POTENTIAL DRUG- DRUG INTERACTIONS BETWEEN ANTI-TUMOR AGENTS AND OTHER PRESCRIBED MEDICATIONS IN LUNG CANCER PATIENTS: A RETROSPECTIVE STUDY.

A Project Report Submitted to

MANIPAL ACADEMY OF HIGHER EDUCATION

In partial fulfillment for the degree of Doctor of Pharmacy
(Pharm D)

MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

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MARCH 2020

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Certificate

This is to certify that this project entitled **"Potential Drug- Drug Interactions Between Anti- tumor Agents and Other Prescribed Medications in Lung Cancer Patients: A Retrospective Study",** by **Ms. Rosella Ayesha Pinto** and **Ms. Arpita Roy** for the completion of 5th year Pharm D and 2nd year Pharm D (PB) comprises of the bonafide work done by them in the Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and Kasturba Hospital, Manipal, under the guidance of **Dr. Mahadev Rao,** Professor and Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and **Dr. Karthik S Udupa,** Professor and Head, Department of Medicine Oncology, Kasturba Medical College, Manipal Academy of Higher Education.

I recommend this piece of work for acceptance for the partial fulfilment of the completion of the 5th year Pharm D and 2nd year Pharm D (PB) program of the Manipal Academy of Higher Education, Manipal for the Academic year 2019- 2020.

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Declaration

We hereby declare that the project entitled,

"Potential Drug- Drug Interactions Between Anti- tumor Agents and Other Prescribed Medications in Lung Cancer Patients: A Retrospective Study" was carried out under the guidance of **Dr. Mahadev Rao,** Professor and Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal. The extent and source of information derived from the existing literature have been indicated throughout the project work at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree purpose for this or any other university.

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Acknowledgement

We are extremely thankful to our teachers, family and friends for giving us the opportunity to carry ourselves forward in the path of dream and for their unflagging love, care, attention, concern and support throughout our lives.

We humbly owe gratitude and sincere regards to our respected teacher and guide **Dr. Mahadev Rao,** Professor and Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, for his valuable guidance, encouragement, untiring patience and support laid by him during all stages of our work. His encouragement and fruitful suggestions have enabled to make our work worthy of presentation.

Our sincere thanks to **Dr. Karthik S. Udupa** for his support and cooperation.

We would like to thank our departmental non- teaching staff, **Mrs. Ashalatha** and **Mr. Abhilash** for their endless support and cooperation.

Special thanks to the staff of Inpatient Medical Records Department, **Kasturba Hospital, Manipal** who have made us capable for successful completion of our study.

Lastly, we offer our regards and blessings to all those who supported us in any respect during the project.

LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
AUC	Area Under Curve
BP	Blood Pressure
CBC	Complete Blood Count
C_{max}	Maximum or Peak Serum Concentration
COPD	Chronic Obstructive Pulmonary Disease
CYP	Cytochrome P-450
DDIs	Drug- Drug Interactions
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
HTN	Hypertension
H_2RAs	H_2 Receptor Antagonists
INR	International Normalized Ratio
IV	Intravenous
NET	Neuroendocrine Tumour
NSAIDs	Non- Steroidal Anti-Inflammatory Drugs
NSCLC	Non- Small Cell Lung Carcinoma
OTC	Over-the-counter
OS	Overall Survival
PD	Pharmacodynamic
P-gp	P-Glycoprotein

PJP	Pneumocystis Jirovecii Pneumonia
PK	Pharmacokinetic
PPIs	Proton Pump Inhibitors
PT	Prothrombin Time
PTB	Pulmonary Tuberculosis
RR	Respiratory Rate
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
TKIs	Tyrosine Kinase Inhibitors

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ABSTRACT

BACKGROUND: Cancer patients are more prone to drug interactions as multiple medications are administered concomitantly along with cytotoxic agents in addition with drugs targeted to treat underlying comorbidities, and these are poorly evaluated. In the challenging field of cancer where the number of patients diagnosed increases in a geometric manner, the difficulties faced by healthcare professionals to treat the patients poses a great deal of arduous task in designing an optimum therapeutic regimen. This study addresses the current dilemma and suggests to bring about a resolution to the existing problem.

OBJECTIVES: The primary objective of this study is to characterize, in a group of lung cancer patients, the frequency of clinically pertinent interactions involving anticancer drugs along with prescribed drugs and other anti-tumour agents. Secondary objective involves identifying the types of drugs mainly involved, their severity and adverse consequences, and discussing its management.

METHODOLOGY: The study was conducted in Kasturba Hospital, Manipal, a tertiary care setting. 197 patients receiving chemotherapy fulfilled the inclusion criteria. Drug interactions were recorded from two sources, Micromedex Healthcare services and Epocrates (free version), and categorised as pharmacokinetic and pharmacodynamic interactions. Severity and significance of the drug interactions were assessed as per the two sources. A descriptive analysis of the data collected was carried out using Microsoft Excel Spreadsheet.

