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Prospective Observational Study on the Risk Factors of Chemotherapy-Induced Myelosuppression and Its Management in a Tertiary Care Hospital

D. Keziah[1] M. Bindhiya[1] M. Jayaprakash[1] Rodrigues A. Prudence[2]

[1] PSG College of Pharmacy, Coimbatore, Tamil Nadu, India
[2] Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India

Address for correspondence Keziah D., Pharm D (continuing), 21 PPS Colony, Anna Nagar, Coimbatore south – 641004, Tamil Nadu, India (e-mail: projectcim218@gmail.com).

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Abstract

Introduction Myelosuppression is a commonly observed dose-limiting side effect of majority of chemotherapeutic drugs, characterized by a decrease in blood cell production. They cause neutropenia, thrombocytopenia, and anemia and can be life threatening in few susceptible individuals. Attempts to lessen chemotherapy-induced myelosuppression have been minimally effective. Managing myelosuppression has been a challenge to medical practitioners and pharmacist. Identifying their risk factors and the management strategies can help prevent the debilitating effects on chemotherapy patients.

Objectives The aim of this study was to determine the risk factors for chemotherapy-induced myelosuppression and identify its management in a tertiary care hospital. We also observed the cycle it predominantly occurs and its prevalence rate in the region.

Materials and Methods The study is a prospective observational cohort study conducted in a tertiary care hospital in Coimbatore, Tamil Nadu. The sample size was calculated using RAO software for a study duration of 4 months from 73 patients who were prescribed the inclusion criteria drugs paclitaxel, carboplatin, 5-fluorouracil, doxorubicin, and cyclophosphamide. The complete blood count was obtained and followed up to find myelosuppression occurrence on day 8 of first three cycles. The National Cancer Institute grading system was used to assess the severity of myelosuppression. It was done from May 2022 to August 2022. Chi-squared tests and percentages were adopted by using the SPSS software.

Result The result for primary objective is that among the total 73 patients employed, 30 patients were found to be myelosuppressive (41%) and the prevalence rate was 41%. Risk factors such as age, gender, and diagnosis showed statistically significant association (confidence interval: 95% 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.

The results for secondary objectives were that cycle 1 was reported to be highly myelosuppressive with 27%. The treatment options that was highly used was

Keywords

- chemotherapy-induced myelosuppression
- myelosuppression
- risk factors
- myeloprotective agents
- complete blood count

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granulocyte-colony stimulating factor (90%), followed by packed red blood cell transfusion (7%).

Conclusion The incidence of chemotherapy-induced myelosuppression from this study showed that it was important to monitor the complete blood count levels in patients undergoing chemotherapy. Early assessment of risk for developing myelosuppression may prevent or reduce its severity.

Introduction

Cancer is a group of diseases, where some of the body's cells grow uncontrollably and spread in the body. Cancer is among the leading causes of death worldwide. According to National Cancer Institute (NCI) in 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide; accounting for nearly 10 million deaths in 2020. Chemotherapy is treatment of cancer with drugs that uses powerful chemicals to kill fast growing tumor cells in your body. There are many different chemotherapy drugs that are used alone or in combination to treat different types of cancers.[1] In chemotherapy, drugs interfere with DNA synthesis and mitosis to destroy the cancer cells. Hence, it is not only effective to treat most types of cancers, but also possesses a series of side effects. These chemotherapy side effects may be mild and treatable or can cause life threatening complications.

