POTENTIAL DRUG- DRUG INTERACTIONS ASSOCIATED WITH CANCER CHEMOTHERAPY – A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract:

Introduction: Drug-Drug Interactions(DDIs) are an avoidable cause of patient harm, may occur due to either increased effect causing toxicity or decreased effect leading to therapeutic failure and should be considered for differential diagnosis of symptoms.

Objective: The main objective of this Prospective study which lasted for 6 months is to identify DDIs in Hospitalised patients and to categorize the severity and onset of interactions by the assistance of Micromedex software and to provide necessary guidance on their management for better patient care.

Results: A total of 300 cases were reviewed. Of them 148 prescriptions reported 378 interactions and 152 prescriptions were without DDIs. The Mean age was 54.5(11-90) years, 69% of patients were found to be female, rest 31% were male. In total, 38% patients were diagnosed with gyneacological cancer, 37% with gastrointestinal cancer. Of all the interactions, 59.52% were classified as major, 40.21% as moderate and 0.26% as minor. Based on pharmacological mechanism, 48.13% of interactions were pharmacokinetics in origin where as 36% of interactions were pharmacodynamic and 15.87% of interactions were of unknown mechanism.

Conclusion: Clinical interventions on DDIs were frequently required among the patients starting with anti-cancer therapy. Structured screening for these potentially clinically relevant DDIs by oncologists in close collaborations with clinical pharmacologists should take place before the start and during anti-cancer treatment.

***IndexTerms*:** Drug-Drug Interactions, Micromedex, Pharmacokinetics, Pharmcodynamics.

I. INTRODUCTION

A drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession[1]. A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation recipients, environmental factors, other drugs or disease[2]. Interactions between drugs (Drug-Drug Interactions) may be beneficial or harmful. Harmful drug-drug interactions (DDIs) are important as they cause 10-20% of the adverse drug reactions requiring hospitalizations and they can be avoided[3]. Elderly patients are especially vulnerable with a strong relationship between increasing age, the number of drugs being taken and the frequency of potential drug-drug interactions[4]. Knowing how drug-drug interactions occur and how to manage them is an import part of clinical practice. Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents.

Interactions with other medications can cause small changes in the pharmacokinetics or pharmacodynamics of chemotherapeutic agent that could significantly alter its efficacy or toxicity[5]. In vivo DDIs can be classified into two groups: Pharmacokinetic and Pharmacodynamic DDIs. In pharmacokinetic DDIs, the pharmacokinetic properties (absorption, distribution, metabolism or excretion) of a certain drug are altered by another drug. In pharmacodynamic DDIs, an additive, synergistic or antagonistic effect occurs when two drugs are used concomitantly (e.g. fluorouracil and leucovorin)[6].

Despite being generally acknowledged that DDIs may harm patients, their frequency in oncology is still high[7]. Studies in general medicine have found frequency of potential drug interactions ranging from 16% in patients in emergency rooms to 70% in ambulatory patients. In cancer patients, several studies conducted by our group found that approximately 30% of overall cancer patients are at a risk of DDIs[8].

Level of severity of potential DDIs has been differentiated into Major (life threatening), Moderate (exacerbation of patient's condition) and Minor (limited clinical effects)[9].

Clinicians wanted to classify relevant drug interactions, know how to manage them and differentiate them from irrelevant and unimportant interactions. Different DDI programmes are used to identify potentially harmful interactions in the inpatient setting. An applicable DDI programme should have both high sensitivity and specificity. In our analysis, we have been employed –Micromedex software. The main objective of the study was to identity potential DDIs prospectively, as retrospective study may be inconvenient to know about the proper effects.

II. ABBREVIATIONS

DDIs- Drug-Drug Interactions, OTC- Over the Counter, PDI- Potential Drug Interactions, IREP- Isoniazide-Rifampicin-Ethambutol-Pyrazinamide, BP- Blood Pressure, ECG- Electrocardiogram.