RESULTS: Among 196 patients receiving chemotherapy, 555 drug interactions were found in 185 patients using both, Micromedex and Epocrates. Based on mechanism of action, 76% of the interactions were found be to pharmacodynamic, 20% of the interactions fell under the pharmacokinetic category, and 4% of the interactions were found to be occurring via both mechanisms, pharmacokinetic as well as pharmacodynamic. 112 drug interactions were found in Micromedex alone while 589 interactions were found using only Epocrates.

CONCLUSION: Numerous drug- drug interactions were found in patients admitted to Kasturba Hospital, Manipal. This suggests a strong need for collaboration between the oncologists and clinical pharmacists, who with their clinical knowledge can help minimise the number of drug- drug interactions by conducting medication therapy reviews regularly, and help resolve the current issue in the future.

INTRODUCTION

INTRODUCTION

Cancer is a group of disease, involving uncontrolled multiplication and spreading of abnormal forms of one's own body cells.

Chemotherapy is a treatment option for majority of cancers. In chemotherapy, drugs are targeted to destroy cancer cells. In olden days, cancers were treated with a single drug. But nowadays, a combination of drugs is given to overcome the cancer cell heterogeneity and development of drug resistant cells to kill the total tumour cells.

Since cancer chemotherapy involves administration of more than one drug, the incidence of drug–drug interactions (DDIs) prevail, and majority of these interactions result in adverse drug reactions (ADRs). 20–30% of all ADRs have been reported to be caused by DDIs in the general population.[(1)] A meta- analysis has showed that 7% of the hospitalisations may be drug- related. DDIs in about 4% of the cancer patients have also reported to cause death.[(2)]

Risk factors leading to drug interactions include the use of drugs that are significantly influenced by inhibition or induction of drug metabolism (Eg: TKIs- Tyrosine Kinase Inhibitors), the use of drugs that have a considerable potential to inhibit or induce drug metabolism (antifungal medications), and the use of drugs with narrow therapeutic window as in the case of warfarin. Risk factors may also be patient-specific involving older age, renal or hepatic dysfunction, and the use of multiple prescribed medications. Generally, cancer patients receive diversiform drugs concomitantly, consisting of cytotoxic agents, supportive care agents, targeted agents and hormonal agents to treat underlying conditions. This leads to an increase in the plausibility of DDIs, where simultaneous administration of two drugs alters the pharmacological effect of the other drug.[(3)] Population analysis have shown that older patients receive multiple drugs due to increased comorbidities. Additionally, the risk of drug-drug interactions is augmented by altered age leading to exacerbating changes in the overall physiology causing comorbidities; eg, changes in the gastric mucosal layer resulting in altered absorption and hepatic and renal impairment, thereby altering excretion.[(4)]

DDIs occurring in a clinical setting can be majorly differentiated as pharmaceutical, pharmacokinetic, and pharmacodynamic interactions.[(4)] Pharmaceutical DDIs occur when there is a manifestation of two physically or chemically incompatible compounds. Example: Thiol mesna leading to the inactivation of cisplatin. When the two are combined together for infusion, it will result in the formation of a mesna- platinum adduct. A pharmacokinetic

interaction occurs when the absorption, distribution, metabolism, or excretion of one drug is precipitated by another drug. These types of interactions generally involve factors influencing absorption, or due to effects on the cytochrome P-450 isoenzymes. When medications are administered intravenously, there is 100% bioavailability as it bypasses hepatic metabolism. Pharmacodynamic DDIs occur when there is a direct influence of drugs on each other leading to a modification in its pharmacologic effect, that may be a synergistic effect, additive effect, or antagonistic effect, and are usually a result of overlapping mechanisms of action or toxicities.[4] Pharmacodynamic interactions may be both, harmful (ototoxicity due to cisplatin and furosemide[5]) or beneficial (enhanced pharmacologic effects of gemcitabine with cisplatin).

A major treatment advance for many cancers has been the introduction of effective oral therapies, as it is desired to improve efficacy while curtailing toxic effects. Patients usually prefer prescription of oral anticancer therapies rather than infusion as the former reduces hospitalisation costs and also aids in saving. However, since most of the anticancer drugs are metabolised by CYP enzymes[4] and due to chronic use, oral anticancer agents pose a potential risk for DDIs than injectable agents.[6,7] Meagre collaboration between general practitioners, medical oncologists, and pharmacists also leads to potential DDIs frequently going unnoticed.[8]

Over a considerable period, it has been recognized that there is progressive increase in the use of proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H_2RAs) to mitigate gastroesophageal reflux disease (GERD) and indigestion intrinsic to malignancy and anticancer therapy. These drugs have the capacity to reduce drug exposure of particular molecular targeted oral chemotherapeutic agents, as they are weakly basic in nature and exhibit pH-dependent solubility. [9, 10] Tyrosine kinase inhibitors (TKIs) constitute a remarkable fraction of all oral anticancer medications and are mostly given continuously on a regular basis rather than cyclically. Pharmacokinetic drug interactions are affected by CYP inducers and inhibitors and since most TKIs are substrates of the CYP3A4 enzyme, pharmacokinetic interactions among TKIs are prevalent.[11]