Chemotherapy-induced myelosuppression (CIM) is the most common dose-limiting and fatal complication of cancer treatment. Myelosuppression is caused by destruction of proliferating progenitor cells that produce mature red and white blood cells and platelets in peripheral circulation. As immature cells in the marrow are destroyed, pre-existing mature cells are eliminated, and the nadir of the individual's blood cell count is attained. At that time, cells are maturing and are ready to release into peripheral blood so within a short period the blood count has returned to near normal state and the next dose of chemotherapy is administered.[2]

Myelosuppression is a crucial factor in determining how much drug is to be given. After treatment has begun, if bone marrow has not recovered before the next cycle of chemotherapy, dosage reduction or delay starting the cycle will depend primarily on intent of treatment.[3] *If the patient is in a clinical trial,* the grade of toxicity will correspond with appropriate course of action. According to NCI grading scale, myelosuppression is graded, and the type is decided. Myelosuppression is the umbrella term for anemia, thrombocytopenia, and neutropenia.[4] Grade I myelosuppression may require no modification in the treatment plan, whereas a grade III or IV toxicity may require not just a delay in treatment but dose reduction, depending on the outcome.[5] Transfusions of packed red blood cells (PRBC) and platelets are common treatments when chemotherapy causes anemia and thrombocytopenia.[2]

The granulocyte colony-stimulating factors (G-CSF) and granulocyte macrophage-colony stimulating factors (GM-CSF) reduce the severity and duration of neutropenia after therapy. Antibiotics are given to prevent infection.[6] Regular peripheral blood count monitoring is the standard practice. The other mainstay of early detection is education of patients, caretakers, and healthcare staff with the signs and symptoms suggestive of cytopenia's, and importance of prompt blood count confirmation and appropriate management. Dose reduction or delay before scheduled courses maybe suggested if unexpectedly severe or prolonged cytopenia occur. Primary or secondary prophylaxis happens by giving G-CSF.[7]

In this study, the association of risk factors (age, gender, body surface area, comorbidities and chemotherapeutic drug combinations) with myelosuppression is studied. To identify myelosuppression, data from complete blood count (CBC)-platelets, RBC and white blood cells along with absolute neutrophil count (ANC) were noted on the day 8 and the nadir day reports.[8] The risk factors of CIM were studied using five chemotherapeutic drugs that are commonly used in chemotherapy (paclitaxel, carboplatin, cyclophosphamide, doxorubicin, and 5-fluorouracil).[9]

Therefore, this study aims to serve as a resource for healthcare professionals to enhance their understanding of myelosuppression and its regular monitoring in patients receiving chemotherapy. The primary objective of our study is to determine the prevalence rate of myelosuppression and its risk factors in cancer patients. The secondary objective was to identify the cycle in which increased myelosuppression occurs and the treatment options used.

Materials and Methods

The study is a prospective observational cohort study conducted in a tertiary care hospital in Coimbatore, Tamil Nādu. The sample size of 73 was calculated using the RAO software from data obtained by daily patient flow and study duration. The study was carried out for a duration of 4 months, and data was collected from patients who were prescribed with the inclusion criteria drugs paclitaxel, carboplatin, 5-fluorouracil, doxorubicin, and cyclophosphamide. The CBC was obtained and followed up to find myelosuppression occurrence on day 8 of blood reports, since the administration of drug for the first 3 cycles. The NCI grading system was used to assess the severity of myelosuppression of carboplatin, paclitaxel, 5-fluorouracil, adriamycin, and cyclophosphamide. The study was done from May 2022 to August 2022. Chi-

squared tests and percentages from SPSS software were used for statistical analysis. The result for primary outcome is that among the total 73 patients employed, 30 patients were found to be myelosuppressive (41%) and the prevalence rate was 41%. Risk factors such as age, gender, and diagnosis showed statistically significant association (confidence interval: 95% 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. The results for secondary outcome were that cycle 1 was reported to be highly myelosuppressive with 27%. The treatment options that was highly used was granulocyte-colony stimulating factor (90%), followed by packed red blood cell transfusion (7%).