III. RESEARCH METHODS

2.1 Population and sample: A prospective observational study on potential drug interactions were carried out in a tertiary care hospital for 6 months on 300 cancer patients with solid tumors on chemotherapy excluding patients who were on radiation therapy, treated with anticancer agents with a prime focus on variety of patient care processes including safe administration of medications; which were located in convenient places with a basic objective of providing appropriate treatment to the disease.

2.2 Data and sources of Data: It is an observational study often protensive in nature for which the tectonic outcomes of interest occur after study commencement (including study protocol, analysis plan and study initiation).

Data on demographic characteristics, use of co-medication, OTC drugs and comorbidities were collected in a structured interview with the patient. Medications were subdivided into relevant four categories- anticancer drugs, supportive care drugs, drugs to treat comorbidities, OTC drugs.

Following the interview, the patient's prescriptions were screened for potential drug interactions by the drug interaction software-Micromedex which has been shown to have an accuracy of >95% in detecting interactions. DDIs were classified by severity into three groups such as major, moderate, minor and were pharmacologically classified as Pharmacokinetic DDIs, Pharmacodynamic DDIs and Interactions with unknown mechanism. The DDIs found in the database were included in the analysis when either an 'anticancer' or 'supportive drugs' or 'co morbid drugs' or 'OTC' as defined above was involved.

Drugs were also screened by clinical pharmacologist for combination of drugs resulting in potential DDIs and peer review of literature from Research & Review articles was done.

2.3 Statistical analysis: Statistics(confidence interval, chi-square test, P value) were applied to characterise the whole study sample with regard to demographics, cancer type, prescriptions with and without Drug-Drug interactions (Table 1) and level of severity, mechanism based on Pharmacokinetics and Pharmcodynamics (Table 2).

The number of potential interactions per patient was the dependent variable. Co variables were age, cancer type. Gender was not included as a co-variable due to the fact that certain cancer types only occur in men or women

With the sample size of 300, the 95% confidence interval for the assessment was between ±1.13 to ±5.49 for baseline characters. Based on presence of 378 DDIs, the 95% confidence interval was found to be ±0.51 to ±4.95 for severity and mechanism of potential drug interactions. Almost every P value of characteristics was statistically significant.

Table 1: Baseline characteristic

Characteristics	Number(N)	Percentage(%)	Confidence intervals	Chi^2 test	P value
Study population	300	100	-	-	-
Age(years)*	54.5(11-90)	-	-	-	-
Sex				14.44	0.00014469
-Female	207	69	±5.23		
-Male	93	31	±5.23		
Cancer type				89.07	0.000156
-Gynaecological	114	38	±5.49		
-Gastrointestinal	111	37	±5.46		
-Breast	53	17.6	±4.31		
-Lung	16	5.33	±2.54		
-Genitourinary	3	1	±1.13		
-others	3	1	±1.13		
Distribution based on presence of DDIs				0.017834696	0.89376110
-With DDIs	148	49.33	±5.66		
-Without DDIs	152	50.66	±5.66		

***Mean(range)**

Table 2: Based on severity, mechanism of potential drug interactions among cancer patients

Characteristics	Number(N)	Percentage(%)	Confidence interval	Chi^2 test	P value
DDIs	378	100			
Level of severity				54.82	0.0001176
-Major	225	59.52	±4.95		
-Moderate	152	40.21	±4.94		
-Minor	1	0.26	±0.51		
Mechanism				55.372	0.0001296
a)Pharmacokinetic					
-Absorption	34	8.99	±2.88		
-Distribution	0	0			
-Metabolism					
-Inhibition	12	3.17	±1.77		
-Induction	126	33.33	±4.75		
-Excretion	10	2.64	±1.62		
b) Pharmacodynamic					
-Synergistic	54	14.28	±3.53		
-Additive effect	49	12.96	±3.39		
-Additive toxicity	33	8.76	±2.85		
c) Unknown	60	15.87	±3.68		

IV. RESULTS AND DISCUSSION

Patient characteristics: During the study period (February 2018 to July 2018), a total of 300 patients were enrolled in the study. The mean of age was 54.5(11-90) years and 69% of patients were found to be female and rest 31% includes male. In total, 38% patients were diagnosed with gyneacological cancer, 37% of gastrointestinal cancer. Among the reviewed 300 patients, 148(49.33%) of prescriptions reported potential DDIs and 152(50.66%) prescriptions were without DDIs(Table 3)

