JURNAL FARMASI SAINS DAN KOMUNITAS
Journal of Pharmaceutical Sciences & Community

p-ISSN 1693-5683; e-ISSN 2527-7146

Vol. 22, No. 1, May 2025, pp. 51-58

Research Article

Hematology Toxicities in Paclitaxel-Carboplatin Cancer Regimens

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https://doi.org/10.24071/jpsc.007064

J. Pharm. Sci. Community, 2025, 22(1), 51-58

Article Info

Received: 2023-08-21
Revised: 2024-01-17
Accepted: 2024-04-15

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Keywords:
Adverse drug reactions; Anemia; Cancer; Carboplatin; Myelosuppression

ABSTRACT

Chemotherapy is one therapy for patients with cancer. Treatment using the carboplatin-paclitaxel regimen is usually used for cervix, breast, and ovarium cancer. A research study on hematology toxicity caused by paclitaxel carboplatin is needed to help prevent the debilitating effects on chemotherapy patients. This research aims to give information about the hematology toxicity, incident, severity, relationship between risk factors due to the incidence of myelosuppression, and the relationship between pre-post chemotherapy due to myelosuppression. Common Terminology Criteria for Adverse Events – 5th Version was used to measure the severity of Adverse Drug Reactions (ADRs). The ADRs were evaluated by severity, descriptive statistics, and bivariate analysis (contingency coefficients and Event Tree Analysis. Anemia (66.46%) had the highest incidence followed by leukopenia (18.18%), neutropenia (13.22%), and thrombocytopenia (9.09%). Type of cancer was significantly associated with incidence of anemia (p-value 0.014), leukopenia (p-value 0.001), and thrombocytopenia (p-value 0.002). The number of cycles of chemotherapy using carboplatin-paclitaxel regimens significantly affects the incidence of anemia. Patients who use paclitaxel-carboplatin as a chemotherapy regimen confirmed a decrease in hematologic data such as hemoglobin (p-value 0.001), leukocyte (p-value 0.000), and thrombocyte (p-value 0.000).

INTRODUCTION

Cancer is an illness that is characterized by uncontrollable growth and spread of unusual cells (Workalemahu *et al*., 2020). Global Cancer Observatory in 2020 estimated that there were 19.3 million patients diagnosed as cancer cases with about 10.0 million patient deaths. Mortality cases in cancer are high (Sung *et al*., 2021). Cancer can have various treatments, including radiation, chemotherapy, and surgical operations. The target of chemotherapy is inhibition of tumor multiplication and cell proliferation, in order to avoid metastasis and organ or system invasion (Amjad *et al*., 2023).

Adverse Drug Reactions (ADRs) are reactions that result from interventions associated with treatment with a medicinal product, and the reaction can be defined as an uncomfortable feeling or appreciably harmful event. The reaction in toxic effects of chemotherapy is also due to the effect on normal cells. Inhibition of cancer accretion can take place at several levels within the cells and their environment (Amjad *et al*., 2023). Health-related Quality of Life (QoL) is an important result after chemotherapy. Many ADRs experienced by patients with cancer may have unwanted effects on QoL during the chemotherapy and subsequent disease-free survival (Assi *et al*., 2021).

Carboplatin is a chemotherapeutic platinum analogs agent. ADRs of carboplatin are cytopenia, alopecia (hair loss), mucositis diarrhea, nausea vomiting, anemia, thrombocytopenia, neutropenia and leukopenia

(Oun *et al*., 2018). Paclitaxel is a taxane chemotherapy agent. Paclitaxel is indicated for breast, lung, and ovarian cancer. ADRs of paclitaxel are gastrointestinal disturbances, edema, high blood pressure, fever, rash, rhinitis, and pain (Amjad *et al*., 2023; Meitasari *et al*., 2021). Recent research about the neurotoxicity and ADRs of Carboplatin Paclitaxel regimens found that Carboplatin Paclitaxel has ADRs incidence from neurotoxicity, including sensory neuropathy (sensory peripheral) (77.69%), motor neuropathy (motoric peripheral) (3.31%), joint pain or arthralgias (53.72%), and weakness in muscles (37.19%) (Meitasari *et al*., 2021).