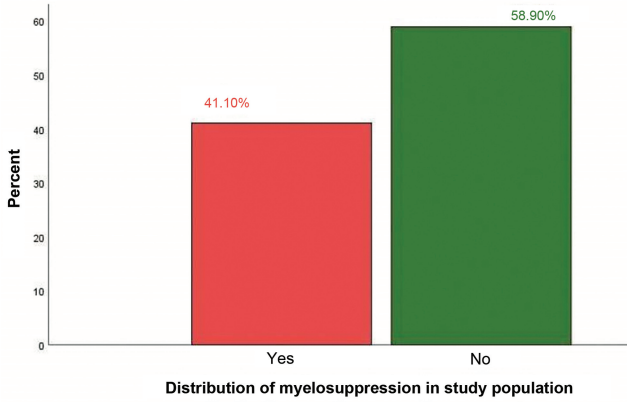

Fig. 1 Occurrence and nonoccurrence of myelosuppression in study population.

Inclusion Criteria

- All types of cancer with chemotherapy drugs (paclitaxel, carboplatin, cyclophosphamide, 5-fluorouracil, and doxorubicin) in weekly and 3 weekly dosage regimens.
- >18 years of age.
- Cancer patients in cycles 1, 2, and 3.

Exclusion Criteria

- Patients who are not receiving chemotherapy.
- Psychiatry patients with cancer.
- Cycles excluding 1, 2, and 3 due to difficulty to obtain data and patient follow-up.
- Patients receiving concurrent chemotherapy and radiation therapy.

Statistical Analysis

The data were entered in Ms excel spread sheet and analyzed using Statistical Package for Social Science (SPSS) version 26.0. Qualitative and Quantitative variables were compared and analyzed using chi-squared test.

Ethics

The study was approved by Institutional Human Ethics Committee, PSG hospitals, Coimbatore, Tamil Nadu, India. (Approval no: PSG/IHEC/2022/Appr/Exp/118; approved on May 04, 2022). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

In this study, 73 patients were recruited based on their inclusion and exclusion criteria. The age wise distribution was found by grouping the patients according to World Health Organisation (WHO) scale as age groups (15–24) with 6%, age group (35–64) with 71%, and more than 65 years with 23%. The gender wise distribution showed 21% male and 80% female in the study. The study categorized the body mass index (BMI) for patients in C1, C2, and C3. The BMI was categorized as less than 18.5 (underweight), 18.5 to 24.9 (normal range), 25 to 29.9 (overweight) and more than 30 (obese). The highest distribution of myelosuppression was in the BMI range 18.5 to 24.9 (normal range) as 48% ($n=35$).

In this study, among the total population the social history was taken into accounted and 10% ($n=7$) patients were smokers, 4% ($n=3$) were alcoholics, and 3% ($n=2$) were smokers and alcoholics. The past medical history showed diabetes mellitus (DM) 27% ($n=5$), hypertension (HTN) 6% ($n=4$), both DM 2 and HTN 14% ($n=10$), no comorbidities 56% ($n=41$), and no past medical history as 18% ($n=13$). The past medication history, chemotherapy, and oral hypoglycemic agents (OHA) showed 7% ($n=5$), chemotherapy, and anti-HTN showed 6% (n = 4), chemotherapy, OHA, anti-HTN combined showed 14% ($n=10$), chemotherapy alone showed 56% ($n=41$), and none showed 18% ($n=13$). Family history was also included based on genetic lineage.

Among 73 patients, 41% ($n=30$) were found to have myelosuppression (►**Fig. 1**). The objective was met by calculating the prevalence rate by,

$$\text{Prevalence rate} = \frac{\text{no. of new cases of myelosuppression}}{\text{total study population}} \times 100$$

$$= \frac{30}{73} \times 100$$

$$= 41\%$$

The occurrence of myelosuppression in the population was 41% ($n=30$). ►**Table 1** shows the relationship of myelosuppression with gender, age, and disease condition in this study. Also, other postulated risk factors like BMI, past medical and medication history, social history, and family history did not show significant statistical association. In this study, a total of 30 patients got myelosuppression among which grade 1 was 27% ($n=20$), grade 2 was 10% ($n=7$), grade 3 was 11% ($n=8$), grade 4 was 3% ($n=2$), and prophylaxis was given for 3% ($n=2$). The highest distribution was in grade 1 with 27% ($n=20$).