Table 3

Characteristics	Number(N)	Percentage(%)
Study population	300	100
Age(years)	54.5(11-90)[a]	-
Sex		
-Female	207	69
- Male	93	31
Cancer type oncology		
-Gynaecology	114	38
-Gastrointestinal	111	37
-Breast	53	17.6
- Lung	16	5.33
- Genitourinary	3	1
- others	3	1
Distribution based on presence of DDIs		
-With DDIs	148	49.33
-Without DDIs	152	50.66

[a]**Mean(range)**

Drug-Drug interactions:

In total, 378 DDIs were identified and assessed. Of all the cases, 59.52% interactions were classified as major, 40.21% as moderate and 0.26% as minor. Based on pharmacological mechanism, 48.13 % of interactions were pharmacokinetic in origin whereas 36% of interactions were pharmacodynamic and finally 15.87% of interaction were of unknown mechanism(Table 4). The DDIs with combinations including the anticancer agents, supportive care drugs, co morbid drugs and OTC drugs are shown in the tables below. Of the total 378 interactions reported – 95 interactions were between anticancer agents (Table 5), 118 interactions were between anticancer agents and supportive drugs (Table 6), 30 interactions were between anticancer agents and co-morbid drugs (Table 7), 59 interactions were observed among supportive drugs (Table 8), 38 interactions were between supportive and co-morbid drugs (Table 9), 35 interactions were between supportive and OTC drugs(Table 10), 3 interactions were among comorbid drugs(Table 11).

Table 4

Characteristics	Number(N)	Percentage(%)
DDIs	378	100
Level of severity		
-Major	225	59.52
-Moderate	152	40.21
-Minor	1	0.26
Mechanism		
a)Pharmacokinetics	(**182**)	(**48.13**)
-Absorption	-34	-8.99
-Distribution	0	0
-Metabolism		
-Inhibition	-12	-3.17
-Induction	-126	-33.33
-Excretion	-10	-2.64
b)Pharmacodynamics	(**136**)	(**36**)
-Synergistic	-54	-14.28
-Additive effect	-49	-12.96
-Additive toxicity	-33	-8.76
c) Unknown	**60**	**15.87**

Table 5: Interactions between Anti-cancer drugs

Combinations	Number	Effect	Severity
Cyclophosphamide+doxorubicin	54	Increased risk of cardiomyopathy	Major
Fluorouracil+methotrexate / leucovorin*	10+29	Increased fluorouracil toxicity	Major / moderate
Cisplatin+ doxorubicin	2	Increased risk of leukemia	Major

*****Fluorouracil+methotreaxate=10, Fluorouracil+leucovorin=29

Table 6: Interactions between Anti-cancer and supportive drugs

Combinations	Number	Effect	Severity
Doxorubicin + dexamethasone	55	Decreased doxorubicin exposure	Major
Methotrexate+pantoprazole	7	Increased methotrexate toxicity	Major
Cylophosphamide+ ondansetron	56	Decreased cyclophosphamide systemic exposure	Moderate

Table 7: Interactions between Anti-cancer and co-morbid drugs

Combinations	Number	Effect	Severity
Cyclophosphamide+phenytoin	9	Increased risk of phenytoin toxicity	Major
Doxorubicin+phenytoin	9	Decrease doxorubicin and phenytoin exposure	Major
Cisplatin+furosemide	1	Results in additive ototoxicity and nephrotoxicity	Major
Cyclophosphamide+hydrochlorthiazide	1	Increased risk of cyclophosphamide exposure	Major
Paclitaxel+phenytoin	9	Result in loss of palcitaxel efficacy	Moderate
Fluorouracil + hydrochlorthiazide	1	Increased risk of myelosupression	Moderate

