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Original Article

Association and Correlation of Different Chemotherapy Regimens and Doses with Incidence and Severity of Thrombocytopenia among Solid Cancer Patients

Zuraidah Mohd Yusoff[1], Abdulrasool Mahmood Wayyes[2], Marwah Mohammed Hareeja[2], Saif Salah Abbas[2]*

[1] *Clinical Pharmacy Discipline, School of Pharmaceutical Sciences, University of Sains Malaysia, Minden Penang, Malaysia*

[2] *Faculty of Pharmacy, Al-Rafidain University College, 10052 Baghdad, Iraq*

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Abstract

Background: Thrombocytopenia is an abnormal decrease in platelet count and a detrimental side effect of chemotherapy. It leads to hemorrhage in vital organs and negatively impacts the quality of life (QOL). ***Aims***: To evaluate the effect of chemotherapy regimens and doses on thrombocytopenia incidence and severity among patients with solid tumors. ***Methods***: This retrospective observational study was conducted at Penang Hospital, Malaysia. It includes 341 cancer patients with thrombocytopenia who were admitted between 2003 and 2009. The main statistical tests used were the Chi-square test and logistic regression. The level of significance was set at $P<0.05$. ***Results***: Of the 341 patients included, 21 (6.2%) had thrombocytopenia before chemotherapy and developed in the remaining 320 (93.8%) after chemotherapy. The majority of patients had moderate thrombocytopenia ($n=172$; 53.8%), followed by mild ($n=97$; 30.3%), and severe thrombocytopenia ($n=51$; 15.9%). The 5-fluorouracil, epirubicin, cisplatin (FEC) regimen had strong associations and correlations with thrombocytopenia incidence and severity, but the associations and correlations for thrombocytopenia severity were stronger than those for incidence. The dosage of 5-FU, cyclophosphamide, docetaxel, and cisplatin play a critical role in thrombocytopenia incidence and severity. ***Conclusion***: Monitoring hemoglobin levels for cancer patients treated with FEC, 5-FU+5-FU, Docetaxel, and Cisplatin specifically with high doses must be emphasized and a focus of particular attention.

***Keywords*:** Chemotherapy regimens, doses, solid cancer, thrombocytopenia.

ارتباط نظم العلاج الكيميائي المختلفة والجرعات مع حدوث وشدة التجلطات الدموية بين مرضى الأورام السرطانية الصلبة

الخلاصة

الخلفية: نقص الصفائح الدموية هو تأثير جانبي ضار للعلاج الكيميائي و يؤدي إلى نزيف في الأعضاء الحيوية ويؤثر سلبا على نوعية الحياة. **الأهداف**: تقييم تأثير أنظمة العلاج الكيميائي وجرعاتها المختلفة على حدوث نقص الصفيحات الدموية وشدتها بين المرضى الذين يعانون من أورام سرطانية صلبة. **الطرائق**: أجريت هذه الدراسة الرصدية بأثر رجعي في مستشفى بينانغ، ماليزيا. وشملت 341 مريضا بالسرطان يعانون من الجلطات الدموية الذين أدخلوا المستشفى بين عامي 2003 و 2009. وكانت الاختبارات الإحصائية الرئيسية المستخدمة هي اختبار كاي والانحدار اللوجستي. تم تعيين مستوى الأهمية في P أقل من 0.05. **النتائج**: من بين 341 مريضا حصلت التجلطات لدى 21 (6.2٪) قبل العلاج الكيميائي و320 المتبقية (93.8٪) حدثت بعد العلاج الكيميائي. كان معظم المرضى يعانون من نقص الصفائح المعتدل (53.8٪)، تليها الخفيفة (30.3٪)، ثم تجلط الدم الحاد (15.9٪). كان لنظام 5-fluorouracil وepirubicin و(FEC) cisplatin ارتباطات قوية مع حدوث الجلطات وشدتها، ولكن شدة الجلطات الدموية كانت أقوى من تلك الخاصة بالإصابة. ولعبت جرع 5-FU و سيكلوفوسفمايد و دوسيتاكسيل و سيسبلاتين دورا حاسما في حدوث الجلطات وشدتها. **الاستنتاج**: يجب التأكيد على مراقبة مستويات الهيموغلوبين لمرضى السرطان الذين عولجوا بجرع عالية من FEC، 5-FU+5-FU، Docetaxel، و Cisplatin والتركيز على الأهتمام الخاص بهم.