Treatment using the carboplatin-paclitaxel regimen is usually used for cervix, breast, ovarium, and various types of cancer. A research study on the hematology toxicity caused by paclitaxel carboplatin is needed to help prevent the debilitating effects on chemotherapy patients. This research aims to give information about the type, of hematology toxicity, incident, the severity of ADRs, the relationship between the identified risk factors due to incidents of myelosuppression, and the relationship between pre-post-chemotherapy due to the myelosuppression of patients who are given paclitaxel carboplatin regimens. We hope data in this study can be used to anticipate and possibly mitigate ADRs in patients undergoing the treatment with paclitaxel carboplatin regimens.

METHODS

This research was conducted using an observational study with a cross-sectional design, by a prospective approach directly to the patient. This research was carried out for 4 months in Dr. Moewardi Hospital Surakarta. Permission from the ethical committee of Dr. Moewardi Hospital in Surakarta was obtained before the initiation of this study with the number 1.084/IX/HREC/2020. The minimal sample size in this research was counted with the Slovin formula and the result was 97 respondents. The inclusion criteria are 18-75-years-old patients with cancer who use Paclitaxel-Carboplatin regimen therapy and have had minimal >1 cycle chemotherapy. The exclusion criteria are patients with comorbid HIV AIDS, disorders in the kidney, tuberculosis, disorders in mental, liver disorders, and gastrointestinal disorders. The total number of respondents in this research was 125 but 3 patients were excluded because the respondents have disorders in their liver.

Causality of Adverse Drug Reactions (ADRs) uses the WHO UMC assessment scale. The Common Terminology Criteria for Adverse Effects – Version 5 (CTCAE 5) was used to measure the severity of ADRs. CTCAE codifies descriptive terminology that can be utilized for adverse event reporting. The grade refers to the severity of the adverse event. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event. The ADRs were evaluated by the severity and descriptive statistics were used for obtained patient characteristics. The associations were determined between independent variables (age group, sex, number of cycles, duration of stay in hospital) and dependent variables (anemia, leukopenia, thrombocytopenia). The data analysis used contingency coefficients and Event Tree Analysis (ETA). McNemar and Wilcoxon's tests were used to identify the relationship status of hematologic status between pre- and post-chemotherapy.

RESULTS AND DISCUSSION

Patients in this study are 100% women because in Dr. Moewardi Hospital paclitaxel carboplatin is given for ovarian, cervix, and breast cancer therapy. In this research, many of the women are patients with breast cancer. Paclitaxel carboplatin is a regimen chemotherapy that is indicated and an effective regimen used for advanced breast cancer (Lobefaro *et al*., 2023). Despite that, carboplatin-paclitaxel is also effective for cervical, ovarian, and non-small cell lung cancer (Dechow *et al*., 2021). In Indonesia, adult patients are classified as 17 to 65 years old, and in this study 89.3% of adult patients use carboplatin-paclitaxel for therapy. Cases of patients with cancer with age <65 years old were <10.6% among those >65 years old (Pilleron *et al*., 2019).

In this study patients who were included as respondents were those who completed at least a second chemotherapy with carboplatin-paclitaxel. A total of 30.6% completed the second chemotherapy, and 26.6% completed the third chemotherapy, and the number of cycles can be seen in Table 1. The carboplatin-paclitaxel regimen can be given to the patient every 21 days for 6 cycles (Chan *et al*., 2016). In this research, 35.5% of patients were doing one-day care chemotherapy, and 49.6% stayed in the hospital for 2 days.

Routine blood counts were tested every cycle of chemotherapy, on the day before chemotherapy and around 7 and 14 days after chemotherapy. Patients who experience abnormalities in blood counts will be treated with chemotherapy until the blood counts are at

the safety limit level. The routine blood counts are erythrocytes, hemoglobin, leukocytes, neutrophils, and thrombocytes. A study about hematologic toxicities from chemotherapy that uses carboplatin-paclitaxel in lung cancer found that patients had a high incidence of anemia and thrombocytopenia (Yuliandra *et al*., 2019). This finding is similar with the result of our research (Table 2) that found anemia has the highest incidence followed by leukopenia, neutropenia, and thrombocytopenia.

One recent study in Taiwan in 2020 determined that thrombocytopenia usually begins to appear after day 14 and is predictively cumulative, contributing to the consideration of a carboplatin dose reduction. Patients with the paclitaxel-carboplatin regimen had a higher risk of developing neutropenia grade ¾ and it reached a statistically significant difference. Patients with myelosuppression are often forced into postponing the therapy or modifying (decreasing) the dosage of the therapeutic agent (Huang *et al*., 2020). The research in Brazil showed that the most common toxicity of carboplatin-paclitaxel was myelosuppression: grades 3 and 4 anemia, neutropenia, and thrombocytopenia were observed in 43.0%, 17.8%, and 9.2% of the cases, respectively (Garces *et al*., 2013).