One of the most significant reasons for morbidity and mortality in cancer patients involves DDIs, since the toxic effects of the drugs get amplified, thereby reducing their therapeutic potency. In oncology, DDIs are of major concern due to the narrow therapeutic index that chemotherapy medications pose. Therefore, an inappreciable rise or decline in cytotoxic

activity of a drug due to an interaction by various medications can result in alterations in their pharmacokinetic (PK) and pharmacodynamic (PD) activity.

Considering DDIs, pharmacists can play a vital role in minimising their occurrences. Identification and handling of DDIs is crucial in order to provide safe and efficacious anti-cancer treatment.

AIMS AND OBJECTIVES

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Aim: To evaluate the effectiveness of the drugs used for lung cancer therapy in Kasturba Hospital, Manipal.

Objectives:

i. **Primary Objective:** To characterize the prevalence of clinically pertinent interactions involving anticancer drugs along with the prescribed drugs and other anticancer agents, in a cohort of lung cancer patients.

ii. **Secondary Objective:** To determine the types and classes of drugs mainly involved, their severity and ADRs, and discuss its management.

LITERATURE REVIEW

REVIEW OF LITERATURE

Cancer patients are at a greater risk of experiencing drug-drug interactions and it has been the objective of several studies conducted. A few instances have been discussed below with regard to pharmacodynamic and pharmacokinetic interactions.

1) PHARMACODYNAMIC DRUG INTERACTIONS

Pharmacodynamic DDIs occur when there is a direct influence of pharmacological effect of one drug by another drug when given in combination. Here, one drug may have an additive, synergistic, or antagonistic effect on another. These interactions are particularly important to be identified when chemotherapy drugs that are nephrotoxic are administered together. Drugs possessing an additive effect can result in renal failure that may be mild-to-moderate.[12] Whereas, when the effect of one drug is impeded by another, the effects of these drugs are antagonistic.

Often, a PD interaction is desired if mutually potentiating or synergistic effects are used for therapeutic advantage, e.g., using different drug classes for pain control. Two drugs exhibiting synergistic activity will require lower doses when given in combination. Combinations of gemcitabine with cisplatin and pemetrexed respectively, have particularly shown favourable results in regard to their synergistic properties.[13,14] The mechanisms that contribute to this effect include nucleotide-pool modulation, cellular DNA repair capacity, and drug metabolism.

Commonly co-prescribed drug classes having the highest risk of QT-prolongation include anti-infectives, anti-emetics, anti-depressants, anti-psychotics, high-dose loperamide, and pain killers such as tramadol. Likelihood of QT prolongation may also be caused by drugs inhibiting the metabolism of oral anticancer therapies. There are reports suggesting mild QTc prolongation with paclitaxel.[15,16] However, it appears to have only a low risk of incidence (1%- 5%).

Studies have reported that Erlotinib increases INR when used concomitantly with warfarin. Hence, patients need to be closely monitored along with necessary dose adjustments.[17]

It has been found that there is a probable decline in renal function in consequence to continued pemetrexed administration when combined with NSAIDs.[18] In patients receiving the combined chemotherapy of carboplatin and pemetrexed along with NSAIDs, drug interactions

between pemetrexed and NSAIDs have reported to cause severe hematologic toxicities which may be induced by inhibiting the tubular secretion of pemetrexed.[19] Therefore, it is imperative to take required safety measures against such adverse side effects while using these combinations, by conducting periodic examinations.

Shan F et al. performed a meta-analysis in patients with advanced non-squamous non- small cell lung cancer (NSCLC) to assess the effect of the maintenance therapy involving the combination of pemetrexed and bevacizumab. Patients showed to develop a statistically increased risk of grade 3 and 4 adverse experiences.[20] Bevacizumab or pemetrexed alone, as a single-agent maintenance therapy was found to be efficacious, but due to insufficient evidences to support benefit of survival and high toxicity, this combination is not recommended.[21]

Combination of cisplatin and vinorelbine was found to be effective in treating advanced NSCLC. However, in a study conducted by *Hotta K et al*, grade 4 neutropenia was recorded in 86% of all cycles and grade 3 leukopenia was noted in 57% of the cycles, while reaction at the injection site and grade 3 infection were reported to be the most severe non- haematological toxicity symptoms.[22]

Findings of a study conducted by *Lee EH et al.* displayed that continuous high dose steroid (20 mg prednisolone for ≥ 3 weeks) therapy and concurrent chemo- radiation therapy were risk factors for Pneumocystis Jirovecii Pneumonia (PJP),a serious infection caused in patients with lung cancer and was associated with a very poor prognosis.[23]

