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Research Article

Assessment Of Drug Drug Interactions Associated With Cancer Drug Therapy In Inpatient Department

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ABSTRACT

The drug-drug interactions (DDI) are a type of drug-related problem. When the two drugs are co-administered shows unwanted effects, which are preventable medication errors not seen with a single drug.

Aim and objective: The purpose of the study is mainly to identify and document the potential drug-drug interactions associated with cancer drug therapy.

Methodology: This study is a prospective study conducted in the inpatient department receiving anticancer therapy. The DDIs were identified by using some software such as drugs.com, uptodate.com [lexicomp] upon medication chart review of about 200 cases with solid & hemato malignancies.

Results: A total of 200 cases, 164 cases were identified with drug-drug interactions.389 drug-drug interactions were present in 164 cases (100%). The drug-drug interactions were classified into 2 types such as pharmacodynamic interactions and pharmacokinetic interactions and others. The pharmacodynamic interactions were found to be 281(72.2%) and pharmacokinetic interactions were 98(25.19%) and unknown mechanism includes 10 (2.57%).

Conclusion: The prevalence of DDIs is more so, physicians should be aware of PDDIs to improve therapeutic outcomes and to decrease drug-related problems.

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INTRODUCTION:

Drug-drug interactions are a type of drug-related problem. When the two drugs are co-administered shows unwanted effects, which are preventable medication errors not seen with a single drug1. Reduced transport function of OATP1B1 and OATP1B3 can lead to clinically relevant drug-drug interactions [(2).] Drug-drug interactions can cause considerable adverse drug reactions [(3).]

Drug-drug interactions are classified as pharmacokinetic drug interactions and pharmacodynamic interactions. The pharmacokinetic interactions are showing interaction at the level of absorption, distribution, metabolism and elimination process of the drug means one drug may show alteration at ADME properties of another drug [(1)]. The pharmacodynamic interactions are synergism, antagonism, and additive effects which mean one drug may potentiate synergistic, antagonistic, additive effect of another drug when both the drugs were co-administered. (e.g:5-FU and leucovorin)(4). Pharmacodynamic drug interactions can be beneficial (e.g., enhanced pharmacologic effects with fluorouracil and leucovorin), but maybe also potential harmful [(4)]. Drug-drug interactions (DDIs) may pose a real threat of undesired adverse events, of increased or decreased efficacy of antineoplastic agents and may ultimately impact on patients' quality of life. [(5)] Increasing age and polypharmacy are associated for a number of reasons. These include: Increased prevalence of multimorbidity absence of a primary care provider able to coordinate the care of different specialists and increased use of alternative forms of treatments. Also, older individuals may keep taking medications they no longer need when multiple physicians and multiple sites of care are involved [(6)]. Concomitant administration of multiple drugs may lead to unanticipated drug interactions and resultant adverse events with their associated costs. [(7)] Cancer patients are at high risk of drug-drug interactions since they take many medications (anticancer agents, drugs for supportive care and comorbidities, over-the-counter products) [(8)].

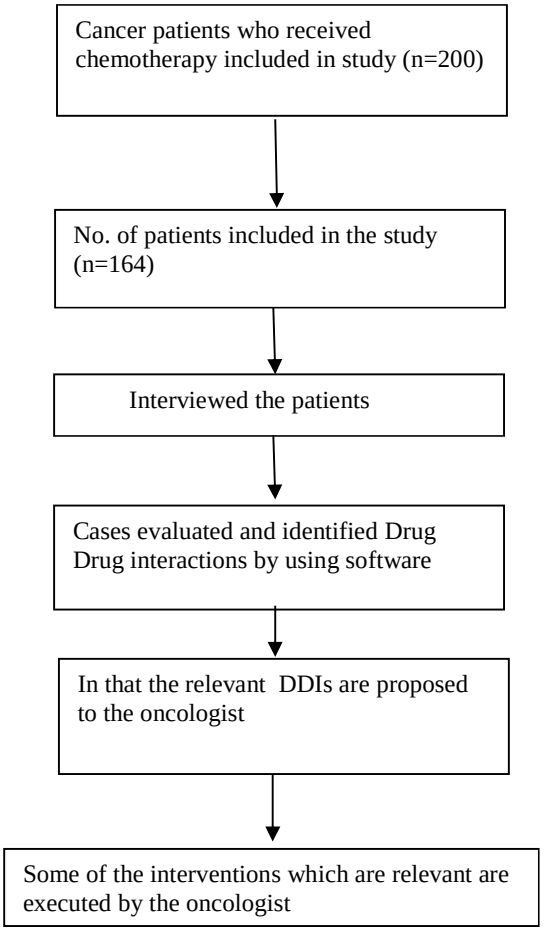
MATERIALS AND METHODS:

