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A PROSPECTIVE OBSERVATIONAL STUDY ON DRUG – DRUG INTERACTION IN AN ONCOLOGY DEPARTMENT

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ABSTRACT

Objectives: To determine the incidence, the clinical relevance and high risk of drug - drug interactions(DDIs) between chemotherapeutic agents and other drugs in oncology department. **Methods**: This prospective observational study was carried out between February 2017 and July 2017 with a total of 170 patients admitted in the medical oncology wards with different types of malignancies, receiving cancer chemotherapy and medications for other illness in oncology department. **Results:** Out of 170 subjects,74(43.52%) were males and 96(56.47%) were females. A maximum number (68) of interactions were seen in the age group of 50-60 years and a minimum number of interactions were between the age group of 20-30 and 70-80 (25), one of the factor involved in interaction is polypharmacy. A total of 260 (DDIs) were seen in 170 patients. Among 260 interactions,79(30.38%) were major, 140(53.84%) were moderate, 41(15.76%) were minor. In gender wise distribution, the major DDIs were 42 in males and 37 in females, the moderate DDIs were 59 in male and 81 in female, where as the minor DDIS were 16 in males and 25 in females. As concern with the mechanism of DDIs, pharmacokinetic interactions were 96, pharmacodynamic interactions

were 128 and 36 were not specified. **Conclusions:** The study concludes that the DDIs are more common among cancer population. It can be preventable by proper monitoring and evaluation of the prescriptions. Hence clinical interventions are required to improve the patient's quality of life.

KEY-WORDS: Cancer Chemotherapy; Drug – Drug interactions; Oncology.

1. INTRODUCTION

Drug interactions are more common among patients receiving chemotherapy because of its narrow therapeutic index and inherent toxicitie.[1]

The term drug interaction is defined as the pharmacological or clinical response to the administration or co-exposure of a drug with another substance that modifies the patients response to the drug.[2] Drug interaction are most often used to illustrate drug-drug interactions, but there are various substances and factors that can modify the pharmacokinetics or pharmacodynamics of medications.[1]

Drug interactions are generally results in coccurrent use of two or more drugs which leads to increased or decreased therapeutic efficacy. Patients receiving chemotherapy are more prone to drug interactions because of multiple medications. Moreover, most cancer patients are elderly and need additional medications for comorbidities.[1]

Cancer patients are particularly exposed to drug interactions which can alter the efficacy and toxicity of treatment, leading to rigorous clinical consequences. The occurrence of drug interactions in cancer patients are high and they most often involve medications to treat comorbidity conditions. The pharmacist, as a member of the multidisciplinary team, can contribute significantly by checking the treatment prescribed, detecting interactions to lessen the medication – related problems and to optimize drug therapy for these patients.[3]

Cancer patients are particularly at risk for drug interactions as they often use several drugs as part of the cancer treatment on top of the medication prescribed to control comorbidities.[4] DDIs are generally classified as pharmacokinetic and pharmacodynamic interactions.[5] Criterias for assessing DDIs are explained in Table No.1 and pharmacokinetic parameters such as absorption, distribution, metabolism and elimination, where as pharmacodynamic characteristics could be exaggerated by unspecific membrane interactions, the drugs synergism or antagonize the effect at the point of target of action. Clinically beneficial of

drug interactions are explored to get functional drug combinations.[5,6] Since many anticancer agents are metabolised through this mechanism, DDIs involving cytochrome P450 can occur in oncology patients.[7]

Table No.1. criteria for assessing drug- drug interactions.[8]

Criteria for assessing DDIs	Description
Minor	The effects are usually mild consequences may be troublesome or invisible but should not significantly affect the therapeutic outcome. Additional treatment is usually not required.
Moderate	The effects may cause deterioration in a patient's clinical status. Additional treatment, hospitalization, or extension of hospital stay may be necessary.
Major	The effects are potentially life threatening or capable of causing permanent damage.

