

Assessment of Potential Drug - Drug Interaction among the Patients Receiving Cancer Chemotherapy: A Cross-sectional Study

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Abstract

Objectives: To identify and assess the various potential drug-drug interactions (pDDIs) among the patients receiving cancer chemotherapy, using the database from Lexicomp® Solutions with the ultimate goal of raising awareness among clinicians for safe medication usage. **Materials and Methods:** It is a prospective, cross-sectional study engaged at a tertiary care hospital in South India. Data regarding clinically prescribed drugs were obtained from the patients admitted to the oncology unit of a tertiary care hospital within the time frame of 6 months (June 2018 to December 2018). Frequency and clinical relevance, the onset, and Severity of pDDIs were assessed using the database from Lexicomp® Solutions version 4.1.2. Data were analyzed using the descriptive statistics. Statistical significance was analyzed using the Mann-Whitney and Chi-square tests. Pearson's correlation coefficient was used to identify the correlation between the incidence of drug-drug interactions with age, the number of drugs prescribed, and the type of cancer. **Results:** A total of 895 pDDIs were seen, including 261 with chemotherapeutic drugs and 634 with supportive medication. It was observed that around 14.18% of cyclophosphamide showing interaction with Ondansetron among chemotherapeutic drugs, whereas 9.14% of lithium presenting interaction with Ondansetron among supportive therapy. A statistically significant higher interaction was noted among supportive medications provided when compared to anticancer drugs ($P = 0.001$). **Conclusions:** The majority of pDDIs observed among the patients receiving chemotherapy with supportive medications as compared to anticancer chemotherapy. There is an urgent need for special safety measures to monitor and prevent drug interactions in the oncology unit.

Keywords: Chemotherapy, drug-drug interaction, oncology, supportive medication

INTRODUCTION

Cancer is a significant leading public health burden in recent years, and it is a substantial cause of morbidity and mortality worldwide.^[1] Cancer patients often receive multiple medications to treat both cancer and comorbid conditions (noncommunicable diseases). They are particularly susceptible to drug interactions as most anticancer drugs are potent, toxic drugs with a narrow therapeutic index.^[2] The drugs received for noncommunicable diseases and cancer-related symptoms are also responsible for this.^[3]

A drug interaction is "the pharmacological or clinical response to the administration of a drug with another substance that modifies the patient's response to the drug."^[4] It can be due to pharmacokinetics, pharmacodynamics, or combined mechanisms. Pharmacokinetic interactions are mainly due to interference in the absorption, distribution, metabolism, and

excretion of a drug. These are primarily due to the cytochrome P450 enzyme system, P-glycoprotein pump, and the competitive protein-binding properties of anticancer medicines in oncology.^[5] Pharmacodynamics interactions could be due to additive, potentiating, or antagonistic effects, which can significantly alter anticancer drugs' efficacy or toxicity.^[6]

The drug interactions are responsible for about 20%–30% of adverse drug reactions among patients receiving cancer

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chemotherapy.^[7] They are also responsible for the death in 4% of all cancer patients and reduced pharmacological effects.^[8] Hence, it is essential to understand the prevalent drug-drug interactions (DDIs) among cancer patients receiving cancer chemotherapy and the relation between DDIs and other features such as demographic determinants and the mechanism responsible for these. It will help the treating oncologists/clinicians to optimize the treatment with reduced side effects.

There is a lack of sufficient information about DDIs in cancer therapy and their effects. Only a few studies are available in India that have focused on this issue in recent years.^[6,9] This study was planned to provide a detailed assessment of potential DDI (pDDI) in the oncology unit using various parameters such as the severity of the reaction, risk categorization, and documentation of the observed interactions based on previously published literature. It will help raise the clinicians' awareness while prescribing these drugs to monitor patients' possible interactions.