A prospective interventional study was conducted in patients with cancer, treated with anticancer agents. Here the interactions were found between the anticancer drugs, anticancer with other supportive drugs. In addition, data on supportive care and co-medication were collected. As the entire drug information was collected from medication chat. Till now we have studied about 200 patients for identifying the drug-drug interactions who are taking anticancer treatment. A complete detail of a patient was collected in the study which includes patient demographic details such as their age, sex, etc., (table no.1) and the use of co-medication and OTC drugs, supplements were collected and the Collection of data regarding the medication having the different dosage forms and different route of administrations.

Here the interactions were identified between the anticancer drugs and the anticancer drugs with other supportive drugs. We have identified the drug interactions by using some software's like www.drugs.com, www.medscape.com interaction checker. The drug interactions had shown both pharmacokinetic and pharmacodynamic interactions and also other forms of interactions such as drug-food interactions these interactions were associated with QT – prolongation or increases of falling CNS – depressant agent and also with GI – interactions (drug combination between NSAIDs, corticosteroids, anticoagulant, aspirin, bisphosphates, and selective serotonin reuptake inhibitors).

The pharmacokinetic interactions were shown both enzyme inhibition and enzyme induction. As of sample size 200 among them, 389 drug-drug interactions were identified. The interactions were classified depending upon the severity basis such as major interactions, moderate interactions, and minor interactions. The anticancer drugs show the most common form of interactions with some drugs such as (eg. doxorubicin, ifosfamide, gemcitabine etc) which are major interactions. It also shows the GI interactions and affects the bone marrow with the severity of moderate interactions. The anticancer drug with another anti-cancer drug such as carboplatin with paclitaxel etc. shows the peripheral neuropathy/nerve damage.

Study Design



RESULTS:

Drug Drug interactions were identified by using softwares like drugs.com and medscape.com interaction checker. The results were shown in a Table no.1, 2, 3, 4 and in a figure no.5 and 6.

Table No.1 Demographic details of the patients who received chemotherapy

Demographic details	**N**	**%**
Study population	164	100
Age	(30-80) yrs	-
Gender male	102	62.1
Female	62	37.9

Cancer type		
Solid malignancy	94	57.3
Hemato malignancy	70	42.68
Cancer type solid malignancy	94	57.3
Carcinoma esophagus	12	7.3
Carcinoma stomach	9	5.4
Carcinoma rectum	14	8.53
Breast carcinoma	7	4.26
Pancreatic carcinoma	5	3.0
Carcinoma endometrium	8	4.87
Metastatic carcinoma cervix	5	3.0
Non small cell lung carcinoma	15	9.1
Epithelial ovarian cancer	11	6.7
Colon carcinoma	8	4.87
Cancer type hemato malignancy	70	42.68
Acute lymphoid leukamia	16	9.75
Hodgkins lymphoma	10	6.0
Acute myeloid leukamia	17	10.3
Multiple myeloma	12	7.3
Non hodgkins lymphoma	15	9.1
No.of drugs used per patient	10-15	-
Anti cancer drugs	2-4	-
Supportive drugs	8-11	-

Table No.2 Identified drug drug interactions by using software.