2) PHARMACOKINETIC DRUG INTERACTIONS

Pharmacokinetic drug interactions arise as a result of four basic principles: absorption, distribution, metabolism, and elimination. The interaction is considered clinically significant if it causes toxicity or alters therapeutic response of a drug.

a. Absorption

Absorption of various oral chemotherapy agents is often influenced by multiple factors, including acid-suppressive agents. Ultimately, these factors impact the solubility and bioavailability of chemotherapy agents. Drugs exhibiting low oral bioavailability are generally affected often, while those with high bioavailability are rarely affected. For example, a study

which evaluated the effect of omeprazole on a single dose of erlotinib, showed to reduce the C_{max} and AUC of erlotinib by about 61% and 46%,[24] respectively while in another study, AUC and C_{max} of erlotinib were reduced by ranitidine by 33% and 54% respectively.[25] It also resulted in a reduction of 44% and 70% for the AUC and Cmax of gefitinib, respectively.[26]

Drug transporters present in the gut epithelium may also be responsible for impaired drug absorption. For example, P-glycoprotein (P-gp) significantly hinders the uptake of numerous oral anticancer drugs, one of them including paclitaxel. On administering ciclosporin, a P-glycoprotein inhibitor, it blocked P-gp activity, thereby increasing the bioavailability of paclitaxel and attaining appropriate plasma drug concentrations.[27-31]

b. Distribution

Specific drug characteristics such as high protein-binding (>90%) and narrow therapeutic index, increase the likelihood of altered distribution. Major factors affecting the distribution of drugs include the ability of the drug to bind to proteins like albumin, lipoproteins, immunoglobulins, erythrocytes, and $alpha_1$-acid glycoprotein. Highly protein bound anticancer drugs like paclitaxel and etoposide have shown to provoke protein displacement of warfarin, another protein- bound drug, consequently increasing the patient's INR.[32]

c. Metabolism

Metabolism primarily occurs in the liver involving the cytochrome P450 enzymes. These enzymes are accountable for majority of the phase I process of the oxidative metabolism of drugs. Out of the 100 isoenzymes, most of the anti-cancer drugs are mainly metabolized by the following 6 enzymes: CYP3A4, CYP2C9, CYP1A2, CYP2E1, CYP2D6, and CYP2C19, out of which the first three isoenzymes are most clinically significant. The CYP3A4 isoenzyme is known to metabolize about 50% of all medications.

Drugs such as cyclophosphamide; paclitaxel and docetaxel; nilotinib, erlotinib and a few other oral chemotherapy agents are partially metabolized by the CYP3A4 isoenzyme. When combined with other CYP3A4 substrates, inhibitors, or inducers it can alter their activity. There are various drugs which competitively inhibit or induce cytochrome P450 enzyme–binding sites. This can alter the metabolism of mainly oral chemotherapy agents, thereby altering their efficacy and safety.[33]

Careful assessment of drug interactions is also recommended when a patient starts treatment with oral anticancer agents. Antifungals such as itraconazole, voriconazole, posaconazole, and

ketoconazole are strong inhibitors of CYP3A4, which interact with a large majority of TKIs. Erlotinib, an EGFR TKI, is metabolized largely by CYP3A4 and by CYP1A2 to an insignificant extent. When administered with ketoconazole, it resulted in elevated erlotinib concentrations. On the other hand, when it is given along with CYP3A4 inducers such as rifampin, it demonstrated to decrease erlotinib's concentrations and effectiveness by causing a 60%- 70% reduction in AUC.[17] Thus, dose adjustment is essential for the co-prescribed oral anticancer agents that are major CYP3A4 substrates.

In addition to PD interactions, a number of PK interactions also occur between oral anticancer therapies and direct oral anticoagulants. Metabolism of all direct oral anticoagulants occurs via either the CYP3A4 isoenzyme or P-gp transporter, or both. Concurrent use of chemotherapeutic agents and warfarin causes inhibition of the CYP450 class of enzymes resulting in drug interactions. Warfarin is a major CYP2C9 substrate as well as a minor substrate of the CYP3A4, CYP2C19, and CYP1A2 isoenzymes. Patients taking gemcitabine and warfarin concurrently, too have displayed a significant rise in INR which could be due to either a decline in the synthesis of clotting factors, or due to diminished warfarin metabolism which may be a result of CYP450 inhibition.[35] Thus, patients receiving anticoagulation therapy with warfarin should regularly check their INR and dose adjustments must be done accordingly.