* Corresponding author: Saif S. Abbas; Faculty of Pharmacy, Al-Rafidain University College, 10052 Baghdad, Iraq; email: saif_s_abbas90@yahoo.com

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INTRODUCTION

Thrombocytopenia is a term used to denote abnormal decreases in platelet numbers. Thrombocytopenia is common in cancer patients; it usually results from the use of conventional chemotherapy and, at times, can be a dose-limiting factor for chemotherapy administration. The incidence of thrombocytopenia among solid cancer patients is rather low, ranging between 10%-25% among breast cancer, ovarian cancer, and germ cell cancer patients who were treated with intensive chemotherapy, but it is high among acute leukemia patients [1-10]. Thrombocytopenia is a major detrimental side effect of chemotherapy as it can lead to hemorrhage in vital organs, particularly the brain, specifically in solid cancer patients who were treated with chemotherapy. Chemotherapy-induced thrombocytopenia can occur via different mechanisms, either by suppressing megakaryopoiesis, which prevents platelet production, or by directly damaging the platelets. Chemotherapies like antimetabolites and alkylating agents can induce severe thrombocytopenia as they cause bone marrow suppression, specifically after the first cycle of chemotherapy [9-15]. The incidence and severity of thrombocytopenia mainly depend on factors such as chemotherapy, chemotherapy schedule, chemotherapy intensity, and type of cancer. Treatment with single or combination chemotherapy also plays a major role in the incidence and severity of thrombocytopenia incidence and severity, since the use of combination chemotherapy leads to severe thrombocytopenia more than the use of single chemotherapy [1,3,5,6,9-13]. As the severity of thrombocytopenia increases, cancer patients may suffer from malaise, weakness, fatigue, and petechia. These signs and symptoms are significantly related to physical, emotional, psychological, and emotional consequences, i.e., quality of life, in cancer patients [9,10,16,17]. The present study aimed to investigate the association between the incidence and severity of thrombocytopenia and various chemotherapy regimens and doses.

METHODS

Study design and setting

We performed a retrospective observational study at Penang Hospital, located in the state of Penang Island, Malaysia. Penang Hospital is the largest public hospital in north Malaysia and is a referral center for cancer patients. Ethical approval for this study was obtained from the Clinical Research Centre of the Ministry of Health, Malaysia.

Study sample

Patients aged ≥18 years old with solid cancer and thrombocytopenia who were admitted to the oncology clinic of Penang Hospital from 2003 to 2009 and treated with chemotherapy only were eligible to be included in the study. Patients suffering from hematological diseases or treated with radiotherapy were excluded, as were patients with immune thrombocytopenic purpura (ITP), autoimmune diseases, thromboembolic disease, active infection requiring antibiotic treatment, leukemia, or stem cell/ bone transplant. Patients suffering from arterial arrhythmias, congestive heart problems, or who had surgery on any vital organ that may affect platelet level were also excluded [18].

Data collection

Data was taken from patients' medical records using a standardized form. Information was collected on age, gender, ancestry (Chinese, Malay, Indian), cancer type, cancer stage, presence of metastases, use of chemotherapy, chemotherapy regimen, number of chemotherapy cycles, chemotherapy doses in each cycle, and thrombocytopenia treatment. Information on platelet levels was collected at the time of cancer diagnosis and after chemotherapy administration. Thrombocytopenia severity was classified according to calcium levels as mild (<150 - ≥100 × 10^3/mL), moderate (<100 - ≥50 × 10^3/mL), severe (<50 - >20 × 10^3/mL), and life-threatening (platelets level ≤ 20 × 10^3/mL).

