisitas hematologis, trombositopenia

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Introduction

Lung cancer is a disease of uncontrolled growth of cells that starts off in one or both lungs. Most of the lung cancers such as lung carcinomas are derived from epithelial cells.[1] Lung cancer is ranked fourth of all cancers in Indonesia and has become the second leading cause of death after cardiovascular disease.[2,3] Lung cancer management is conducted with a series of treatment such as surgery, radiation therapy, chemotherapy, and combination therapy.[4] Some chemotherapeutic agents such as cisplatin and carboplatin are well-known for their poor therapeutic index and with high toxic effects, thus improper doses and regimens may result in some serious adverse effects and fatalities. Chemotherapy drugs generally work on cells that are actively dividing. Therefore, the effect is not only experienced by the cancerous cells but also in normal tissues with a high rate of proliferation such as gastrointestinal and hematopoietic systems.[5]

First-line regimens of chemotherapy that are recommended by The National Comprehensive Cancer Network (NCCN) for Lung Cancer comprise a combination of platinum (cisplatin or carboplatin) with other cytotoxic drugs, such as paclitaxel, gemcitabine, vinorelbine, pemetrexed, and docetaxel.[6] Cisplatin and carboplatin are nephrotoxic cytotoxic agents that can contribute to a decrease in creatinine clearance up to 60–80%. On the other hand, carboplatin is reported to have smaller nephrotoxicity. However, the accumulation of its long-term use may also cause similar toxic effects. Renal tubular damage induced by cisplatin or carboplatin may affect the pharmacokinetics of cisplatin which is excreted by the kidney. The concentration of unbound molecules of these two drugs may increase, causing a reduced renal excretion after several cycles. As a consequence, their myelosuppressive effect on bone marrow activity can be worsening.[7]

The clinical manifestation of myelosuppressive effect may present as anemia, leukopenia, and thrombocytopenia. Severe leukopenia (leukocyte count <2000/mm^3) and thrombocytopenia (platelet count <100,000/mm^3) are adequate indicators to discontinue therapy in patients whose hematopoietic system were normal at the beginning of therapy.[5,8] The grade of toxicity has also become one of the criteria to take into account before conducting chemotherapy. Chemotherapy can only be prescribed when the toxicity does not exceed grade three based on the WHO toxicity grading scale. Therefore, it is necessary to study the toxicity of chemotherapy for lung cancer patients and to monitor the toxicity scale.[9]

Methods

Study design

The study was a qualitative descriptive research conducted by the cross-sectional method using four-year medical record data of male and female lung cancer patients in 2010–2014 who underwent chemotherapy at the pulmonary ward in Dr. M. Djamil Hospital, Padang, West Sumatra, Indonesia. Samples were collected using total sampling technique. This study has been approved by the hospital's Education and Research Office (No. LB.00.02.07.1971).

Population and sample

The population was all medical records of patients who had been diagnosed with lung cancer and underwent chemotherapy at the pulmonary ward of Dr. M. Djamil Hospital Padang, West Sumatra, Indonesia. Data were collected from patients' medical records that met inclusion criteria: diagnosed with lung cancer and received first-line chemotherapy regimens. Patients who underwent chemoradiotherapy and those diagnosed with primary hematologic diseases or impaired kidney and liver function before chemotherapy were excluded from the study.

Data collection and analysis

The collected data consisted of types and stages of lung cancer, regimens of chemotherapy, performance status, and the results of the hematologic examination. Staging of cancer was based on TNM classification system converted into stage I to IV,[10,11] meanwhile the grading for hematological toxicities was based on WHO toxicity scale taken from hemoglobin levels, leukocyte, granulocytes and platelet counts.[12] The performance status of the patients was examined using the Karnofsky scale to assess their capability to tolerate the use of chemotherapeutics.[13] Data were analyzed descriptively and presented in tables and charts.