When erlotinib is concurrently administered with phenytoin, it can cause decreased erlotinib concentrations and efficacy due to induced hepatic metabolism. Combination of erlotinib and phenytoin has also resulted in elevated serum phenytoin concentration leading to phenytoin toxicity.[34]

d. Excretion

Most of the anticancer drugs are eliminated after undergoing metabolism. Chemotherapy agents such as methotrexate and platinum compounds are excreted primarily by the kidneys. Cisplatin influences the renal clearance of topotecan[36], resulting in enhanced toxicity such as myelosuppression.[37]

Christopher J. S. found that coadministration of ibuprofen and pemetrexed significantly reduced the systemic clearance of pemetrexed.[38]

Rodman et al. (1992) found that when etoposide was administered with the anticonvulsants such as phenobarbital or phenytoin to paediatric patients with cancer, etoposide clearance was increased to 170% of that of etoposide alone.[39]

Oral Anti-cancer Therapy

There is a remarkable increase in the number of studies that examine the pharmacokinetic variability between parenteral and oral administration.

Acid suppression (AS) by antacids, H_2RAs, and PPIs disrupt absorption of oral anticancer therapies by suppressing the secretion of acid by the parietal cells and raising the intragastric pH from ~1.2 to ~4. Most of the TKIs including gefitinib and erlotinib, manifest weak basic properties and pH-dependent solubility.[9, 10, 40] They are more ionic in an acidic environment and more soluble, since they get optimally absorbed. Therefore, due to the hypochlorhydic conditions brought about by these agents, equilibrium tends to shift from the ionized to the non-ionized form, thereby reducing their absorption. This results in diminished exposure to the drug and as a consequence, affects the efficacy of gefitinib and erlotinib.

One such study was conducted retrospectively in NSCLC patients who were treated with gefitinib and erlotinib.[8] Among 269 patients, 57 patients (21.2%) used acid-lowering therapy. Use of these drugs was associated with reduced overall survival (OS). Among patients with brain metastases, the OS was shorter with utilisation of acid-lowering therapy at 11.8 months compared to 16.3 months among non- users.

METHODOLOGY

METHODOLOGY

Study subjects

The study was conducted at Kasturba Medical Hospital, Manipal, and included all patients with lung cancer admitted to Shirdi Sai Baba Cancer Hospital and Research Centre, between January 2015 and July 2019.

Ethical Clearance: The ethical approval was obtained from the Institutional Ethics Committee of Kasturba Hospital, Manipal.

Inclusion criteria: Lung cancer patients with a solid tumour and those who received chemotherapy fulfilled the inclusion criteria. Secondly, drug interactions were taken into account only if the anti-cancer drugs and co-medications were administered concomitantly.

Exclusion criteria: Patients who were discharged beyond the physician's request.

Data collection

For every patient under inclusion, all drugs administered concomitantly to the patients along with the chemotherapy regimen, i.e., the co-medications, including multivitamins were identified and recorded. Data was gathered from the medical records department, and included the following demographics: age of the patient, sex, cancer stage, type of lung cancer, smoking status, co-morbidities, chemotherapy regimen and other co-medications administered, including discharge medications.

DDIs were checked for each anti-tumour drug taken by every patient. Anti-cancer drugs were taken into consideration irrespective of the class of drug, days of administration, and route of administration [intravenous (I.V.) and oral]. Two drug interaction sources were utilised to identify the interactions between the anticancer drugs and non- anticancer drugs: IBM Micromedex Drug Reference, and Epocrates (free version).[41, 42]

In Micromedex, DIs are classified into five categories of severity: contraindicated, major, moderate, minor and unknown. Only the first three categories were chosen for this study because interactions of minor severity lack clinical significance. Epocrates classifies DIs in terms of their management, namely- contraindicated, avoid use or use alternative, monitor or modify treatment, and caution advised. All of the four categories were taken into consideration and none were dismissed.

All interactions found in atleast one of the two sources were recorded. DDIs were classified into two based on their mechanism of actions, either as PK or PD.

Statistical analyses

Data obtained were entered into Microsoft Excel Spreadsheet and a descriptive analysis was carried out with regard to the characteristics of drug interactions. The drugs mainly involved were identified, along with their severity and adverse consequences, as well as source(s) of information.

RESULTS

RESULTS

Patients: On the basis of inclusion criteria, 196 patients receiving chemotherapy were evaluated, out of which 129 (65.8%) were males and 67 (34.2%) females, with a range of 27-86 years. Among 196 patients, 3 patients underwent surgery and 57 received radiation along with chemotherapy. The demographic characteristics of the patients are summarised in Table 1. Patients took an average of 6 co-medications. Figure 1 presents the number of chemotherapy cycles received by the patients. In 196 patients, a total of 23 anti-cancer drugs were identified as shown in Table 2.