Table 8: Interactions between Supportive and co-morbid drugs

Combinations	Number	Outcome	Severity
Dexamethasone+nifedipine	5	Increase nifedipine exposure	Major
Ondansetron+tapentadol/Mirtazepine*	1/1	Increased risk of serotonin syndrome	Major
Ondansetron+tizanidine	1	QT prolongation	Major
Dexamethasone+phenytoin/IREP[a]	9/1	Decreased dexamethasone effectiveness	Moderate
Dexamethasone+ aspirin	5	Increased risk of GI ulcer	Moderate
Autrin+ phenytoin	9	Decreased Phenytoin effectivesness	Moderate
Autrin+levothyroxine	3	Result in hypothyroidism	Moderate
Glimeperide+ ranitidine	2	Increased glimeperide effect	Moderate
Telmisartan+KCl	1	Increase risk of hyperkalemia	Moderate

*****Ondansetron+tapentadol=1, Ondansetron+mirtazepine=1
[a]Dexamethasone+phenytoin=9, Dexamethasone+IREP=1

Table 9: Interactions between Suportive and OTC drugs

Combinations	Number	Effect	Severity
Dexamethasone+tramadol	26	Decreased tramadol exposure	Major
Dexamethasone +mefanamic acid/naproxem/diclofenac*	2/1/5	Increased GI ulcer/bleeding	Major
Tramaodol+metoclopromide	1	Increased risk of CNS depression	Major

*****Dexamthasone+mefanamic acid=2; Dexamethasone+naproxen=1; Dexamethsone+diclofenac=5

Table 10: Interactions between co-morbid drugs and OTC drugs

Combinations	Number	Outcome	Severity
Telmisartan+mefenamic acid	1	Result in renal dysfunction/increased BP	Moderare
Atenolol+naproxen	1	Increased BP	Moderate

Table 11: Interaction between OTC drugs and co-morbid drugs

Combinations	Number	Outcome	Severity
Aspirin+ metoprolol	1	Increased risk of BP	Moderate

Although most of the interactions were reported major, no significant clinical effects were observed in patients. In certain cases, it was difficult to assess the clinical effects of DDIs. In few pharmacodynamic interactions, where the effect of one drug is reduced by other drug, was observed in case of doxorubicin and dexamethasone where the concomitant administration of these two drugs results in decreased doxorubicin exposure (Table 6). As in case of combination of Cyclophoasphamide, Hydrochlorthiazide, ondansetron – Hydrochlorthiazide is reported to interact with Cyclophosphamide leading to increased Cyclophosphamide exposure (Table 6), whereas Ondansetron is reported to decrease Cyclophosphamide concentration (Table 7). In the same way there were few interactions leading to increased risk of GI bleeding and ulcer formation, but as these patients were receiving Proton Pump Inhibitors like pantoprazole, the effect was not clinically significant.

As the pharmacokinetic outcomes of these interactions were not visible, majority of the potential drug-drug interactions were not observed clinically. The criteria of assessing and managing severity and pharmacological changes are particularly important in finding out the risk and benefit of therapeutic alternative with appropriate dosage adjustment or modification of the dosing schedule, so that the negative effects can be avoided. All these findings indicate that, it is very much essential for DDIs to be assessed and monitored regularly.

IV. LIMITATIONS

In some of the interactions which have resulted in alteration of electrolyte levels, we have no access to measure those. We had no opportunity to observe some interactions like ECG changes (QT prolongation), tendon ruptures etc.

V. CONCLUSION

Potential Drug–Drug Interactions are very common among cancer patients on Cancer Therapy. Overall, the potential DDIs did not cause any serious problem to the patients. However, a close monitoring of the medical chart is necessary to identify the potential DDIs which may lead to serious clinical problems in patients. An increase in sensitivity of results of Micromedex is possible by the combination of expert pharmacist intervention.

Clinical Pharmacist plays a prominent role in identifying Drug–Drug Interactions. Hence this study is conducted to increase the Health related Quality of Life of patients.

VI. SCOPE OF STUDY

Similar studies can be conducted in various departments of hospital in order to improve the quality of treatment and hospital standards.

We wish to continue the present research further and design another study in which this Drug–Drug Interactions can be used as patient safety indicators which can avoid the occurrence of adverse drug reactions thereby contributing to the present knowledge of adverse drug reaction monitoring. Development of quality assessment scales for DDIs.

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