Results

Among 46 lung cancer patients who received chemotherapy, a number of 22 patients met the criteria for the study with a total of 40 cycles of chemotherapy. The patients were dominated by male (68.2%) and those aged 41–60 years old (72.8%). Adenocarcinoma was the most common type of lung cancer found in the study (77.3%). The characteristics of lung cancer patients receiving chemotherapy are presented in Table 1, meanwhile, the number of chemotherapy cycles received by the patients is demonstrated in Figure 1, in which most of the patients (68.2%) received only one cycle of chemotherapy.

Table 1 Characteristics of Lung Cancer Patients Receiving Chemotherapeutic Agents

Patient Characteristics	Number of Patients	Total (%)
Sex		
Male	15	68.2
Female	7	31.8
Age		
21–30	1	4.5
31–40	2	9.1
41–50	8	36.4
51–60	8	36.4
61–70	1	4.5
71–80	2	9.1
Type of Lung Cancer		
Adenocarcinoma	17	77.3
Squamous cell carcinoma	3	13.6
Large cell carcinoma	2	9.1
Staging*		
IIB	3	13.6
IIIA	2	9.1
IIIB	1	4.5
IV	16	72.7
Performance Status**		
30–40%	0	0.0
50–60%	0	0.0
70–80%	22	55.0
90–100%	18	45.0

*Based on TNM classification (T for extent of the primary tumor, N for involvement of lymph nodes, and M for distant metastases)[14,15], **Based on Karnofsky Performance Status Scale[13]

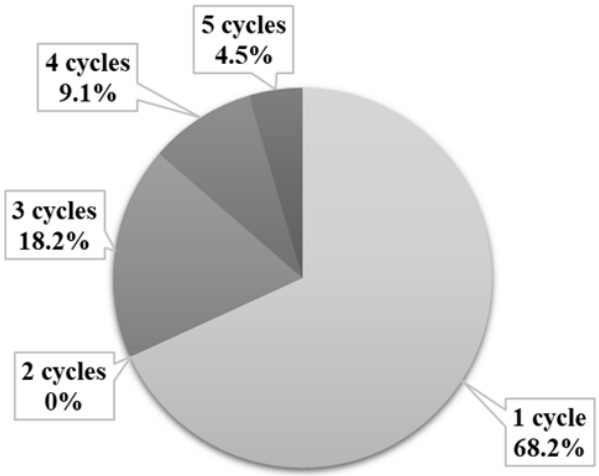

Figure 1 Percentage of Patients Who Received Certain Cycles of Chemotherapy for Lung Cancer (n=22)

There was a total of four combinations of chemotherapeutic agents used by the patients. Carboplatin-paclitaxel was the most frequent combination in all three types of lung cancer (72.2%). Table 2 summarizes entire combinations of chemotherapeutic agents used by the patients in different types of lung cancer. On the other hand, there were three different hematologic toxicities (dominated by anemia) investigated from the patients caused by three out of four chemotherapeutic combinations. Thrombocytopenia was experienced by all patients who received carboplatin -paclitaxel (Table 3). The number of chemotherapy cycles causing hematologic toxicities and their grading distribution is presented in Figure 2.

Discussion

Surgery and radiation therapy are powerful treatments to remove and destroy cancer cells. However, this kind of treatment can only work in certain body areas. Chemotherapeutic agents come to solve this limitation because they can work throughout the whole body and even kill cancerous cells that have metastasized to other body parts.[5] Unfortunately, chemotherapy poses a major concern in adverse effects to some organ systems, including hematologic functions. Some of them are considered to cause fatalities and death, especially in elderly patients.[14,15] In addition, the evaluation of hematologic toxicities from chemotherapy, especially for lung cancer patients in Indonesia, is rare to be reported to our knowledge. Therefore, the evaluation of hematologic toxicities is a necessary initial step towards improving the quality of the treatment and the patients' quality of life as well.