MATERIALS AND METHODS

The present study was a prospective, cross-sectional, descriptive study conducted at a tertiary care hospital from India's southern part. After obtaining permission from the Institutional Ethics Committee (INST. EC/EC/053/2018-19), data from the medical records were obtained from the patients admitted to the oncology unit for cancer chemotherapy during the study period of 6 months (from June 2018 to December 2018). Both males and females above 18 years and who received more than two drugs were included in the study. Data regarding demographic characters such as age, gender and diagnosis, cancer type and stage, duration of hospital stay, and information on the drugs prescribed, including anticancer drugs, supportive care agents, and medications for noncommunicable diseases, were collected. Quantification and classification of the pDDIs into different levels based on severity, risk rating, and scientific evidence as explained below was done using the database from Lexicomp® Solutions version 4.1.2. Analysis of each prescription for the frequency of total pDDIs, clinically relevant pDDIs, was carried out. Interactions classified as major and moderate in severity and X/D/C in risk rating Lexicomp® Solutions were considered clinically relevant. Depending on the mechanism involved, interactions were categorized into pharmacokinetics, pharmacodynamics, and unknown mechanisms. The frequently interacted drug combinations were also analyzed.

Severity

Major: Interaction might lead to permanent damage or life risk.

Moderate: Interaction can harm or treatment required.

Minor: Small or no clinical effect is observed and no treatment required.

Unlikely: No effect observed.

Risk rating

X: Contraindicated (drugs which should never be used together because of severe, life-threatening interactions).

D: Potential for serious interaction-consider therapy modification.

C: Potential for serious interaction – typically requires close monitoring.

B: No action needed.

A: No known interaction.

Scientific evidence (Documentation): Excellent/Good/Fair/Unlikely.

Statistical analysis

The sample size was calculated using the following formula:

$$N = Z^2 p (1 - p) / d^2$$

Where,

n = number of prescriptions

$Z\alpha$ = value under the standard normal table for the given value of confidence interval (CI), i.e., 1.96 at 95% CI.

p = proportion of the sample population with CI of 95%, i.e., 8.7%

d = margin of error, i.e., 5%

The sample size of 242 rounded off to 255.

Data captured on the MS Excel worksheets (2010), analyzed as mean, frequency, and percentage using the Statistical Package for the Social Sciences (SPSS) software version 22.0 (developer-IBM Corporation) SPSS Inc., Chicago, Illinois, United States, and the results were expressed using the descriptive statistics. The Chi-square test and Mann-Whitney test were used for analyzing the statistical significance. $P < 0.05$ was considered statistically significant. The correlation between the number of interactions with age and the amount of drug administered was done using the Pearson's correlation coefficient.

RESULTS

Among the 255 patients evaluated during the study period, females had more pDDI ($n = 124$, 48.26%) than males ($n = 103$, 40.39%). Patients belonging to the age group of 41–60 years ($n = 114$, 44.7%) had more interactions when compared to the other age groups > 61 years ($n = 75$, 29.41%), and interactions were less in younger age group patients, i.e., 18–40 years ($n = 38$, 14.9%). The mean age of patients was 53.627 ± 13.599 [Table 1].

Patients received treatment for different types of malignancies mainly of the breast ($n = 64$, 25.09%), gastrointestinal organs ($n = 60$, 23.52%), genitourinary organs ($n = 39$, 15.29%) and lungs ($n = 30$, 11.76%) followed by hematological ($n = 27$, 10.58%), head and neck cancers ($n = 27$, 10.58%), and

Table 1: Correlation of Age, Gender with drug interaction

	With interaction (%)	Without interaction (%)	P
Age			
18-40	38 (14.9%)	4 (1.56%)	0.001*
41-60	114 (44.7%)	17 (6.66%)	
>61	75 (29.41%)	7 (2.74%)	
Gender			
Male	103 (40.39%)	11 (4.313%)	0.735
Female	124 (48.62%)	17 (6.66%)	

*Statistical significance set at $P < 0.05$ **Table 2: Significance of drug Interaction with anticancer drugs and Supportive treatments**

Drug Interactions	n	Mean Rank	P
Anti-Cancer	255	213.23	0.001*
Supportive	255	297.77	

*Statistical significance set at $P < 0.05$

miscellaneous ($n = 8$, 3.13%). Around 59 patients (23.13%) had metastatic lesions. Chemotherapeutic drugs were given as palliative treatment in 59.21% patients, as an adjuvant in 29.80%, and as curative in 10.98%. Among the patients enrolled for the study, 36 of them had comorbid disorders, most common being diabetes ($n = 15$, 5.8%) followed by hypertension ($n = 5$, 1.96%).