The factors affecting drug-drug interactions consists of polypharmacy, age, gender, and number of patients visited to the hospital.[9] The patients receiving multi-drug therapy are of wide concern for DDIs. Such interactions are an significant cause of adverse drug reactions and it could lead to an increased risk of hospitalization and higher health care costs.[10] Importance and severity of DDIs are hospitalization and life-threatening.[11] Due to the lack of information in relation to the drugs to treat comorbidities, prescribing oncologists may not always be conscious of drug – drug interactions in their patients.[12]

2. METHODOLOGY

This prospective observational study carried out in the medical oncology wards in a tertiary care hospital with the approval of ethical committee. Cancer patients were admitted for receiving cancer chemotherapy during the time period of February 2017 to July 2017 were included in the study. Patients data including demographic details, lab investigations and medications prescribed including anti-cancer drugs, supportive care agents and medications for co-morbid conditions were collected using a special questionnaire designed for the study. Patients with different malignancies of about 20-85 years were enrolled in the study whereas the pregnant and lactating woman patients also undergone surgery were excluded in the study.

Patients drug profile was subjected to screening the drug – drug interactions and the serious interactions were identified and reported to the oncologist for ensuring the patient safety and to avoid unwanted side effects.

Drug interaction screening was carried out by using *Drug interaction facts software*. For more significant information, standard books like Stockley′s Drug Interactions, Micromedex, Lexicomp were reffered.

Drug interaction fact software used to screening the drug - drug interactions and if one interaction is identified, it provides a description of pharmacological mechanisms for the interaction and classifies the interaction by level of severity and scientific evidence (Table No.2). The final sample consisted a total of 170 patients.[13]

Table No.2. Interaction classification by level of severity and level of scientific evidence.

Level of severity	**Description**
Major	An adverse effect can cause permanent damage or life risk.
Moderate	An adverse effect can harm and treatment is required.
Minor	Small or no clinical effect, with no treatment required.
Levels of scientific Evidence	**Types of scientific data**
Established	Adverse effect confirmed by large clinical trials.
Probable	Adverse effect with high likelihood of occurrence but without definitive randomized clinical trials.
Suspected	Adverse effect likely to occur; data derived from case reports.
Possible	Averse effect may occur but data are scarce.
Unlikely	Adverse effect may theoretically occur.

2.1 Statistical analysis

The data was analyzed using Graph Pad version 5.03. Chi square test was used to analyze the incidence and to identify the high risk of drug interactions. P-value of ≤ 0.05 was considered to be significant. Using this value the significance for our study was calculated.

3. RESULTS AND DISCUSSION

In our study, 170 patients were enrolled. Out of 170 prescriptions, 260 interactions were identified. The drug-drug interactions were categorised as mild, moderate and major according to their level of severity and adverse effects. Mild interaction does not require any change in the management, where as moderate drug-drug interactions can result in worsening of the disease of the patient or a change in the therapy. The severe drug-drug interactions are life threatening or they may need medical treatment or an intervention to reduce or to put off the major adverse effects.[14]

Out of 170 patients, 74 (43.52%) were males and 96(56.47%) were females (Table No.3). It was evaluated that the highest number of patients were in the age group of 50-60 years were

58(34.11%) (Table No.4). These results are related to the study conducted by Nag *et al*., Elderly persons were exposed to more multiple drug regimens than younger persons, which enhances the risk of DDIs.[8]

Table No. 3: Gender distribution of patients: (N=170).

Gender	No.of Cases	Percentages
Male	74	43.52%
Female	96	56.47%

Table No. 4: Distribution of age groups: (N=170).

Age in years	No.of cases	Percentage %
20-30	9	5.29%
30-40	10	5.88%
40-50	32	18.82%
50-60	58	34.11%
60-70	45	26.47%
70-80	14	8.23%
80	2	1.17%

A total of 260 drug-drug interactions were seen in 170 subjects. Among 260, 41(15.76%) were minor,140 (53.84%) were moderate and 79(30.38%) were major (Table No.5). A highest number (67) of drug interactions were seen in the age of above 50-60 years, followed by between 60-70 years (56) and a least number of interactions were in between the age group of 20-30(25). One of the main factors which involved in interaction is polypharmacy. (Table No.6)

Table No. 5: Level of severity of interactions.

Levels of severity	No of interaction	Percentage
Major	79	22.30%
Moderate	140	53.84%
Minor	41	15.76%

Table No.6: The table shows distribution of drug-drug interaction in different age groups.

Age in Years	Drug-drug interaction			Total
	Major	Moderate	Minor	
20-30	6	15	4	25
30-40	8	20	6	34
40-50	18	24	8	50
50-60	17	38	12	67
60-70	19	29	8	56
70-80	10	12	3	25
84	1	2	0	3

The amount of DDIs increases by means of increase in number of drugs per prescription, where maximum (90) DDIs were seen with more than a 15 number of drugs, and minimum (23) DDIs were seen in 3-5 number of drugs per prescription (Table No.7).[15] These outcomes are equivalent to the earlier studies as Kohler GI *et al.*,.[16] In our study, the quantity of drugs taken per patient as well as the number of interactions per patient are elevated during hospitalization.