Table 1. Characteristics Patients

Characteristics of Patients	Patients (n= 121)	
	n	%
Gender		
Male	0	0
Female	121	100
Age (years old)		
16-25	1	0.8
26-35	2	1.6
36-45	19	15.7
46-55	43	35.5
56-65	43	35.5
65-75	13	10.7
Ethnic		
Java	121	100
Kind of Cancer		
Ovarian Cancer	44	36.3
Cervical Cancer	38	31.4
Breast Cancer	39	32.2
Number Cycle		
2	37	30.6
3	32	26.4
4	21	17.4
5	17	14.0
6	14	11.6
Stay in Hospital (days)		
1	43	35.5
2	60	49.6
3	18	14.9
Comorbidity		
Without	98	81.0
Diabetes Mellitus (DM)	14	11.6
Hypertension (HT)+ DM	4	3.3
HT+DM+Ashtma	1	0.8

Table 2. Incident and Severity of Hematology Toxicity due Carboplatin Paclitaxel

Hematology Toxicity	Incident	Severity		
		Grade 1	Grade 2	Grade 3
Anemia	78 (66.46%)	58 (74.35%)	15 (19.23%)	5 (0.06%)
Leukopenia	22 (18.18%)	22 (100%)	0	0
Neutropenia	16 (13.22%)	0	16 (100%)	0
Trombositopenia	11 (9.09%)	10 (90.90%)	1 (0.10%)	0

Cancer patients with anemia have a high prevalence and there is a significant clinical impact on patient prognosis and QoL (Madeddu *et al*., 2018). Anemia grade 1 is classified by hemoglobin count range of 11.0-10.0 g/dL, hemoglobin count <10.0-8.0 g/dL (grade 2), and hemoglobin count <8.0-4.9 g/dL (grade 3). In this study, anemia was suffered by 66.46% of our patients. These results matched another recent study that found anemia was the considerable hematologic toxicity experienced by more than 50% of the patients (Yuliandra *et al*., 2019). Anemia is a common ADR that correlates with dose-dense chemotherapy during curative breast cancer treatment leading to delays in chemotherapy and increases in the cost. Low-grade cancer, grade 3 or 4 thrombocytopenia, and grade 2 or higher anemia after 2 cycles of therapy are risk factors for blood transfusions during treatment (Sharma *et al*., 2022).

Leukopenia and neutropenia in cytotoxic chemotherapy are positively correlated with survival in various kinds of cancer. The severity of leukopenia developed the possibility of serious infection (Liu *et al*., 2013). The research in South Korea found that almost all patients who are undergoing chemotherapy are at risk for the occurrence of leukopenia, though the incidence varies according to regimen, dose, and cancer type (Lee *et al*., 2016). In this study patients with leukopenia caused by carboplatin-paclitaxel was 18.18% and all of that was grade 1 (leukocyte:3700-3000/mm^3). Neutropenia is a hematologic toxicity that is caused by a decrease in the number of neutrophils. The incidence of neutropenia caused by carboplatin-paclitaxel (Table. 2) was 13.22% and all of that was grade 2 (neutrophil: ANC 1499-1000 mm^3). Mild and severe neutropenia in advanced non-small cell lung cancer (NCLC) may be representative markers of adequate therapy dosage; the deficiency of neutrophils indicates under dose whereas severe neutropenia indicates overdosage (Jin *et al*., 2016).

Of the patients treated with carboplatin paclitaxel in this study, 9.09% sustained thrombocytopenia. Patients with non-hematologic events with therapy combination carboplatin-paclitaxel had thrombocytopenia as a common ADR. Thrombocytopenia caused by chemotherapy is associated with the dose of chemotherapy and the type, with regimens containing platinum (carboplatin, cisplatin) and gemcitabine. Patients with platelet counts below 25x109/L have a high risk of bleeding and need platelet transfusions (Kuter, 2022).

Recent research was conducted in America on 419 patients' post-chemotherapy who had grade ≥3 thrombocytopenia, neutropenia, and/or anemia episodes in minimal 2 lineages (33.9%). Patients who were tested in the laboratory reached a total of 20.6% of patients who had both ADRs grade 3 anemia and ≥ 3 neutropenia, and 21.5% of patients had both ADRs grade 3 and grade ≥3 thrombocytopenia. Also, some patients had both ADRs grade ≥3 neutropenia and grade ≥ 3 thrombocytopenia (22.8%) (Hart *et al*., 2023).