In the present study, the combinations of chemotherapeutic agents were investigated for their toxic effects to the hematologic system, especially for the three major components of

Table 2 Combinations of Chemotherapeutic Agents Used in Several Types of Lung Cancer

Chemotherapeutic Combination	Number of Patients (%)			
	Adenocarcinoma	Squamous Cell Carcinoma	Large Cell Carcinoma	Total
Carboplatin-Paclitaxel	12 (72.7)	1 (50.0)	3 (100.0)	16 (72.7)
Carboplatin-Gemcitabine	2 (11.8)	1 (50.0)	-	3 (13.6)
Carboplatin-Vinorelbine	2 (11.8)	-	-	2 (9.1)
Cisplatin-Gemcitabine	1 (4.4)	-	-	1 (4.4)

Table 3 The Incidence of Hematologic Toxicities in Patients Receiving Combination of Chemotherapeutic Agents for Lung Cancer

Chemotherapeutic Combination	Number of Patients (%)	Number of Incidence of Toxicity (%)		
		Anemia	Leukopenia	Thrombocytopenia
Carboplatin-Paclitaxel	16 (72.7)	8 (50.0)	5 (31.3)	16 (100.0)
Carboplatin-Gemcitabine	3 (13.6)	2 (66.7)	-	-
Carboplatin-Vinorelbine	2 (9.1)	1 (50.0)	1 (50.0)	-
Cisplatin-Gemcitabine	1 (4.5)	-	-	-

blood cells. The grade for these toxic effects was based on the Karnofsky performance scale, a very popular scaling system to determine the patients' capability to tolerate the medications that they receive, especially for serious illness such as the use of chemotherapy for cancer patients. The Karnofsky score is presented in percent, in which the lower the score, the worse the rate of survival. Simply put, 100 means perfect health while 0 means death.[13] On the other hand, the staging of the lung cancer suffered by the patients was determined by TNM classification. This classification system is based on the anatomical extent of the cancers that represents the size of the tumour (T), the involvement of the lymph node (N), and the metastasis status (M).[10,11] The study found that the toxic effects were present in most of the chemotherapeutic combinations. These toxicities comprised anemia, leukopenia, and thrombocytopenia with various severity ranging from grade 1 to 3.

The data show a marked difference between the number of male and female patients. A report from the US Centers for Disease Control and Prevention (CDC) suggests that men are more likely to be suffering from lung cancer than women.[16] The American Cancer Society also approximates that the overall risk of developing lung cancer in men is around 1 in 14, higher when compared to a 1 in 17 chance for women. In addition, the risk becomes higher when the individual smokes tobacco.[17] Although not assessed in the present study, evidence suggests that tobacco smoking is the major cause of lung cancer. In fact, Indonesia has been reported to have 76.2% more men smokers than on average countries with medium human development index. In contrast, tobacco smoking among women

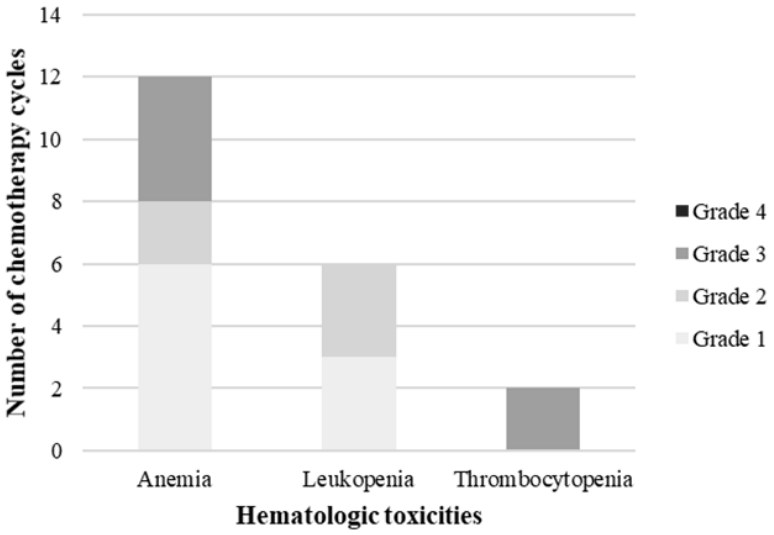

Figure 2 Number of Chemotherapy Cycles with Hematological Toxicities and Their Grading Distribution (n=40)

is 3.6% fewer.[18] However, although more smoking men were presented than women, studies show more significant percentage of women who develop lung cancer have never smoked.[19,20] Another risk factor that could differentiate between sexes is the biological aspects. These include the genes that may make them more vulnerable to harmful effects of carcinogens.[21] The various genetic association is also proposed to either increase the risk of developing the disease or preventing it.[22] Besides, the difference in hormonal regulation may influence the progression of cancer between men and women.[23]