Statistical analysis

A chemotherapy regimen, incidence and severity of thrombocytopenia, and the presence of metastases were considered categorical variables. The total doses of chemotherapy were considered continuous variables. Data analysis was performed using the Statistical Package of Social Science (SPSS®) software program version 15. The distribution of categorical variables was tested, using a parametric test (Chi-square). The level of significance for associations was set at $P<0.05$. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for that association between different chemotherapy regimens and thrombocytopenia. For continuous data, the Spearman correlation test was used when the data was not normally distributed, as assessed by the Kolmogorov-Smirnov test. For data that showed a significant correlation, linear regression was used to find the strongest correlation and association between chemotherapy doses and thrombocytopenia incidence and severity.

RESULTS

The majority of the thrombocytopenic patients (n=341) were women (n=216; 63.3%); males represented only (n=125) 36.5%. Chinese were the predominant race (n=200; 58.6%), followed by Malay (n=105; 30.8%), and finally Indian (n=36; 10.6%). The mean age was 52.4 years (20-81 years). The majority of patients (n=104; 30.5%) were between 50-59 years old. The most common cancer type among thrombocytopenic patients was breast cancer (n=121; 37.8%), followed by colon cancer (n=54; 16.9%) and ovarian cancer 43 (13.4%). Most patients (n=214; 62.8%) suffered from early-stage disease and only a small number (n=127; 39.7%) had advanced-stage disease. Twenty-one (6.2%) of the 341 patients suffered from thrombocytopenia before chemotherapy, while 320 developed thrombocytopenia after receiving chemotherapy. Among patients with thrombocytopenia before chemotherapy, 16 (76.2%) were diagnosed at the same time as their cancer, while in 5 (23.8%), thrombocytopenia was detected during their 2nd visit to the hospital after a cancer diagnosis. 320 patients developed thrombocytopenia after chemotherapy, 140 (43.8%) of whom were diagnosed after the 4th cycle of chemotherapy. This was