Table 3 describes the results of the bivariate analysis of factors for the occurrence of anemia, leukopenia, neutropenia, and thrombocytopenia. The factors that were tested were cancer type, comorbidity, age, number of cycles, and length of stay in hospital. The result of the type of cancer (ovarian, breast, cervix) has a significant effect on anemia, leukopenia, and neutropenia. Recent research in Tamil Nadu, India shows that factors that induced myelosuppression such as age, gender, and diagnosis showed statistically significant association with 95% confidence intervals (CI) and p-value <0.005. The drugs paclitaxel, carboplatin, 5 fluorouracil, cyclophosphamide, and Adriamycin proved to be highly myelosuppressive with a *p*-value of 0.049 (Keziah *et al*., 2023).

Table 3. Associating Characteristic Patients and ADRs Myelosuppression

P value	Age	Kind of Cancer	Number Cycle	Stay in Hospital	Comorbidity
Anemia	0.594	0.014*	0.029*	0.357	0.356
Leukopenia	0.478	0.001*	0.329	0.217	0.629
Neutropenia	0.544	0.002*	0.208	0.211	0.335
Thrombocytopenia	0.578	0.497	0.155	0.226	0.821

*p values were statistically different. Significance level p=0.05

Table 4. Difference of Hematologic Findings Between Before and After Chemotherapy

Hematology Toxicity	Chemotherapy				*p* value
	Pre		Post		
	Median	Range	Median	Range	
Hemoglobin (g/dL)	11.9	7.2	11.5	8.0	0.000*
Leukocyte (mm^3)	6.2	7.5	5.3	8.8	0.000*
Thrombocyte (mm^3)	297	365	258	517	0.000*

**p* values were significantly different. Analysis was using Wilcoxon test with *p*=0.05 significance level
Values in leukocyte and thrombocyte times by 1000.

Table 5. Chemotherapy Carboplatin Paclitaxel Induced Myelosuppression

Hematology Toxicity		Chemotherapy		Total	*p* value
		Pre	Post		
Hemoglobin	Low	25	40	121	0.001*
	Normal	5	51		
Leukocytes	Low	26	83	121	0.000*
	Normal	2	10		
Platelet	Low	11	109	121	0.000*
	Normal	0	1		

**p* values were significantly different. Analysis was using McNemar test with *p*=0.05 significance level.

In this study, gender cannot be analyzed as a risk factor because all the genders were female. A study in China describes that female patients have a higher chance of incidences of leukopenia than male patients (p=0.042) and later stages of the disease (p=0.022). Another possible point for the higher occurrence of hematologic ADRs in women is having more body fat and higher baseline body mass index (BMI) than men, which could act on the distribution of cytotoxic drugs and increase potential toxicity (Liu *et al.,* 2013).

The number of cycles of chemotherapy using carboplatin-paclitaxel regiments affects significantly the incidence of anemia. This finding is in line with research in Ciptomangunkusumo Hospital that found hemoglobin, leukocyte, and thrombocyte levels were significantly decreased after adjuvant carboplatin-paclitaxel chemotherapy on every cycle with p-value <0.001 (Paniroi and Nuryanto, 2015). Research in the United States of America showed that anemia happens in 51.3% of patients who use carboplatin-paclitaxel on the first cycle (Xu *et al*., 2014). Patients with liquid and solid cancer have growth of severe anemia on the 1st cycle of chemotherapy which is related to an increased risk of dose delay and/or dose reduction in the subsequent chemotherapy cycle, regardless of gender, age group, race, chemotherapy cycle, stage of cancer, absolute neutrophil value, liver function, platelet value, and renal function (Bryer and Henry, 2018). The cycle level prevalence grows in proportion to the chemotherapy due anemia by the number of cycles in patients receiving chemotherapy. The incident proportion of overall anemia events and moderate severity anemia decreased in cycle 6 (14%) and increased from cycles 1 (13%) to 5 (21%) (Cannavale *et al*., 2019).