	N	%
Total DDIs no.	389	100
Pharmaco dynamic interactions mechanism	281	72.2
GI interaction	68	17.4
QT prolongation	56	14.3
CNS interaction	53	13.6
Electrolyte imbalance	42	10.7
Kidney damage	35	8.99
Lowering of blood cells	26	6.68
Pharmaco kinetic interactions mechanism	98	25.19
Enzyme inhibition	52	13.36
Enzyme induction	46	11.82
Unknown mechanism	10	2.57

Table No.3 potential drug drug interactions involving anti -cancer drugs

Anti- cancer drugs which have interactions	**Description**	**Severity**
Doxorubicin/ifosfamide/carboplatin/pemetrexed/ Gemcitabine/capecitabine/oxaliplatin/cyclophosphamide/etoposide Methotrexate/daunorubicin/ifosfamide/bleomycin/vinblastine	GI interaction and affect bone marrow	Moderate
Carboplatin/paclitaxel/ methotrexate/cytarabine	Peripheral neuropathy/ nerve damage	Moderate
Dexamethasone/paclitaxel/irinotecan/doxorubicin/daunorubicin/ Vincristin/carboplatin/etoposide	Enzyme induction	Moderate
Methotrexate /hydrocortisone	Enzyme inhibition	Moderate

Doxorubicin/ondansetron/levofloxacin/oxaliplatin/epirubicin/arsenic trioxide	QT prolongation	Moderate
Carboplatin/pantoprazole/cisplatin/dexamethasone/methotrexate/ Trimethoprim/prednisolone	Electrolyte disturbances	Moderate

Table No.4 Overview of Drug Interactions

S.no	Drugs	Severity	Type of interaction	Interaction	N
1	Methotrexate-Trimethoprim	Major	Pharmacodynamic	Myelosuppresion(additive effect)	2
2	Zincovit-Capecitabine	Major	Pharmacodynamic	Folic acid increases the effect of capecitabine(GI interaction)	10
3	5-Fluorouracil-Leucovorin	Major	Pharmacodynamic	Leucovorin increases the effect of 5-FU leads to anemia, bleeding manifestations, nerve damage	18
4	Arsenic Trioxide-Palonosetron	Major	Pharmacodynamic	CVS interaction(QT Syndrome)	11
5	Dexamethasone-Paclitaxel	Moderate	Pharmacokinetic	Enzyme induction by dexamethasone leads to decreased concentration of paclitaxel	23
6	Dexamethasone-Doxorubicin	Moderate	Pharmacokinetic	Enzyme induction by dexamethasone leads to decreased concentration of doxorubicin	34
7	Doxorubicin-Palonosetron	Moderate	Pharmacodynamic	CVS interaction(QT prolongation)	18
8	Carboplatin-Paclitaxel	Moderate	Pharmacodynamic	CNS interaction	20
9	Etoposide- Ifosfamide	Moderate	Pharmacokinetic	Vd of ifosfamide decreases due to etoposide leads to renal dysfunction	5
10	Methotrexate-Valproic Acid	Moderate	Pharmacokinetic	Liver toxicity	3
11	Carboplatin-Ifosfamide	Moderate	Pharmacodynamic	GI interaction	11
12	Capecitabine-Oxaliplatin	Moderate	Pharmacodynamic	GI interaction	16
13	Dexamethasone-Irinotecan	Moderate	Pharmacokinetic	Enzyme induction by dexamethasone leads to decreased levels of irinotecan	2
14	Ondansetron-Oxaliplatin	Moderate	Pharmacodynamic	CVS interaction	8
15	5-FU – Oxaliplatin	Moderate	Pharmacodynamic	GI interaction	4
16	Pantoprazole-Gefitinib	Moderate	Pharmacokinetic	Pantoprazole decreases the absoption of gefitinib	2
17	Furosemide- Cisplatin	Moderate	Pharmacokinetic	Furosemide increases the adverse effects of cisplatin	3

18	Cyclophosphamide-Fosaprepitant	Minor	Pharmacokinetic	Fosaprepitant is a enzyme inhibitor increases blood levels of cyclophosphamide	1
19	Bleomycin-Doxorubicin	Minor	Pharmacodynamic	GI interaction	1
20	Dacarbazine-Doxorubicin	Minor	Pharmacodynamic	GI interaction	2
21	Carboplatin-Pantoprazole	Minor	Pharmacodynamic	Hypomagnesia	2
22	Sulphamethoxazole-Doxorubicin	Minor	-	-	1
23	Doxorubicin-Vincristin	Minor	-	-	5

Figure No.5 Indicates about severity of DDIs with anticancer drugs.