895 pDDI was observed in 227 patients (i.e., 89.02% patients) with an average of 3.94 pDDI per patient, and the majority of the patients were having drug interactions in the range of 1–2 (38.02%). Among these, 261 were interactions involving chemotherapeutic agents. Five hundred and thirty-six interactions (536) were due to supportive medications, and 98 interactions were due to the drugs received for comorbid disorders during cancer chemotherapy. Among the observed interactions, 601 (67.14%) were clinically relevant interactions.

Of the 895 pDDI, 286 (34.52%) were moderate in severity followed by 309 (31.95%) major, 155 (17.31%) minor, and 145 (16.20%) were unlikely. In the risk rating among the majority of the clinically relevant interaction belonged to “C” Category ($n = 422$, 47.15%), followed by “D” ($n = 168$, 18.77%) and “X” ($n = 11$, 1.22%). Concerning the documentation of pDDI, 623 (69.06%) had “Fair” documentation in literature, followed by 254 (28.37%) “Good” documentation, and 12 (1.34%) had “Excellent” documentation –categorization of the interactions based on malignancy depicted in Figure 2.

A total of 209 drug combinations were involved in observed 895 drug interactions, 60 (28.70%) combinations involving at least one chemotherapeutic agent, and 149 (71.29%) combinations involving supportive drugs. There was a statistically significant higher drug interaction was observed in supportive drugs (Mean rank = 297.77) when compared to anticancer drugs (Mean rank = 213.23) ($P = 0.001$) [Table 2].

Among the 895 interactions involving 209 combinations, 370 (41.34%) interactions with 87 combinations were due to pharmacodynamic mechanisms. 359 (40.01%) with 83 combinations were due to pharmacokinetics and 165 (18.34%) of them with 39 combinations had no established mechanism. Among the pharmacokinetics’ observed mechanism, 57.95% were due to alteration in the drug’s metabolism, mainly involving CYP enzymes [Figure 1].

Most commonly interacted drug among chemotherapeutic agents was cyclophosphamide ($n = 69$, 7.7%), 5-Fluorouracil ($n = 39$, 4.35%), and docetaxel ($n = 35$, 3.91%), whereas among the supportive medications, it was ondansetron ($n = 349$, 38.99%) and aprepitant ($n = 298$, 33.21%). The clinically relevant pDDI among chemotherapeutic agents was seen more frequently with Paclitaxel + Carboplatin and Epirubicin + Cyclophosphamide. Whereas in supportive medication, Lithium + Ondansetron and Dexamethasone + Aprepitant were seen [Table 3 tabulates drug combination and characteristic of interaction].

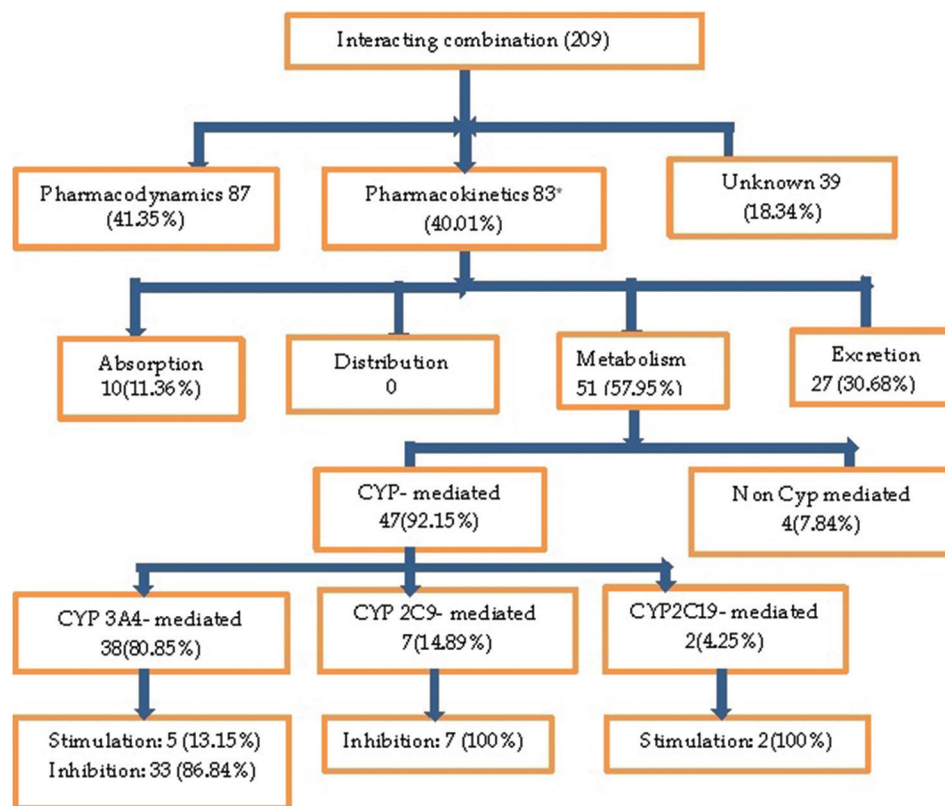
Analysis of the drug interaction classification in different types of malignancy showed a statistical significance in major and moderate interaction in Severity, category “C” in risk rating, and Good and fair in the documentation [Figure 2].