In this study age, length of stay, and comorbidity had no significant association with incidents of leukopenia, anemia, neutropenia, and thrombocytopenia. This finding is in line with a finding that anemia and type of regimen chemotherapy, number of cycles, positive lymph nodes, comorbidities, body mass index, and menstrual status did not have a significant relationship statistically (Pourali *et al*., 2017)

Table 4 shows the difference of blood count findings between before and after chemotherapy using carboplatin and paclitaxel. The result of the analysis is leukocyte, hemoglobin, and thrombocyte counts decreased significantly after using carboplatin and

paclitaxel. The median of hemoglobin was dropped by 0.3 gram/dL due to the chemotherapy. The median of leukocytes dropped 900/mm^3 and thrombocytes dropped 39,000/mm^3. The data are reinforced by the results in Table 5. A total of 121 patients were recorded and completed 6 cycles using carboplatin-paclitaxel. Hemoglobin means underwent a decrease of 0.29 g/dL every cycle. The baseline hemoglobin was 11.30±0.887 mg/dL. ANC dropped 543 cells/mm^3 per cycle and those who developed neutropenia were 5.35%. The mean thrombocyte level was 34.225 cells/mm^3 and 23% developed thrombocytopenia (Winarto *et al.*, 2020). Paclitaxel and platinum agents induced myelosuppression by directly decreasing hematopoiesis in bone marrow (Noviyani *et al.*, 2019). An Iranian study found significant numbers of patients suffering anemia pre-chemotherapy (41%) and patients who became anemic during and post-chemotherapy (43.1%). The incidence of anemia in post-chemotherapy was significantly ($p<0.05$) higher in the advanced stages of cancer (Pourali *et al*., 2017).

In Table 5 there are categorical data of hematologic counts and pre or post chemotherapy. The category is low and normal it was conducted by normal hematologic count and low hematologic counts mean anemia, leukocytopenia, and thrombocytopenia. The hematologic count is categorized as normal and low. All three hematologic counts have a p value < 0.05, which means hemoglobin, leukocyte, and thrombocyte decreased significantly after chemotherapy. This table shows the increase of low hemoglobin, leukocyte, and thrombocyte due to post-chemotherapy. Another study also found the same pattern indicating anemia, low erythrocyte, leukopenia, and thrombocytopenia also decreased significantly (Charles *et al*., 2016).

Another American study totaling 1239 was conducted with mostly patients who began 1st line chemotherapy (94.0%). Through chemotherapy containing lines of therapy, 98.6% of patients had minimal 1 case of myelosuppressive ADRs; patients had grade ≥ 3 myelosuppressive episodes in one cycle (62.1%), patients had grade ≥3 myelosuppressive episodes in two cycles (33.9%), and patients had grade ≥ 3 myelosuppressive episodes in all three cycles (15.5%). There is a correlation between multilineage myelosuppression among chemotherapy-treated patients. Decreased incidents of myelosuppression can make chemotherapy treatment safer, reduce the need for supportive care, reduce cost, and prevent complications (Hart *et al*., 2023).

Patients with epithelial ovarian cancer who use a combination of cisplatin and paclitaxel have adverse reactions to hematology toxicity. The values of hemoglobin, leukocyte, and platelet levels were decreased after 6 cycles of chemotherapy. The hemoglobin levels were 12.05–10.69 g/dL (p-value: 0.282); platelet levels were 378.5–326.9 mm^3 (p-value: 0.569) and leukocyte levels were 11.32–8.28 mm^3 (p-value: 0.517). There were significant differences in leukocyte, hemoglobin, and platelet levels pre-1st chemotherapy and post-6th of therapy using cisplatin and paclitaxel. Low ADRs of cisplatin and paclitaxel regiment were observed in this research in grade 1 anemia (Noviyani *et al.*, 2019).

CONCLUSIONS

Anemia (66.46%) had the highest incidence followed by leukopenia (18.18%), neutropenia (13.22%), and thrombocytopenia (9.09%). Type of cancer was significantly associated with the incidence of anemia, leukopenia, and thrombocytopenia. The number of cycles of chemotherapy using carboplatin-paclitaxel regiments significantly affected the incidence of anemia. The myelosuppression events such as thrombocytopenia, anemia, and leukopenia because of the decrease in hematologic data after paclitaxel and carboplatin chemotherapy were clearly established.

ACKNOWLEDGEMENTS

The authors would like to grateful to Penelitian Hibah Grup Riset (Penelitian HGR-UNS) A No. 194.2/UN27.22/PT.01.03/2024.

CONFLICT OF INTEREST

The authors stated no potential conflict of interest in authorship, research, and also publication of this paper.

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