The present findings show that most of the patients had adenocarcinoma (77.3%), in line with the global trend in most parts of the world.[24,25] Higher incidence of adenocarcinoma is often correlated with its risk factor. Some studies have suggested that the shift in the use of cigarette filter ventilation might be responsible for the increasing number of this type of lung cancer.[26,27] Another striking data from the present study was the highest percentage of patients with stage IV lung cancer (72.7%). Ellis and Vandermeer (2011) have found that lung cancer patients, in general, experience considerable delays from the progression of the cancer symptoms to present to the medical provider for examination and then to initiate the appropriate treatment. This delay may result in the advancing of the cancer stage.[28] Nevertheless, the performance status of all patients are noticeably good (at least 70%). The score 70% represents the patients' inability to carry on normal activities but still care for self. Meanwhile, the patients with 80% score can be active for work with efforts although some signs or symptoms of the disease are experienced. On the other hand, patients scored 90% can carry on normal activity with minor signs or symptoms of the disease.[13]

A previous study has demonstrated that the toxicity of chemotherapy depends on the doses received by the patients.[5] However, the present study found that the doses of drugs used in chemotherapy were all appropriate in accordance to the recommendation of NCCN and The Indonesian Society of Respirology, where the doses should be calculated based on patient's body surface area especially for paclitaxel, gemcitabine, vinorelbine, and based on the kidney function for carboplatin.[6,9] Hence, the use of chemotherapy beyond recommended doses might not be considered as the causing factor for toxicities of chemotherapy in the present study.

Many severe toxicities in the use of chemotherapeutic agents are often experienced during the first cycle of chemotherapy. Hematologic toxicities from chemotherapy may generally occur from the first to eighteenth week and most commonly arise in the fifth week or at the end of the second cycle.[29,30] The present study found that hematologic toxicities progressed at the end of the second cycle of chemotherapy, where the grade 3 toxicity increased dramatically from 0 to 37.50%. This might occur because the chemotherapy drugs, in addition to destroying the cancer cells, also kill progenitor cells that produce granulocytes, erythrocytes, and platelets in peripheral blood circulation. These immature cells will be destroyed within 7–14 days after chemotherapy, while the maturation of those cells in the bone marrow takes 8–12 days, therefore those blood components will return to normal level on day 28–35.[30]

Anemia is the most common hematologic toxicity found in this study (30%). Fortunately, its highest incidence (50%) was the grade 1 anemia. The proper dose of chemotherapy might contribute to prevent the incidence of high-grade toxicity of anemia, and perhaps also for leukopenia and thrombocytopenia as it is well recognized that higher doses would bring about greater hematologic toxicities.[30] The present data also showed that most of the patients (68.2%) only received 1 cycle of chemotherapy (Figure 1). The chemotherapy

cycle is reported to be associated with the severity of the toxicity. The more the number of chemotherapy cycles, the more severe the toxicity experienced by the patients.[31]

A number of 11 patients experienced anemia in this study: 8 from those who used carboplatin-paclitaxel (50%); 2 from carboplatin-gemcitabine (67%); and 1 from carboplatin-vinorelbine (50%) as shown in Table 3. Patients who experienced anemia in this study were those using a combination of carboplatin with another anticancer agent. The percentage of anemia toxicity among patients who received a combination of carboplatin with paclitaxel; gemcitabine; and vinorelbine were 50; 66.67, and 50%, respectively. A previous study has also found that most common hematologic toxicity from a combination of platinum-gemcitabine was anemia.[32]