The cycle in which CIM occurred more was cycle 1 with 56% followed by other cycles (►**Fig. 2**). Additionally, grades of

Table 1 Significance of risk factors associated with myelosuppression in study population

Risk factors	*p*-Value
Gender	0.048
Age	0.046
BMI C1	0.313
BMI C2	0.386
BMI C3	0.654
Social history	0.674
Family history	0.406
Past medical history	0.343
Past medication history	0.343
Diagnosis	0.048
Drugs	0.049

Abbreviations: BMI, body mass index; C1, cycle 1; C2, cycle 2; C3, cycle 3.

myelosuppression were assessed according to NCI guidelines. The management strategy used in the tertiary care center for the myelosuppressive patients with myeloprotective agents were found to be G-CSF, PRBC transfusion, and a combination of both. The myeloprotective agent G-CSF 90% was prescribed the most (►**Fig. 3**).

Discussion

CIM is a life-threatening condition and commonly manifests as anemia, neutropenia, and thrombocytopenia and often results in an increased risk of infections, shortness of breath, fatigue, and excessive bleeding.

In this study of chemotherapy patients, female patients (80%) have reported to have more myelosuppression than men (20%). According to Nan Jiang et. Al and WHO Female gender are scientifically proven to have an increased 35% risk of developing side effects than men due to sex differences in inflammatory and immune responses.[10] Many biological differences in male and female in patterns of cancer are due to differences in their sex hormones, such as estrogenic or testosterone.

Age group of 25 to 65 (60%) reported to be more myelosuppressive than other groups of 19 to 24 and seniors of age above 65, similar to the study of Repetto.[3,11] Complications due to age-related physiologic changes that can increase the toxicity are decreased stem cell reserves, decreased ability to repair cell damage, progressive loss of body protein, and accumulation of body fat.[12]

Body weight was reported to have increased risk of developing several cancers including colorectal cancer, breast cancer, renal cell, and pancreatic cancer from studies.[13] One proposed mechanism in increased risk of developing cancer was the reduction in growth factor production with increased body weight. This study showed an increase in myelosuppression in patients who fell under the BMI groups 18.5 to 24.9 and 25 to 29.9, with strong support from the study of Weycker et al.[14] BMI classification was done according to standard WHO classification.

Social history denoted as smoking, alcohol consumption, and other substance use were collected in this study. According to the study of Beyth et al,[15] cigarette smoking was linked to significant decrease in bone marrow concentration of mesenchymal stem cells. In this study, social history was not found to have any relationship with CIM.

Family history consists of the collection of information about the patients and their family members devoted to an understanding of heritable lines. Many diseases have genetic