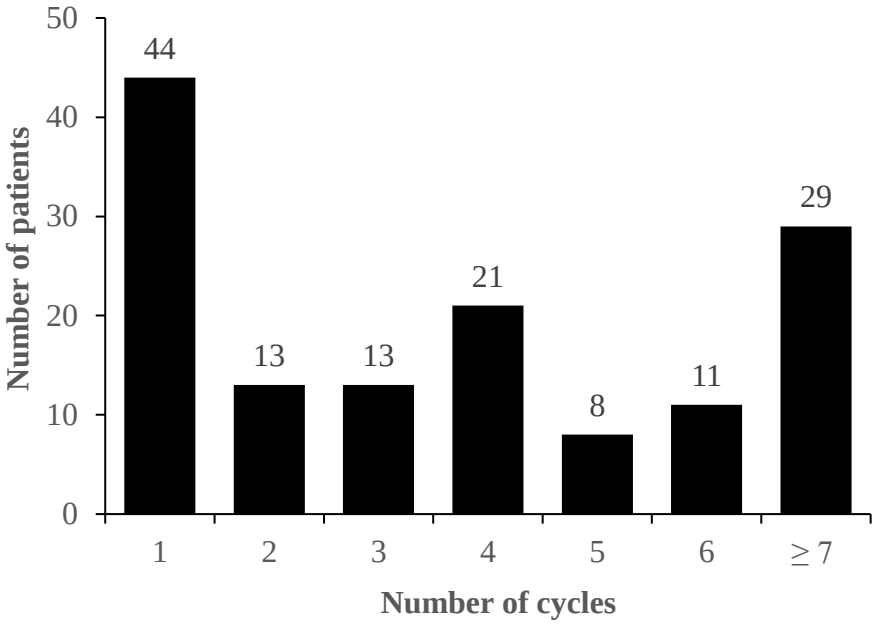

Figure 1. Number of chemotherapy cycles received by lung cancer patients.

Table 1. Patient Characteristics (n= 196)

Gender	Male	129 (65.8)
	Female	67 (34.2)
Age	Mean ± SD	58.81 ± 10.73
	Range	27- 86
	< 60 years	100 (50.8)
	≥ 60 years	97 (49.2)
BMI	Underweight	36 (18.4)
	Normal	90 (45.9)
	Overweight	42 (21.4)
	Class I Obesity	4 (2)
	Class II Obesity	1 (0.5)
	Unknown[1]	22 (11.2)
Tumour stage	Earlier than IV	75 (38.3)
	IV	121 (40.3)
Metastasis	Bone	23 (11.8)
	Brain	17 (8.6)
	Neuroendocrine tumour (NET)	8 (4.0)
	Spine	3 (1.5)
	Others[2]/ Unknown	72 (36.5)
	None	74 (37.6)
Co-morbidities[3]	HTN	58 (29.6)
	Diabetes	43 (29.9)
	COPD	14 (7.1)
	PTB	10 (5.1)
	None	76 (38.8)
Drugs used[4]	Oral chemotherapy	83
	I.V. chemotherapy	316
	Targeted therapy	15

Values are n (%).

[1] Patient unable to stand.

[2] Others include liver, kidney, adrenal, pancreatic, and cervical mets.

[3] Some patients had more than 1 co-morbidity, while other insignificant co-morbidities are not taken into account.

[4] Some patients received more than one chemotherapy agent.

Table 2. List of various anti-cancer agents used

Drug Class	Drug Name	Frequency in patients[1]	Percentage (%)
EGFR inhibitors	Gefitinib	80	40.8
	Erlotinib	6	3.1
	Crizotinib	2	1.0
	Afatinib	2	1.0
Platinum compounds	Carboplatin	83	42.3
	Cisplatin	59	30.1
Anti- Metabolites	Pemetrexed	50	25.5
	Gemcitabine	36	18.4
Anti- Mitotic agents	Paclitaxel	28	14.3
	Docetaxel	7	3.6
Vinca Alkaloids	Vincristine	2	1.0
	Vinorelbine	2	1.0
Anthracyclines	Doxorubicin	2	1.0
Nitrogen Mustard	Cyclophosphamide	2	1.0
Monoclonal Antibodies	Nivolumab	7	3.6
	Bevacizumab	5	2.6
	Denosumab	1	0.5
	Nimotuzumab	1	0.5
	Cetuximab	1	0.5
Topoisomerase Inhibitors	Etoposide	33	16.8
	Topotecan	1	0.5
Miscellaneous	Everolimus	1	0.5
	Bleomycin	1	0.5

[1] Some patients received more than one chemotherapy agent.

Drug- Drug Interactions: Figure 2 presents the chemotherapy medications with atleast one potential DDI identified using Micromedex and Epocrates. Among 196 eligible patients, a total of 595 drug interactions were found in 185 patients using both, Micromedex and Epocrates. Upon categorising them based on mechanism of action, 76% of the interactions were found be to pharmacodynamic, 20% of the interactions fell under the pharmacokinetic category, and 4% of the interactions were found to be occurring via both mechanisms, pharmacokinetic as well as pharmacodynamic (Figure 3). 112 drug interactions were found using only Micromedex, and 589 interactions were found in Epocrates, alone (Figure 4). Characteristics of these DI are presented in Table 3. In terms of severity, there were 107 'major' DDIs, equating to 18% of the total number (n= 595).