followed by those who were diagnosed after the 3rd cycle (121; 37.8%), the 2nd cycle (*n*=57; 17.8%) and the 1st cycle (*n*=2; 0.6%). Most patients suffered from moderate thrombocytopenia (*n*=172; 53.8%), and 97 (30.3%) had mild thrombocytopenia. Only 51 (15.9%) of the patients suffered from severe thrombocytopenia; 37 had minor bleeding and 14 had major bleeding. The majority of patients with moderate or severe thrombocytopenia were treated with only a delay in chemotherapy (*n*=223; 65.4%), whereas 14.9 % (*n*=51) of patients with severe thrombocytopenia were treated with platelet transfusion and delayed or reduced chemotherapy. Patients with mild thrombocytopenia received no treatment; their chemotherapy was not reduced nor halted. Among the 320 patients, 72 (22.4%) were treated with a combination of fluorouracil, epirubicin and cyclophosphamide (FEC), followed by 5-FU+5-FU or 5-FU (*n*=59; 18.4%) and FOLFOX (*n*=33; 10.3%), Cisplatin + 5- FU (*n*= 25; 7.8%), Docetaxel 21 (6.6%), etc. Among cancer patients who developed thrombocytopenia after chemotherapy, 56 (7.7%) were treated with high doses (≥1000 mg) of 5-FU145 (6.2%), 900-999 mg of 5-FU1, 52 (7.2%) with ≥100 mg of epirubicin, and 56 with (7.7%) ≥ 1000 mg of cyclophosphamide. There was a significant association between thrombocytopenia incidence and severity after chemotherapy and chemotherapy regimen, but the association with thrombocytopenia incidence (*P*=0.011) was weaker than that with thrombocytopenia severity (*P*=0.002). The results of logistic regression showed that the chemotherapy regimens most highly associated with thrombocytopenia incidence and severity were FEC (*P*=0.009; odd ratio 5.1), 5-FU plus 5-FU, and 5-FU (*P*=0.024; odd ratio 4.1). The association between chemotherapy regimen and thrombocytopenia severity was greater than that associated with thrombocytopenia incidence, and FEC was highly associated with thrombocytopenia severity (*P*=0.002; OR=7.1) followed by 5-FU+5-FU, and 5-FU (*P*=0.018; odd ratio 6.3) (Table 1). In Table 2, ≥1000 mg 5-FU1 (i.e., the bolus dose given as a part of the FEC regimen or 5-FU+ 5-FU regimen) had the greatest association and correlation with thrombocytopenia incidence (*P*=0.000; *r*=0.819). Lesser associations were shown with lower doses (900-999 mg: *P*= 0.015, *r*= 0.734; 800-899 mg: *P*=0.022, *r*=0.683; 700-799 mg: *P*=0.041, *r*=0.561), but doses of 600-699 mg and 400-599 mg showed an insignificant association. As for cyclophosphamide, only a dose of ≥1000 mg (*P*=0.001, *r*=0.741) and 900-999 mg (*P*=0.033, *r*=0.648) showed a significant association with thrombocytopenia incidence. For cisplatin, only a dose of ≥100 mg showed a significant association with thrombocytopenia incidence (*P*=0.027, *r*=0.695). While, for epirubicin, 5-FU2 (the second dose in the 5-FU+ 5-FU regimen), i.e., the dose given on the second day after the bolus dose of 5-FU1, all of the doses, docetaxel, oxaliplatin, and other doses, all showed insignificant associations with thrombocytopenia incidence. For docetaxel, only a dose of ≥110 mg was significantly associated with thrombocytopenia incidence. In Table 3, ≥1000 mg 5-FU^1 showed the strongest association and correlation with thrombocytopenia severity (*P*=0.000, *r*=0.924), followed by the dosage of 900-999 mg (*P*=0.002, *r*=0.829), and finally the dosage of 800-899 mg (*P*=0.012, *r*=0.795). For cyclophosphamide, the dosage that showed a significant association with thrombocytopenia severity was ≥1000 mg (*P*=0.001, *r*=0.814). The same for cisplatin doses ≥ 1000 mg (*P*= 0.007; r = 0.644) and 90-99 mg (*P*= 0.049; *r*= 0.422). Meanwhile, only a dose of ≥110 mg of docetaxel showed a significant association with thrombocytopenia severity (*P*=0.017, r =0.664). Regarding, the rest doses all showed an insignificant association with thrombocytopenia severity. However, it is clear from the results that the association and correlation of chemotherapy regimens with thrombocytopenia severity was greater than their association and correlation with thrombocytopenia incidence. The Linear regression tests showed a significant association and strong correlation between thrombocytopenia incidence, and a 5-FU1 (the bolus dose that is given as a part of FEC regimen or 5-FU+ 5-FU regimen) dose of ≥1000 mg, a cyclophosphamide dose of ≥1000 mg (*B*= 67446.1, *β*= 0.897, *P*= 0.004) and a dose of 900-999 mg (*B*= 3062.9, *β*= 0.814, *P*= 0.019). Other doses showed an insignificant association with thrombocytopenia incidence (Table 4). 5-FU^1 (which represents the bolus dose that is given as a part of FEC regimen or 5-FU+ 5-FU regimen) at a dose of ≥1000 mg also had the strongest association and correlation with thrombocytopenia severity (*B*=7950056.8, *β*=0.997, *P*=0.001). Cyclophosphamide only at a dose of ≥1000 mg and 900-999 mg showed significant associations with thrombocytopenia incidence (Table 4). The results showed stronger associations and correlations between chemotherapy dose and thrombocytopenia severity than its incidence. The linear regression and correlation tests showed that 5-FU^1 (i.e., 5-FU first dose or bolus dose) dose of ≥1000 mg had the strongest association and the highest positive correlation with thrombocytopenia incidence and severity, followed by cyclophosphamide ≥1000 mg, 900-999 mg 5-FU^1, and cisplatin ≥100 mg. For all of the doses with significant associations, correlations with severity were higher than those with incidence.