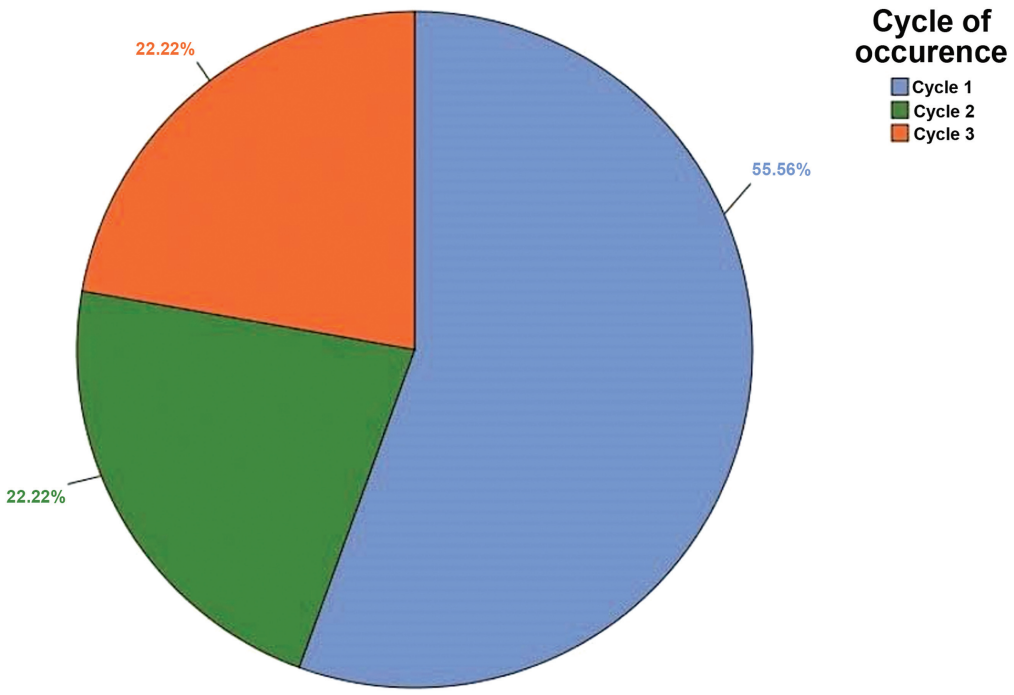

Fig. 2 Cycle wise incidence of myelosuppression in study population.

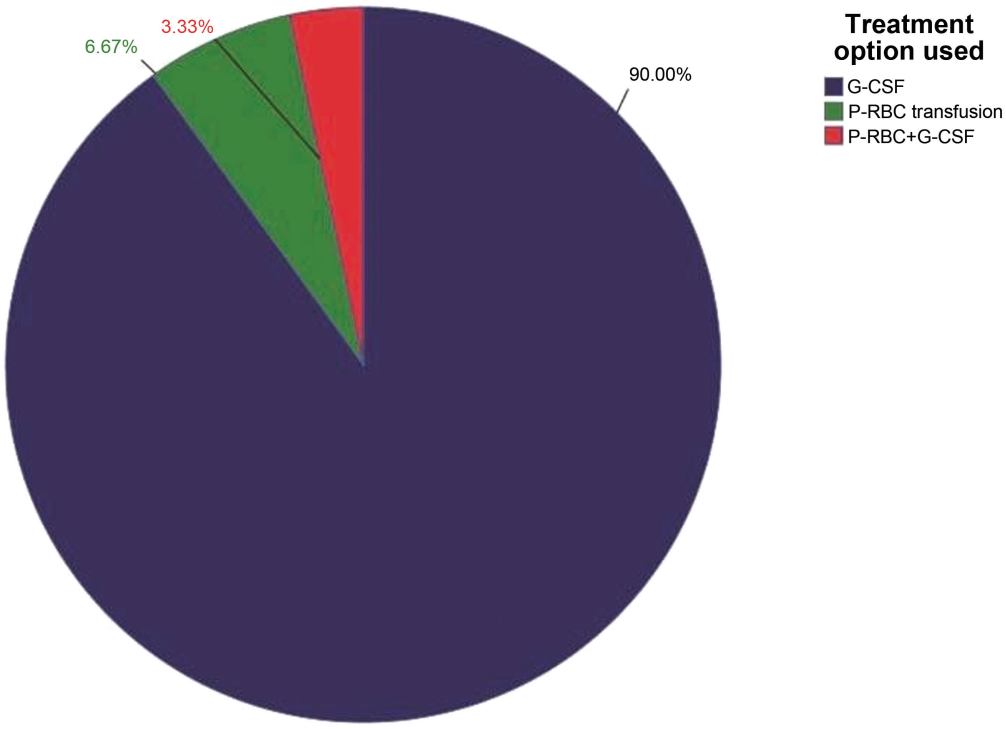

Fig. 3 Myeloprotective class percentage used to treat myelosuppression. G-CSF, granulocyte colony-stimulating factor; PRBC, packed red blood cell.

lineage proposing as one of the significant risk factors. Family lineage of diseases like diabetes and HTN and others were not found to be a significant risk factor for CIM in this study.