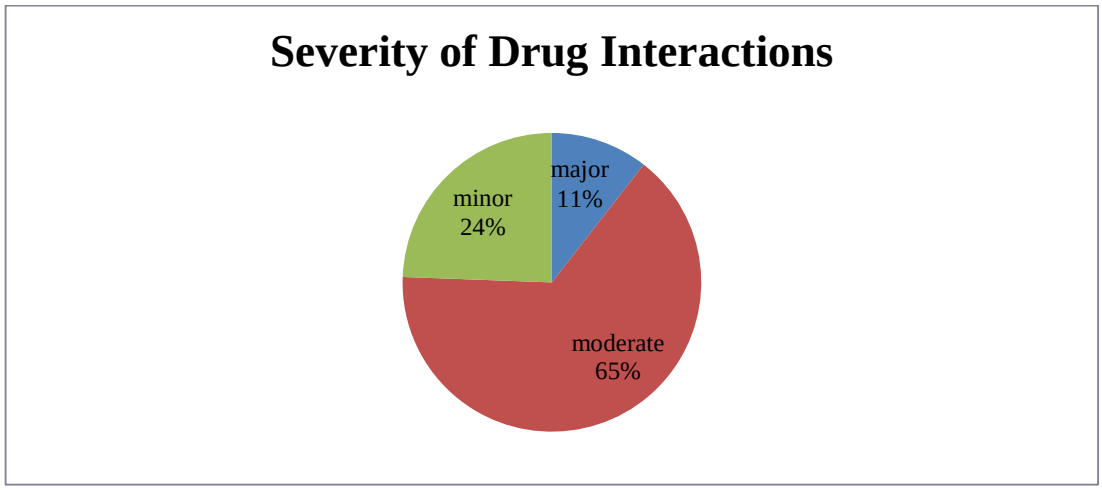
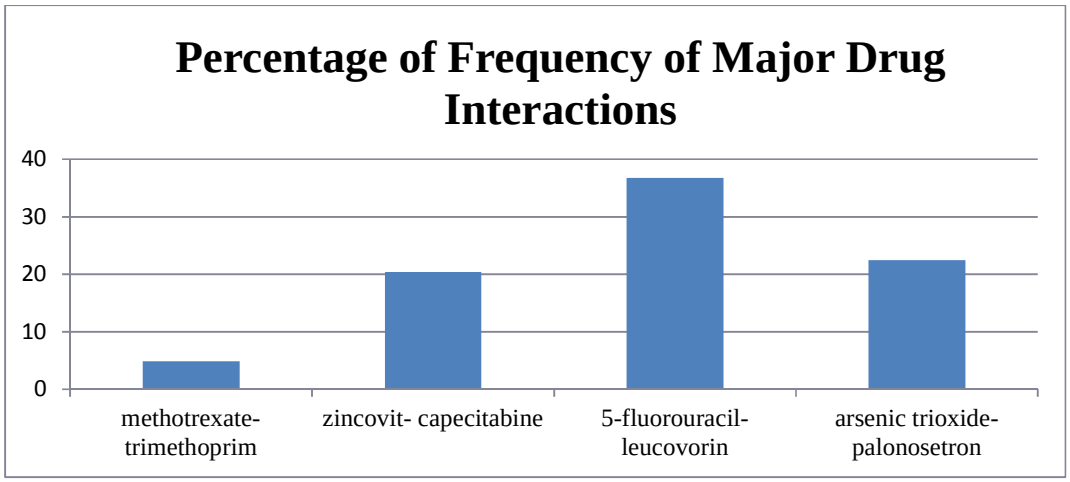