Generally, a combination of platinum-gemcitabine has been well recognized as the third generation of chemotherapy agent which often causes both hematologic and non-hematologic toxicities.[32-35] Gemcitabine is a prodrug that is metabolized and activated in the liver, while the clearance of this drug from the body is undertaken through the kidneys. Clearly, both liver and kidney play significant roles in the pharmacokinetics of this drug.[36] Therefore, the use of this combination is not only leading to decreased kidney function through the mechanism of hypomagnesemia due to carboplatin, but also angiopathy lesions in the nephrons due to gemcitabine. In addition, kidney and liver also play particular roles in the secretion of erythropoietin which is important in the production of blood cells, thus alteration to these organs is very likely to contribute to anemia.[37]

Besides causing anemia, chemotherapy can also cause leukopenia, a decrease in the number of white blood cells. Herein, this kind of hematologic toxicity was found in 15% of the patients, all of them were within grade 1–2. This grade of toxicity is considered to not interfere with the chemotherapy. Several factors reported to significantly affect the incidence of leukopenia in chemotherapy with platinum-based regimens include age, sex, creatinine clearance, and BMI.[38]

All patients who experienced leukopenia from chemotherapy were male subjects, aged <65 years old. Nevertheless, both sex and age factors are difficult to be correlated with the incidence of leukopenia in this study. The incidence of leukopenia was experienced by 6 patients, where 5 of them were those taking carboplatin-paclitaxel (31% among this group) and the rest (1 patient) taking carboplatin-vinorelbine combination (55%). Some previous studies reported higher incidence (45% and 72%) of leukopenia among patients taking a combination of platinum with paclitaxel,[39,40] while number of patients taking carboplatin-vinorelbine who experienced leukopenia from other studies has been reported to vary from 21% to 70%.[41,42]

It can be shown from the present data that thrombocytopenia was experienced in 5% of the total cycles, where all of them were in grade 3 toxicity. Thrombocytopenia occurred at the end of cycle 2 and 4. These patients were those who took carboplatin-paclitaxel combination. Previous studies have also reported that around 10–11% of patients who took carboplatin-paclitaxel combination experienced grade 3–4 thrombocytopenia. However, thrombocytopenia is a quite rare hematologic toxicity from the use of platinum and paclitaxel combination.[30,43]

A major limitation of the present study is the limited number of patients although lung cancer is reported to be the number one cancer that kills men and the leading cause of economic burden in Indonesia.[44] The use of four-year data in this study could not even increase a significant number of data for inclusion, thus did not allow some more sophisticated statistical analyses to be conducted. Nonetheless, the number of

samples in this study was quite representative since the total sampling technique was used, thus reducing the risk of missing potential insights from samples that were not included. In addition, incomplete and insufficient details within the medical records are other issues in collecting more data from a wider period. Future studies may need to consider collecting and evaluating the data from multiple hospitals. More data will allow further analysis that may involve comparative and correlative analyses from the patients' socio-demographic profile. On the other hand, the use of electronic medical records should be implemented to improve the transition to the digital age. This implementation is not only supporting the research but also improving the quality of service and coordination of the healthcare providers.[45,46]

The incidence of hematologic toxicities from chemotherapy may be avoided by studying the patients' individual risk factors. Several predictors have been proposed beyond the average risks. A scoring system known as The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) for example, has been proposed to assess the risk of chemotherapy in elderly patients.[47] On the other hand, clinical pharmacists may take a critical role in improving the safety of chemotherapy by identifying the type of chemotherapy errors, their frequency, and their severity, in addition, to provide supportive care such as managing nausea and vomiting symptoms and hematologic issues experienced due to chemotherapy. Pharmacists are also encouraged to participate in nutrition and control of infection.[48] These responsibilities should be promoted to improve healthcare quality and patient safety, especially in the use of chemotherapeutic agents.

Conclusions

The incidence of hematologic toxicities of chemotherapy in lung cancer patients who received the platinum anticancer drugs at Dr. M. Djamil Hospital Padang, Indonesia comprised anemia (30%), leukopenia (15%) and thrombocytopenia (5%). These toxicities were ranging from grade 1 to 3. Further research needs to be conducted analytically related to risk factors for hematologic toxicities among these patients, thus the management can be delivered more effectively and safer.

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Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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