Medical history denoted the comorbid conditions that coexisted with the primary disease. Given that most of the cancers are diagnosed, these comorbid conditions are preexisting. Examples of comorbid conditions are DM, HTN, cardiovascular diseases, liver diseases, kidney problems, etc. Some of these have common risk factor with cancer. The type and severity of comorbidity may affect treatment outcomes and hence require customization. In this study, comorbid conditions of patients were not found to have significance in causing CIM.

Medication history is the class of drugs given other than chemotherapy drugs in this study. Medication history is proposed to have impact on the occurrence of adverse event due to polypharmacy. Other drugs found to cause myelosuppression are chloramphenicol, Meclofenamic acid, quinidine, trimethoprim-sulfadiazine, and other antifungals. In this study, medication history was found to be an insignificant risk factor to cause CIM.

Breast cancer has been the disease that has reported to show more myelosuppression in our study. Breast cancer has only been seen in woman and no male breast cancer cases were reported in this study. Evidence from several studies showed that woman have more risk of developing adverse reaction to chemotherapy. Women have 100 times greater risk of developing breast cancer due to presence of more breast cells than male. Other factors like race and ethnicity, menstrual cycle, lifestyle changes, and use of contraception can influence the development of myelosuppression in breast cancer.

Drugs in this study are the inclusion criteria drugs, that is, paclitaxel, carboplatin, cyclophosphamide, 5-fluorouracil, and doxorubicin. Cell cycle specific and cell nonspecific drugs are reported to cause rapid myelosuppression that is rapid and recovery is quicker, whereas cell noncycle specific causes myelosuppression that is delayed, prolonged and cumulative with evidence from study of Maxwell and Maher.[1] The same has been reported in our study with 41%.

WBC nadir occurs during every cycle of chemotherapy in patients. Nadir occurs in chemotherapy patients alone or in combination around 8 to 14 days of chemotherapy drugs intake with reference to Barreto et al.[16] Also, myelosuppression can occur in any cycle and it is due to large intrasubject variability. In this study the cycle that shows increased myelosuppression was cycle 1 with 56% followed by cycle 2 and cycle 3, after follow-up of individual patients with their CBC reports.

In this study, gender, age, disease condition, and inclusion criteria drugs (paclitaxel, 5-fluorouracil, carboplatin, cyclophosphamide, and adriamycin) were found to be significant risk factors in the development of myelosuppression.

Limitations

The study was performed in a single-center hospital that resulted in homogenous sample intake. The follow-up of patient's files and collecting sample details were difficult, due to record unavailability. Patient flow was affected due to coronavirus disease 2019 pandemic. Febrile neutropenia patients were not included in this study.

Conclusion

The incidence of CIM from this study showed that it was important to monitor the CBC levels in patients undergoing chemotherapy. Early assessment of risk for developing myelosuppression may prevent or reduce its severity. Drugs prescribed like paclitaxel, carboplatin, cyclophosphamide, and doxorubicin have increased risk of causing myelosuppression. Assessment and prevention of CIM should be considered as one of the important aspects in clinical practice because negligence of monitoring CBC profile may lead to life threatening situations.

Pharmacist can improve appropriate medical care to reduce occurrence of myelosuppression. Dose titrations, capping, prophylactic treatments, and medical intervention provided by pharmacists can be valuable in reducing the harm of chemotherapy adverse effects. Medication chart review, follow-up, and checking for adverse drug reactions aid the process. Further suggesting predictive models allowing better access to a patient's susceptibility to antineoplastic agent-induced myelotoxicity will enable better individualized therapy thought to be unpredictable. Finally, the use of modern novel therapies and molecular information can help mitigate the lethal risks of chemotherapy induced myelotoxicities in hospital setup.

Authors' Contributions

Keziah, Bindhiya, and Jayaprakash were involved in concept, design, definition of intellectual content, literature search, data acquisition, statistical analysis, manuscript editing, and manuscript preparation. Prudence A Rodrigues helped in clinical studies, data analysis, statistical analysis, and manuscript review. The manuscript has been read and approved by all authors and all the requirements have been met.

Conflict of Interest

None declared.

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