Figure No.6 *Frequency of Major Drug Interactions*



DISCUSSION:

It is a prospective study for identification of drug-drug interactions which are clinically relevant should need an intervention in oncology patients. In the total of 200 cases, we found drug- drug interactions in 164 cases; we found 389 drug-drug interactions in 164 cases which were segregated into pharmacodynamic and pharmacokinetic interactions. The PD interactions and PK interactions are divided into major, moderate and minor drug interactions based on the severity of the interaction.

For major drug interactions need an intervention to avoid the drug therapy and should consider alternative therapy. For moderate interactions also need an intervention to monitor the drug therapy.

This prospective study looked over DDI's of anticancer drugs with other anticancer drugs and with supportive medications concluded that the PD and PK drug interactions were associated with the therapeutic outcome. The potential drug-drug interactions were identified by using software (drugs.com, medscape.com interaction checker).

Corticosteroids with anticancer agents resulting more DDI's, where intervention should be needed. Most of the drug combinations show GI interactions, QT-prolongation. However, frequently 5-FU with leucovorin shows anemia, nerve damage, and vitamin deficiencies. Methotrexate with Trimethoprim shows myelosuppression which was major drug interactions which interact pharmacodynamically.

Pharmacokinetically, Dexamethasone, and paclitaxel while co-administration leads to a decrease in plasma concentration and therapeutic efficacy of the paclitaxel due to enzyme induction by dexamethasone. Etoposide and ifosfamide co-administration leads to renal damage because the volume of distribution of ifosfamide decreases due to etoposide. Many drugs frequently show CNS interaction like doxorubicin with palonosetron and peripheral neuropathy occurs due to coadministration of carboplatin with paclitaxel. Electrolyte imbalances also are seen i.e, hypomagnesia and hypokalemia due to coadministration of carboplatin with pantoprazole.

Concomitant use of drugs like methotrexate and trimethoprim shows GI bleeding and myelosuppression which is clinically relevant interaction should need an intervention. Anticancer drugs like carboplatin, doxorubicin, paclitaxel, methotrexate, 5-FU interact frequently with the corticosteroids like dexamethasone which is commonly used in oncology patients shown interaction pharmacokinetically i.e, dexamethasone decreases the effect of anticancer drugs by enzyme induction. Proton pump inhibitors with anticancer agents show GI interaction. These drug-drug interactions may occur were also based on age, gender, type of cancer and comorbidities.

This study was conducted with the objective to decrease this type of drug-related problems which are serious and major. To increase the therapeutic efficacy and safety of the drugs in the oncology patients. DDI's were identified by using the software in this study. Drug interaction checkers are used for detection of GI, QTc, CNS interactions and clinically irrelevant interactions were also detected.

In our study, based on the severity of drug-drug interactions profound assessment was made. The drug interactions which are major needed to intervene to avoid drug therapy or to consider alternative therapy. The DDI's which are moderate should warn regarding interaction and should monitor the drug concentration and effects of the drugs. The study included TDM of the anticancer drugs were needed for hospitalized oncology patients.

CONCLUSION:

Drug-drug interactions were identified and assessed with the use of software and interventions were also made based on the severity of the interaction. Based on the prevalence of the drug interaction in this study, physicians should be aware of drug-drug interactions to provide rationale therapy and to improve therapeutic outcomes and to decrease drug-related problems. It is needed in Cancer patients because they are already suffering from life-threatening cancer and the therapy should reduce the risk due to drug interactions in those patients.

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ABBREVATIONS:

5-FU: 5-Fluoro Uracil
ADME: Absorption, Distribution, Metabolism, Elimination
CNS: Central nervous System
DDIs: Drug Drug Interactions
GI: Gastro Intestinal
PD: Pharmaco Dynamics
PK: Pharmaco kinetics
TDM: Therapeutic Drug Monitoring

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