The correlation between the number of interactions with age and the number of drugs administered showed a positive correlation between the drug interactions and the number of drugs administered. However, there was no correlation between the age and the number of drug interactions observed [Figure 3].

DISCUSSION

The compound course of chemotherapy, altered pharmacokinetics, and pharmacodynamics are responsible for drug interactions in cancer patients. The study’s purpose was to determine the prevalent DDIs in cancer patients on regular chemotherapy cycles. In our study, we observed a high number of episodes of DDIs in cancer patients, with about 89.02% of the patients facing at least one pDDI (with an average of 3.94 pDDI per patient), which was a little higher compared to the other studies.^[9-11] Among the observed interactions, 601 (67.14%) were clinically relevant interactions, which was also higher than the other study findings by Van Leeuwen *et al.*, which had only 20% of the interaction as potentially clinically relevant. One possible explanation may be the polypharmacy in (93%) most of the patients with a high mean number of drugs (8.59 ± 2.5) used by the patients in our study and the inclusion of different dosages forms of the drugs. Another possibility could be due to the use of other sources for the identification of drug interaction. Many studies have shown discrepancies in listing and rating systems between different drug interaction sources.^[12-15]

Around 59.88% of the drug interactions observed in our study were mainly due to supportive medications, and 10.9% interactions were due to the drugs received for



*5 of the interaction had two mechanisms

Figure 1: Showing the different mechanism of drug interaction

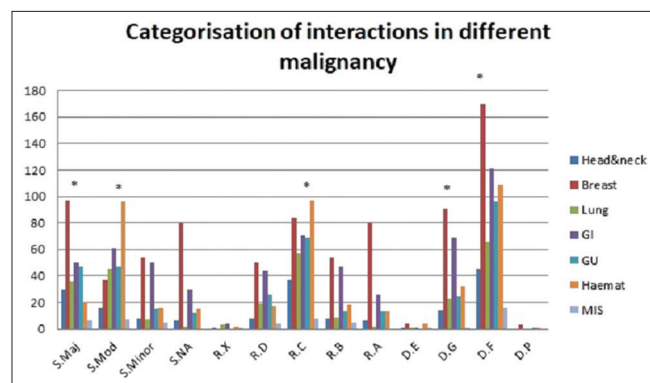


Figure 2: S. Major, S. Mod, S. Minor, NA- Different categories of Severity of interactions. R.X,R.D,R.C,R.B,R.A-Different categories of Risk category of interactions. D.E,D.G,D.F,D.P- Different categories of Documentation of interactions. GI-Gastrointestinal, GU-Genitourinary, Haemat- Haematological, MIS-Miscellaneous

noncommunicable diseases during cancer chemotherapy, with a statistically significant correlation between the numbers of drug interactions observed with the supportive medications prescribed ($P < 0.001$). It is similar to another study that drugs used for other diseases and supportive treatment play a significant role along with anticancer chemotherapeutic agents in DDIs.^[3] We observed a positive correlation seen with the number of drugs (anticancer drugs

and supportive medications) prescribed versus the number of drug interactions, which was similar to the findings in other studies [Figure 3].^[9,16]

In the present research, it was observed that the DDI was more common among females when compared to males. It may be due to the incidence of breast cancer being more among females, and at the specified period of the time frame of data collection, there were more female inmates than males. Furthermore, this could be substantiated by Princeton University's study, which suggested that hospitalization, mortality, and worsened health conditions were other factors favorable towards the female gender than males.^[17] However, there was no statistically significant difference between the number of interactions in males and females. pDDIs were common among 41–60 years of age with statistically significant differences ($P < 0.001$) between the number of interactions in different age groups; this was in contrast to the findings of Gebretsadik *et al.*^[18]