Table No. 7: A relation between number of drugs prescribed in a number of prescriptions and number of drug - drug interactions.

No. of drugs prescribed	No.of prescriptions	No. of drug – drug interactions
3-5	24	23
6-10	38	62
11-15	47	85
> 15	61	90

As per the report of interactions in gender, the major DDIs were 42 in males and 37 in females, the moderate DDIs were 59 in male and 81 in female, where as the minor DDIs were 16 in males and 25 in females. (Table No.8). According to the mechanism of DDIs, pharmacokinetic interactions is of 96, pharmacodynamic is of 128 and 36 were non-specified interactions (Table No.9).

Table No. 8: The table shows the number of drug- drug interaction in gender wise.

Gender	Major	Moderate	Minor	Total
Males	42	59	16	117
Females	37	81	25	143

Table No. 9: Mechanism of drug – drug interactions.

Pharmacokinetic	Pharmacodynamic	Not specified
96	128	36

The level of scientific evidence established were 10(3.84%), probable were 12 (4.61%), suspected were 40(15.38%), possible 195(75%), unlikely 3(1.15%). (Table No.10)

Table No. 10: Level of scientific evidence in identified drug - drug interactions.

Level	No. of interaction (N=260)	Percentage%
Established	10	3.84%
Probable	12	4.61%
Suspected	40	15.38%
Possible	195	75%
Unlikely	3	1.15%

Among all the prescribed drugs of comorbidity conditions, 38(22.35%) were hypertension, 29(17.05%) were diabetes mellitus, 8(4.70%) were thyroid diseases, 2(1.17%) were epilepsy, 4(2.35%) were depression, 8(4.70%) were coronary artery diseases, 5(2.94%) were deep vein thrombosis, 10(5.88%) were hyperlipidemic. (Table No.11)

Table No. 11: The Table shows the comorbidity conditions of the total no of patients. (N=170)

Comorbidity	No of cases	Percentage
Hypertension	38	22.35%
Diabetes mellitus	29	17.05%
Thyroid diseases	8	4.70%
Epilepsy	2	1.17%
Depression	4	2.35%
Coronary Artery Diseases	8	4.70%
Deep vein thrombosis	5	2.94%
Hyperlipidemic	10	5.88%

Some significant drug – drug interactions occurred among the anticancer drugs are summarized in Table No. 12. In our study, the most frequently observed interactions were in between cyclophosphamide with doxorubicin and paclitaxel with cisplatin (Table No.12).

Table No. 12: Drug - Drug interaction between anticancer agents.

Drug drug interaction	Severity	No.of patients
Cyclophosphamide+ Doxorubicin	Major	9
Paclitaxel + Vincristine	Moderate	3
Cisplatin + Docetaxel	Moderate	5
Methotrexate + Cytarbine	Moderate	4
Trastuzumab + Paclitaxel	Moderate	2
Cyclophosphamide + Phenytoin	Major	1
Paclitaxel + Cisplatin	Moderate	8
Ifosfamide + Paclitaxel	Moderate	3
Epirubicin + Cyclophosphamide	Moderate	2

Out of 260 drug- drug interactions, 15 drug interactions were experienced by the patients which comes under different levels of severity.(Table No.13).

Table No. 13: Occurrence of drug- drug interactions.