DISCUSSION

The present study showed a significant association between thrombocytopenia incidence and severity after chemotherapy and chemotherapy regimen and/ or dose. The results clearly showed that the association between chemotherapy regimen and thrombocytopenia incidence was weaker than that for thrombocytopenia severity, since Chi-square *P* values for the association with incidence was 0.041, while for severity it was 0.009. Moreover, the results of logistic regression analyses showed a stronger relationship between thrombocytopenia incidence and severity and the FEC regimen than the 5-FU+5-FU and other regimens. Also, the relationship between FEC and thrombocytopenia severity was more important than the relationship with incidence. Similar findings were seen for the other chemotherapy regimens included in this study. The present study aimed to identify the main risk factors for the incidence and clinical complications of thrombocytopenia, which are associated with chemotherapy regimens. The importance of this point was the emphasis by Hitron *et al*. (2010), who conducted a retrospective study in the USA on 254 patients with solid cancers and treated them with 278 different chemotherapy regimens. They showed that

thrombocytopenia mostly occurred in patients treated with cisplatin/gemcitabine (57%) followed by those who received carboplatin/ gemcitabine (29%) and cisplatin/etoposide (18%). The main difference between the study by Hitron *et al.* and our present study is that they only looked at the chemotherapy regimen that caused thrombocytopenia and other factors that increased clinical complications, i.e., a general overview of clinical complications, not specific like the current study focused only on thrombocytopenia. In addition, no statistical analysis was done. In the present study, we focused on detecting the main role of various chemotherapy regimens and doses in the incidence and severity of thrombocytopenia [17]. Wu *et al*. (2009) stated that thrombocytopenia incidence among solid cancer patients ranged from 10-36% before chemotherapy. After chemotherapy, thrombocytopenia incidence increased to 75%, showing a strong association between thrombocytopenia and chemotherapy. This was also observed in the present study, which showed a very significant association between thrombocytopenia incidence and severity and the chemotherapy regimen. Besides, Wu *et al*. (2009) mentioned that the chemotherapy regimen does play some role in the extent of platelet count drops and the duration of recovery [18]. Therefore, the present study aimed to determine which chemotherapy regimens and doses affect platelet level reduction and recovery. The high association we observed between FEC and thrombocytopenia incidence and severity could be because one of the main side effects of repeating the FEC regimen, i.e., receiving more than one cycle of FEC, is thrombocytopenia [17]. Capotorto *et al*. (2003) compared the standard dose of FEC (5-FU 500 mg/m^2, epirubicin 75mg/m^2, and cyclophosphamide 500 mg/m^2) given every 21 days, with an FEC-G regimen (FEC+ gemcitabine) with the same dose but given every 14 days, and an MMM-G regimen (mitoxantrone 10mg/m^2, methotrexate 35 mg/m2 every 14 days, mitomycin C 10 mg/m2 every 28 days) in the treatment of patients with metastatic breast cancer. Both FEC-G and MMM-G are considered intensified regimens. The study aimed to detect the response rate, survival time, and progression time of the patient, and the mean results showed that there was no difference in these three factors between the three regimens. The main side effects associated with the two FEC regimens were neutropenia, which was significantly associated with the FEC standard dose, and thrombocytopenia, which was significantly higher with both intensified regimens than with standard FEC regimens. The study concluded that increasing the dose of FEC will increase the incidence of thrombocytopenia, which is in agreement with the present study. But the main difference between Capotorto *et al* and the present study is that we focused on thrombocytopenia incidence and severity in patients with various types of solid cancer while their study focused on breast cancer alone [19]. The study conducted by Kahán *et al*. (2008) in Hungary included 51 women with early-stage breast cancer. Patients who have been treated with 60 mg/m^2 epirubicin in the FEC_{60} regimen provide few clinical benefits. However, when the initial dose of epirubicin was 100 mg/m^2, it was associated with hematological and non-hematological toxicities. In their study, patients were also treated with FEC_{75} (75 mg/ m^2 epirubicin) and FEC_{90} (90 mg/ m^2 epirubicin), whereby each patient was treated with 6 cycles of chemotherapy every 14 days. These patients were also given 6 mg pegfilgrastim as a single dose on day 2 of each cycle. The main results showed that these two doses of FEC were feasible with pegfilgrastim and only 2 of the patients showed grade 3-4 hematological toxicity in the FEC_{90} arm. The most predominant side effects associated with this drug were elevated liver enzymes and gastrointestinal disturbance. No events resulted in the discontinuation. The main recommendation was that the detection of proper dose and side effects of the FEC and epirubicin regimens need to be studied in a large sample size. This has been addressed in the present study with a large sample size, but our study looked at various types of solid cancers, not only breast cancer as in Kahán *et al*. (2008) [20]. Moreover, we tried to determine the proper dose for various chemotherapy drugs and not for epirubicin. Zielinski *et al*. (2005) conducted a study on 259 Austrian women who suffered from advanced breast cancer disease. 124 patients were treated with GET 1000 mg/m^2 gemcitabine, 90 mg/m^2 epirubicin and 175 mg/m^2 paclitaxel, and 135 patients were treated with FEC, 500mg/m^2 5-fluorouracil), 90 mg/m2 epirubicin and 500 mg/m^2 cyclophosphamide. The results showed that 93% of patients who received GET suffered from neutropenia compared with 84% of those who received FEC. Thrombocytopenia was not considered problematic for patients on GET because none of the thrombocytopenic patients on GET suffered from bleeding. However, thrombocytopenia was considered as a critical clinical problem for patients treated with the FEC regimen, as they were the only patients who showed bleeding due to thrombocytopenia. Again, this study just focused on breast cancer patients [21]. After FEC, thrombocytopenia seems to be associated with the 5-FU+5-FU regimen (Tables 3 and 4).