The severity assessment of the pDDIs (using Lexicomp drug interaction software) showed that the majority were of "Moderate" in Severity (34.52%) followed by "Major" (31.95%), "Minor" (17.31%), which was a contrast to the findings of other studies,^[8,16] where the majority of the interactions were "Moderate." Mouzon *et al.* reported that around 24% of the interactions were "Major," and 19% of the "Moderate" in Severity in their study.^[11] According to the risk

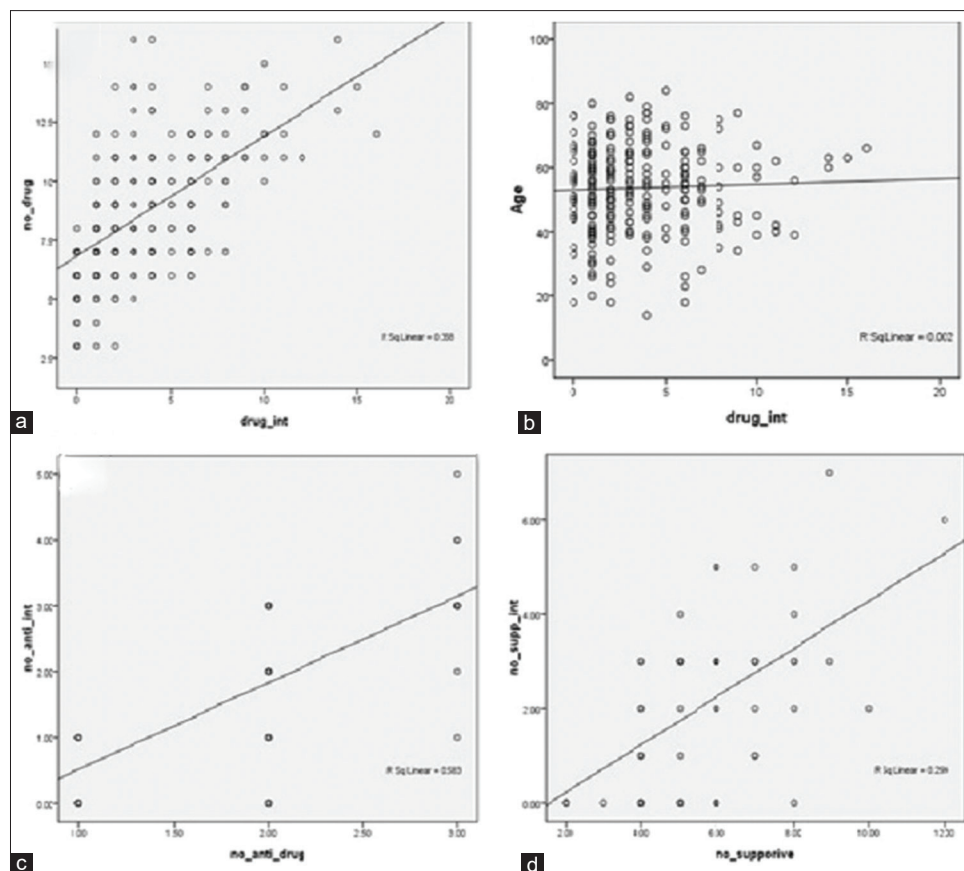


Figure 3: Correlation between; (a) drugs and number of drug interactions (b) age and number of drug interactions (c) number of anticancer drug and number of interactions (d) number of supportive drugs and number of interactions due to supportive drugs

rating, around 1.22% of interactions were contraindicated (“X” category), 18.77% required modification (“D” category), and 47.15% requiring monitoring of therapy. In contrast to studies by Mouzon *et al.*, where 5% of the interaction contraindicated and 43% needed to modify/monitor the treatment.^[11] Our study’s differences could be due to several factors, such as extensive polypharmacy and differences in the type of malignancy treated. It necessitates an increase in awareness and strict vigilance while administering chemotherapy medications. In discussing the reliability of these interactions, most of the interactions (69.06%) had “Fair” documentation in the literature, followed by “Good” documentation (28.37%). Indicating good knowledge and a sophisticated computer-based drug interaction check software with excellent training to the health care providers can help avoid drug interactions that are harmful to these patients and optimize treatment.