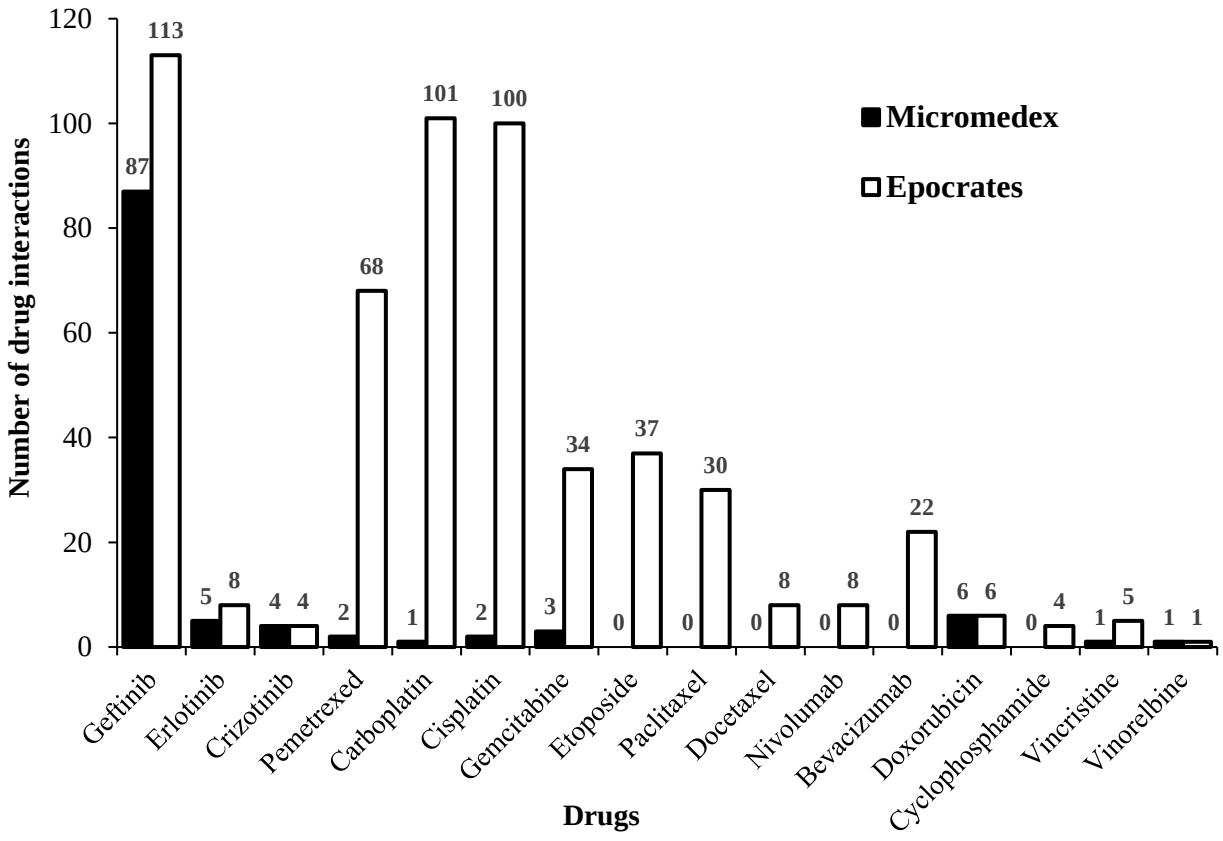

Figure 2. Frequency of DDIs for each chemotherapeutic agent that had atleast one identified DDI.

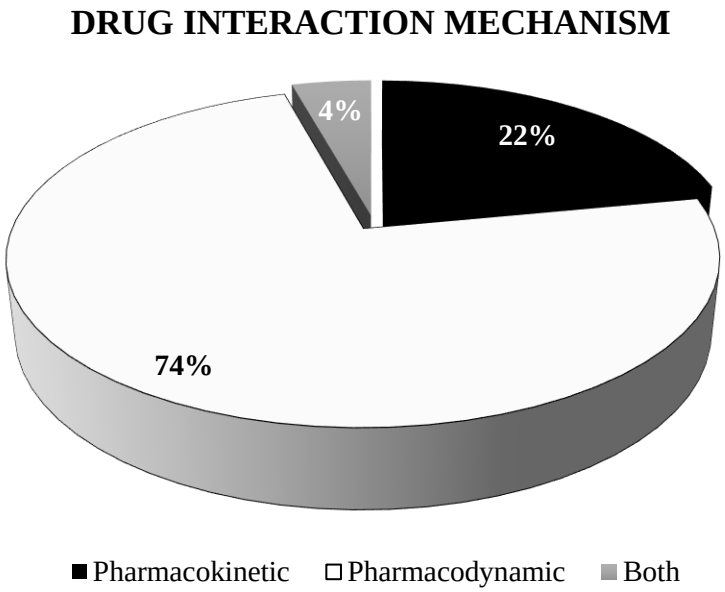

Figure 3. Classification of drug interactions based on their mechanism, commonly obtained from both sources, Micromedex and Epocrates.