Table 1: Logistic regression analyses for the association between chemotherapy regimens and thrombocytopenia incidence and severity

Variable	***P*-value**	**Odd ratio**	**95% CI**
Chemotherapy regimen	0.041 (incidence)		
FEC	0.009	5.1	2.5-12.3
5-FU+5-FU or 5-FU	0.024	4.1	2.1-11.4
Others		Reference group	
Variable	***P*-value**	**Odd ratio**	**95% CI**
Chemotherapy regimen	0.009 (severity)		
FEC	0.002	7.1	2.7-15.9
5-FU+5-FU or 5-FU	0.018	6.8	2.3-13.7
Others		Reference group	

CI: confidence interval; FEC, (5-FU, Epirubicin, Cisplatin)

Table 2: Correlation between chemotherapy doses and thrombocytopenia (TPC) incidence

Risk Factor	Dependent variable	r_s	*P*-value
5-FU[1] dose			
400-599 mg	TPC incidence	0.418	0.488
600-699 mg	=	0.423	0.472
700-799 mg	=	0.561	0.041
800-899 mg	=	0.683	0.022
900-999 mg	=	0.734	0.015
≥700 mg	=	0.819	0.000
5-FU[2] dose			
400-499 mg	=	0.029	0.718
500-599 mg	=	0.103	0.707
600-699 mg	=	0.337	0.484
≥700 mg	=	0.641	0.299
Epirubicin dose			
70-79 mg	=	0.026	0.533
80-89 mg	=	0.031	0.462
90-99 mg	=	0.033	0.479
≥100 mg	=	0.099	0.558
Cyclophosphamide dose			
700-799 mg	=	0.134	0.736
800-899 mg	=	0.487	0.749
900-999 mg	=	0.648	0.033
≥1000 mg	=	0.741	0.001
Cisplatin dose			
60-69 mg	=	0.351	0.491
70-79 mg	=	0.388	0.485
80-89 mg	=	0.379	0.494
90-99 mg	=	0.458	0.372
≥100 mg	=	0.695	0.027
Oxaliplatin dose			
≥110 mg	=	0.141	0.076
<110 mg	=	0.051	0.100
Docetaxel dose			
80-90 mg	=	0.022	0.798
100-109 mg	=	0.036	0.627
≥110 mg	=	0.114	0.559
Others	=	0.098	0.766