We observed statistically significant differences among the characteristics of drug interactions like “Major” and “Moderate” in Severity, “Good” and “Fair” in the documentation, and “C” category in risk rating among the different tumors [Figure 2]. The possible reason for this could be due to the specific regimen followed in the treatment of a particular class of tumors leading to specific interactions.

On analyzing mechanisms associated with these interactions, around 41.35% of interactions were due to pharmacodynamics mechanisms and 40.01% with Pharmacokinetics, and 18.34% with no known mechanism. In contrast with the few studies, the pharmacodynamics mechanism was more common in around 67%–70%.^[16,19] In a study by Singh and Singh, Pharmacokinetics was more common in around 86.44%.^[9] These differences may be due to malignancies treated as the treatment regimens change in each type of malignancy. Among the pharmacokinetics, most interaction due to alteration in metabolism was more common (57.95%); among them, the majority were attributed to CYP enzyme-mediated interactions. The reason for this is that the CYP3A4 system metabolizes many anticancer drugs. Treatments that include these agents are at risk when combined with other CYP3A4 substrates or inhibitors. Cyclophosphamide, paclitaxel, and docetaxel were the most commonly involved anticancer drugs in our study’s clinically relevant drug interaction. Cyclophosphamide mainly involves CYP2B6 and CYP3A4 metabolism pathways, and Paclitaxel/Docetaxel act as CYP3A4 and CYP2C8 substrate, respectively.^[8] Fluorouracil is a second common drug causing drug interaction mainly through delayed absorption, which alters the drug’s C_{max} and T_{max}.^[9] Among the supportive medication, the most commonly interacted drug was Ondansetron and Granisetron, which mainly involves

Table 3: Commonly observed clinically relevant interacted combinations

Anticancer drug combinations	n (%)	Risk	Severity	Documentation	Effect of the interaction
1. Paclitaxel + Carboplatin	20 (7.6%)	D	Major	Fair	Carboplatin increases the myelosuppressive effect of paclitaxel
2. Epirubicin + Cyclophosphamide	15 (5.5%)	C	Major	Fair	Cyclophosphamide increases the cardiotoxic effect of Epirubicin
3. Adriamycin + Cyclophosphamide	15 (5.5%)	C	Major	Fair	Cyclophosphamide increases the cardiotoxic effect of Adriamycin
4. Fluorouracil + Folinic acid	8 (3.1%)	C	Major	Good	Folinic acid increases the toxic effect of fluorouracil
5. Adriamycin + Aprepitant	8 (3.1%)	D	Major	Fair	Aprepitant increases the concentration of adriamycin
6. Trastuzumab + Dexamethasone	7 (2.7%)	C	Major	Fair	Trastuzumab increases the neutropenic effect of dexamethasone
7. Lithium + Ondansetron	58 (9.1%)	C	Major	Fair	Increased serotonergic effect
8. Dexamethasone + Aprepitant	54 (8.5%)	D	Major	Fair	Aprepitant increases the concentration of dexamethasone
9. Flucanazole + ondansetron	25 (4%)	C	Moderate	Fair	Qtc Prolongation
10. Dexamethasone + Flucanazole	21 (3.3%)	C	Moderate	Fair	Flucanazole increases the concentration of dexamethsone

the pharmacokinetic mechanism as they are CYP3A3 and CYP3A4 substrate. Corticosteroids being an inducer of most of the CYP isozymes, the knowledge regarding these drug interactions becomes essential.^[8]

The pharmacodynamics mechanism also has equal importance in the drug interaction with antineoplastic drugs. They cause toxic effects or antitumor activity in an additive, synergistic, or antagonistic manner. The commonly interacting combination among chemotherapeutic drugs was Paclitaxel with Carboplatin. The platinum analogs increase Paclitaxel's myelosuppressive effect.^[9]