S.no	Drug – drug interaction	Interaction effect	Clinical mangament
1	Cyclophosphamide + Phenytoin.	Cyclophosphamide and phenytoin may result in increased plasma concentration of the active metabolite of cyclophosphamide	Cyclophosphamide has been reduced 650 mg from 750 mg**.** Since patient had a complaints of loss of appetite, stomach pain and diarrhoea.
2	Cisplatin + Doxetaxel	Which results in increased risk of peripheral neuropathy.	Patient experienced numbness and weakness. So the duration of cisplatin has been changed.
3	Cyclophosphamide + Doxorubicin	Which results in increased risk of cardiomyopathy.	Cyclophosphamide has been reduced to 650 mg from 750 mg since patients heart rate was irregular and had a complaints of bloating.
4	Paclitaxel + Cisplatin	Paclitaxel after cisplatin may decreases the clearance of paclitaxel and cause myelosupression	Duration of paclitaxel has been changed before cisplatin. Since patient experienced rashes and swelling.
5	Cisplatin+ Docetaxel	Cisplatin enhances the toxicity effect of doxetaxel and cause myelosupressive effect.	Duration of docetaxel has been changed. Since patient experienced rashes and swelling
6	Epirubicin + Cyclophosphamide	Cyclophosphamide enhances the cardiotoxic effect.	Cyclophosphamide dose has been reduced since patient experiences breathlessness and chest pain.
7	Docetaxel + Carboplatin	Docetaxel enhances the myellosupressive effect.	Duration of docetaxel has been changed Since patient ex perienced rashes and swelling.
8	Haloperidol + Imipramine	Haloperidol will increase the level or effect of imipramine by affecting hepatic enzyme CYP2D6 metabolism	Patients AST and ALT level was increased.So the drug haloperidol was changed to different timing.
9	Duloxetine + Tramadol	Duloxetine will increase the level or	Patients LFT level was increased, so the drug

		effect of tramadol by affecting hepatic enzyme CYP2D6 metabolism	tramadol changes to zerodol.
10	Linezolid + Fentanyl.	Fentanyl+ linezolid will increases toxicity of the other by increasing serotonin levels.	Patient had a complaints of headache, diarrhoea, vomiting, also increases blood pressure. These are the symptoms of increased serotonin level, so the drug linezolid changes to cephalosporins.
11	Ivabradine + Isoniazid	Isoniazid may increases the plasma concentration of ivabradine. Co-administration of ivabradine with strong CYP3A4 inhibitors is contraindicated.	Patients SGOT and SGPT was increased. So the drug ivabradine has stopped.
12	Ivabradine +Ticagrelol	Ticagrelor will increase the level or effect of ivabradine by affecting hepatic enzyme CYP3A4 metabolism	Patients SGOT and SGPT levels were increased. So the drug ivabradine changes to Nebivolol.
13	Granisetron + Amitryptyline	Granisetron and Amityrptyline. will increases toxicity of the other by increasing serotonin levels.	Duration of granisetron has been changed since the patient had a complaints of diarrhea and changes in blood pressure.
14	Cyclosporine + Amikacin	Cyclosporine and Amikacin increases the nephrotoxicity and ototoxicity.	Amikacin has stopped and Cyclosporine dose has been reduced. Since patients electrolytes (magnesium and potassium, creatinine) levels elevated.
15	Atgam+ Cyclosporine.	Atgam and cyclosporin both increases immunosupressive effects; risk of infection	Cyclosporine dose has been reduced, since patient experienced loss of appetite and vomiting.

Among the 15 interactions, effects that the patient experienced mostly which includes increased or decreased in hepatic impairment, increase in serotonin levels, myelosupression and cardiomyopathy effect. So the patients were closely monitored in our study and clinical

management has done.[17] To recognize DDIs in cancer patients and avoid them to occur nevertheless, is challenging.

First, there is the concern of lack of communications between specialists (oncologists and family doctors or extra specialists devoted to the patient care). Second, patients could get herbs or further remedies of which doctors are unconscious but might interfere with their therapeutic protocols. Third, toxic effects allocated to determined DDIs could be inaccurately attributed to the side effects of chemotherapy and as a result underestimated.

Finally, chemotherapy agents are not easily controllable because of their narrow therapeutic index, which makes firm to alter the dosage without affecting efficacy or adverse effects.[18]

An additional significant decision in this study was the high predominance of DDIs that may effect in serious adverse events, including QT interval prolongation, GI toxicity, and CNS depression (falling). This has not formerly been described in journals and is of particular concern because of the high risk of impairment to the patients, quality of life and increases of health care costs.

From this study, it was observed that potential drug interaction were frequent in chemotherapy and many were clinically important. These interactions seemed to be more likely to occur in patients who stay longer and who receive a higher number of medications.

4. CONCLUSIONS

The study concludes that the drug – drug interactions are more common among patients receiving chemotherapy because of its narrow therapeutic index and inherent toxicities. Factors like polypharmacy, combination chemotherapy regimen, dose and route of administration etc may contributes to DDIs which may have negative impacts on patients quality of life, morbidity and mortality and length of hospitalization. Hence health care professionals should play a pivotal role in monitoring, detection and prevention of DDIs. Further researches are recommended for the prevention of DDIs among patients receiving chemotherapy.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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