Table 3: Correlation between chemotherapy doses and thrombocytopenia severity

Risk Factor	Dependent variable	r_s	*P*-value
5-FU[1] dose			
400-599 mg	TPC Severity	0.369	0.491
600-699 mg	=	0.399	0.435
700-799 mg	=	0.404	0.229
800-899 mg	=	0.795	0.012
900-999 mg	=	0.829	0.002
≥700 mg	=	0.924	0.000
5-FU[2] dose			
400-499 mg	=	0.472	0.601
500-599 mg	=	0.463	0.578
600-699 mg	=	0.502	0.371
≥700 mg	=	0.749	0.219
Epirubicin dose			
70-79 mg	=	0.004	0.773
80-89 mg	=	0.014	0.621
90-99 mg	=	0.019	0.611
≥100 mg	=	0.024	0.562
Cyclophosphamide dose			
700-799 mg	=	0.491	0.630
800-899 mg	=	0.512	0.622
900-999 mg	=	0.729	0.303
≥1000 mg	=	0.814	0.001
Cisplatin dose			
60-69 mg	=	0.091	0.433
70-79 mg	=	0.123	0.389
80-89 mg	=	0.149	0.373
90-99 mg	=	0.422	0.049
≥100 mg	=	0.644	0.007
Oxaliplatin dose			
≥110 mg	=	0.141	0.076
<110 mg	=	0.051	0.102
Docetaxel dose			
80-90 mg	=	0.068	0.481
100-109 mg	=	0.179	0.041
≥110 mg	=	0.644	0.071
Others	=	0.086	0.573

Table 4: Linear regression of chemotherapy doses with thrombocytopenia incidence and severity

Risk Factor	Dependent variable	B	(*β*)	*P*-value
5-FU[1] dose				
700-799 mg	TCP Incidence	Reference group (Comparison Category)		
800-899 mg		531.4	0.807	0.036
900-999 mg		6643.1	0.926	0.009
≥1000 mg		573950.1	0.994	0.001
Cyclophosphamide dose				
800-899 mg	TCP Incidence	Reference group (Comparison Category)		
900-999 mg		3062.9	0.814	0.019
≥1000 mg		67446.1	0.897	0.004
Cisplatin dose				
90-99 mg	TCP Incidence	Reference group (Comparison Category)		
≥100 mg		439.9	0.718	0.033
Docetaxel dose				
100-109 mg	TCP Incidence	Reference group (Comparison Category)		
≥110 mg		334.7	0.606	0.039
5-FU[1] dose				
700-799 mg	TCP Severity	Reference group (Comparison Category)		
800-899 mg		667.1	0.827	0.044
900-999 mg		82145.0	0.944	0.018
≥1000 mg		7950056.8	0.997	0.001
Cyclophosphamide dose				
800-899 mg	TCP Severity	Reference group (Comparison Category)		
900-999 mg		61946.2	0.828	0.011
≥1000 mg		864750.1	0.901	0.009
Cisplatin dose				
90-99 mg	TCP Severity	Reference group (Comparison Category)		
≥100 mg		1142.3	0.775	0.043
Docetaxel dose				
100-109 mg	TCP Severity	Reference group (Comparison Category)		
≥110 mg		937.1	0.749	0.037