It is one of the most commonly used combinations in treating multiple solid tumors; the effect is mainly due to Cell cycle-dependent antagonistic interactions. This interaction occurred when Carboplatin was injected before Paclitaxel or two drugs were administered simultaneously. The mechanism is that pretreatment or co-treatment of Carboplatin inhibits the paclitaxel-induced I-kappa B-alpha degradation and bcl-2 phosphorylation. It is also demonstrated Paclitaxel's cytotoxic effects on both mitotic arrest and apoptotic cell death could be significantly interfered with carboplatin administration, indicating that Carboplatin and Paclitaxel's interactions are schedule-dependent. The optimal schedule for this combination is sequential administration of Paclitaxel followed by Carboplatin.^[20]

The other important combination showing clinically relevant interactions was Cyclophosphamide with Epirubicin and Doxorubicin (anthracyclines). The effect is enhancing the cardiotoxic effects necessitating the need to monitor cardiac function. Cardiotoxic effects of these agents may be additive or synergistic. Administering Cyclophosphamide by infusion or twice daily or using liposomal anthracycline formulations may reduce risk. Anthracyclines-induced cardiotoxicity is multifactorial. It is dose-related, and oxidative stress causes damage to the myocardium. It is attributed to have a central part, and it is also promoted by other factors like other factors cardiotoxic drugs, heart diseases, advanced age, and concomitant treatment. Cardiotoxicity can affect up to 20%–50%, and it is recognized as chronic heart failure developing months to years after treatment.^[21]

Other studies have classified the pharmacodynamics interactions depending on the system involved, like CNS interactions, GIT interactions, QTc interval prolongation, and other mechanisms. This difference makes the comparison a little tricky; however, this is mainly due to the different tools used like Micromedex, Epocrates, and Stockley's drug interaction used in those studies.^[8,12,22]

Among the supportive medications most commonly observed clinically relevant interaction were Lithium with Ondansetron, Dexamethasone with Aprepitant, Fluconazole with Ondansetron. Indicating that antiemetics drugs are the most commonly involved group, as substantiated by a study by Umar.^[23] Lithium being a serotonergic agent, Ondansetron may enhance its effect, which may result in serotonin syndrome. Hence these patients need to be monitored for signs and symptoms of serotonin syndrome/serotonin toxicity.^[24] Aprepitant by inhibiting the CYP3A4, an enzyme responsible for corticosteroid metabolism, increases its plasma concentration, necessitating the need to monitor systemic corticosteroids' increased effects. The studies have shown an increase in the plasma concentration of Dexamethasone when co-administered with Aprepitant.^[25]

Pharmacokinetic modeling data also predicts decreased Dexamethasone's clearance by 24.7% and 47.5% during co-administration with Aprepitant 40 mg and 125 mg.^[26] Interaction of Fluconazole with Ondansetron is likely of greater significance when Ondansetron is administered by the IV route, which has a higher risk for prolonging the QT interval. Ondansetron may enhance the QTc-prolonging effect of QT-prolonging Moderate CYP3A4 Inhibitors like Fluconazole; hence monitoring the QTc prolongation and for ventricular arrhythmia is required.^[27]

Our study's main strength is that DDI studies are minimal among patients receiving cancer chemotherapy, especially in the Indian literature. Hence, our research's information can improve the understanding of possible encountered drug interactions in patients receiving antineoplastic drugs. It also encourages physicians to be more vigilant while prescribing these drugs, enabling them to recognize any adverse event to change the treatment accordingly. Our study can provide

a framework for future pharmacotherapeutic studies, which can also involve the intervention component and increase the evidence level. As it is a single-center study with a small sample size, the study findings cannot be generalized.

Our study's limitations are the lack of clinical correlation in the patients, as the interactions identified by Lexicomp software were all pDDIs. This study's results may not correlate well with similar studies that have used different PDDI-checking systems.^[28]

CONCLUSION

Cancer patients receiving chemotherapy with altered metabolism and excretory system and severely toxic drugs are more prone to drug toxicities and adverse effects. A well-organized, systematic approach is needed to identify and manage drug interactions. Not all drug interactions are preventable. Dissemination of knowledge among health providers about the most common drug and clinically relevant interactions is a key to prevent these events. Oncologists, pharmacists, and nursing staff involved in the dispensing and administration of these drugs must be trained to recognize these interactions and they should update themselves periodically. There is also a need for specialized studies with clinical correlation and continuing education programs for health-care providers in optimizing therapeutic regimens to provide better health care quality.

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Conflicts of interest

There are no conflicts of interest.

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