It was also reported by Bassam (2016). Moreover, Bassam mentioned that thrombocytopenia is one of the side effects of 5-FU in colon cancer patients. All this seems to support the results of this present study, which showed a strong association between 5-FU and thrombocytopenia incidence and severity [14]. The FOLFOX regimen was the third most likely to cause thrombocytopenia. In a retrospective study by Politano *et al*. (2008) conducted on 97 patients with colon cancer, only 24% of the patients suffered from splenic enlargement of 50% or more, while only 6% of the patients suffered from 100% splenic enlargement after receiving the FOLFOX regimen. The reduction of platelet numbers in patients with splenic enlargement of 50% or more was greater than in those who suffered from spleen enlargement of less than 50%. The main conclusion of this study was that the incidence of spleen enlargement and thrombocytopenia is mainly dependent on the dose intensity of FOLFOX, which leads to a modest reduction in platelet counts. This supports our results whereby FOLFOX was found to be in third place, i.e., depending on their doses [22]. The results of linear correlation and regression showed that 5-FU[1] (5-FU first dose or bolus dose) at a dose of ≥1000 mg has the strongest association and the highest positive correlation with thrombocytopenia incidence and severity, followed by cyclophosphamide ≥1000 mg, 5-FU[1] 900-999 mg, and 5-FU[1] 800-899 mg. For cisplatin, only the dose ≥100 mg showed a significant association with thrombocytopenia incidence and severity. For all the doses which showed significant association with the onset and severity of thrombocytopenia, their correlations with severity were higher than those with onset. The present study aimed to detect the chemotherapy doses associated with hematological side effects, including thrombocytopenia. It is considered an important point since the main hindrance to chemotherapy is the dose-limiting side effects that lead to reduced effects of cancer treatment. Demers *et al*. (2011). So, as mentioned by Demers *et al*. (2011), important research goals include delivering high doses of the drug to tumor sites for maximum treatment efficacy while minimizing side effects on healthy tissues. This is one of the main emphases of the present study, i.e., allowing cancer patients to be treated with a dose of chemotherapy that is as high as possible but that causes only low or no hematological side effects [23]. Vadhan-Raj (2009) mentioned that the effect of dose intensity on some cancers, like lymphoma and breast cancer, has not been well established. It supports the point of view of the present study, since it detects the effects of chemotherapy treatment not only on breast cancer but on almost all solid cancer diseases [24]. The explanation for this finding is that one of the main side effects of 5-FU, especially after a bolus dose, is severe myelosuppression of the bones. Hence, this can explain the high association and correlation of 5-FU[1] dose with thrombocytopenia onset and severity, since the 5-FU is given as a bolus dose, while for 5-FU[2] the FU is not given as a bolus dose [25]. Also, the reason why 5-FU[1] is highly associated and correlated with thrombocytopenia onset and severity is because of its pharmacokinetic characteristics. When it is given by bolus administration, its main side effect will be myelosuppression; while if it is given continuously, its main side effect will be skin toxicity [25]. According to Bassam, anemia and thrombocytopenia are mainly associated with

cyclophosphamide doses and their incidence and severity can be reversed by reducing cyclophosphamide doses [14]. According to Rodgers (2008), breast cancer patients treated with a combination of 5-FU and cyclophosphamide, which is considered very myelosuppressive, will suffer from bone marrow suppression even after five years of completing treatment [26]. Rodgers also indicated that the myelosuppressive effect accumulates with repeated cycles. One of the important points stated was that high dose intensity chemotherapy, even if used for a short period, would cause myelosuppression. This was recognized in the present study when 5-FU and/or cyclophosphamide were given in high bolus doses. Thus, it shows a high association and correlation between anemia and thrombocytopenia. For high doses of cyclophosphamide, docetaxel, and cisplatin, their main side effects will be the suppression of the bone marrow [27]. These points explain the reported strong association and correlation between 5-FU[1], cyclophosphamide, and cisplatin with the onset and severity of thrombocytopenia. Oxaliplatin is a novel platinum derivative with established anti-tumor activity with the incidence of acute anemia or thrombocytopenia produced is rare [28]. This may explain the finding of a nonsignificant association between oxaliplatin doses and the onset and severity of thrombocytopenia.

Conclusion

Based on the results of the present study, patients who are receiving high doses of chemotherapy regimens should be under close supervision to overcome the thrombocytopenia that may arise during treatment.

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Conflicting interests

Nothing declared.

Data sharing statement

The datasets analyzed during the current study will be available from the corresponding author on a reasonable request.

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