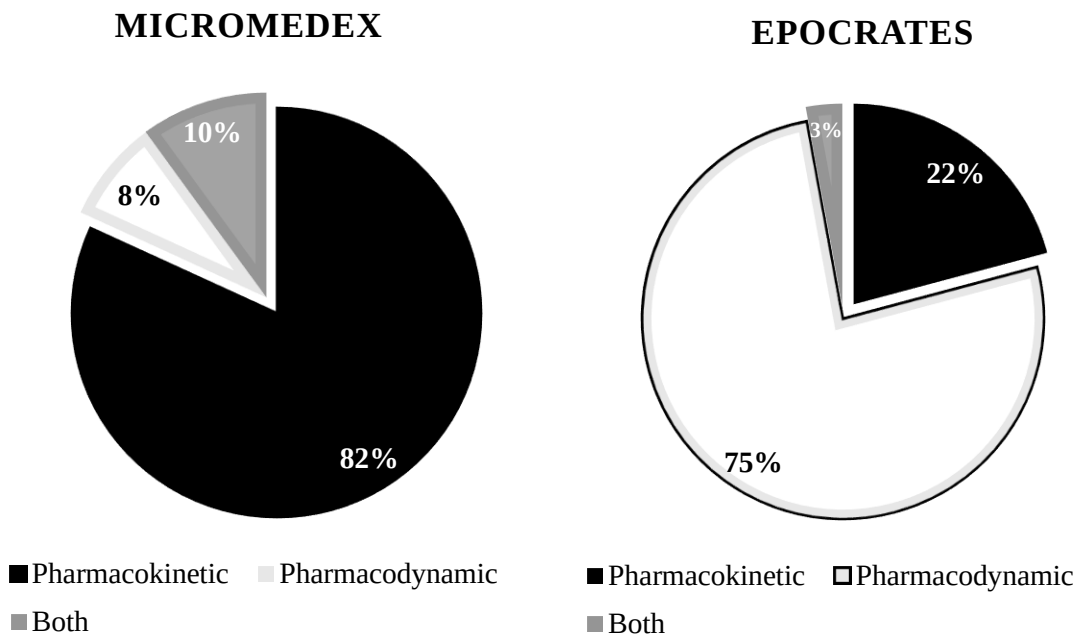

Figure 4. Drug interactions and their mechanisms obtained from two different sources, Micromedex and Epocrates

Table 3. Characteristics of Interactions (n= 595)

Drugs involved	Between an anticancer agent and prescribed drug	474 (79.6)
	Between two anticancer agents	69 (11.6)
	Between an anticancer agent and Miscellaneous Products[1]	52 (8.7)
Significance	**According to Micromedex (n= 112)**	
	Contraindicated[2]	1
	Major interactions[3]	107
	Moderate interactions[4]	4
	According to Epocrates (n= 589)	
	Avoid/Use alternative	128
	Monitor/Modify treatment	333
	Caution advised	128
Adverse Consequences	Increased toxicity of anticancer agent	6
	Increased toxicity of co-medication	26
	Increased toxicity of both agents	75
	Decreased efficacy of anticancer agent	91
	Additive effects	293
	Increased toxicity of anticancer agent + Additive effect	86
	Increased toxicity of co-medication + Additive effect	10
	Decreased efficacy of anticancer agent + Additive effect	2
	Antagonistic effect	6
Management	Monitor treatment	310
	Avoid use	6
	Alter dosage	3
	Use alternative drug	58
	Separate administration by 2 hours	1
	Separate administration by 6 hours	19
	Administer 24 hours before/ after myelosuppressive chemo	6
	Separate administration by 12 hours	64
	Nothing suggested	128
Sources of information	Interactions found in both sources	106
	Interactions found only in Micromedex	112
	Interactions found only in Epocrates	589

Values are n (%).

[1] Miscellaneous Products: Calcium Carbonate, Filgrastim and Zoledronic acid

[2] Contraindicated: The drugs are contraindicated for concurrent use.

[3] Major: The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse effect.

[4] Moderate: The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.

The most common identified DDI was that of Gefitinib + PPIs (which includes pantoprazole, esomeprazole and rabeprazole) (11.5%), followed by Carboplatin + Dexamethasone (11.3%) and Cisplatin + Dexamethasone (9.5%). The most frequently occurring interactions are depicted in Figure 5. The remaining interactions had fewer instances (<6%).

It was found that out of 196 patients, 43 patients (21.4%) experienced 1 drug interaction, 51 patients (26%) experienced 2 drug interactions, and 38 patients (19.4%) had 3 interactions, while the remaining had more than 3 drug- drug interactions.

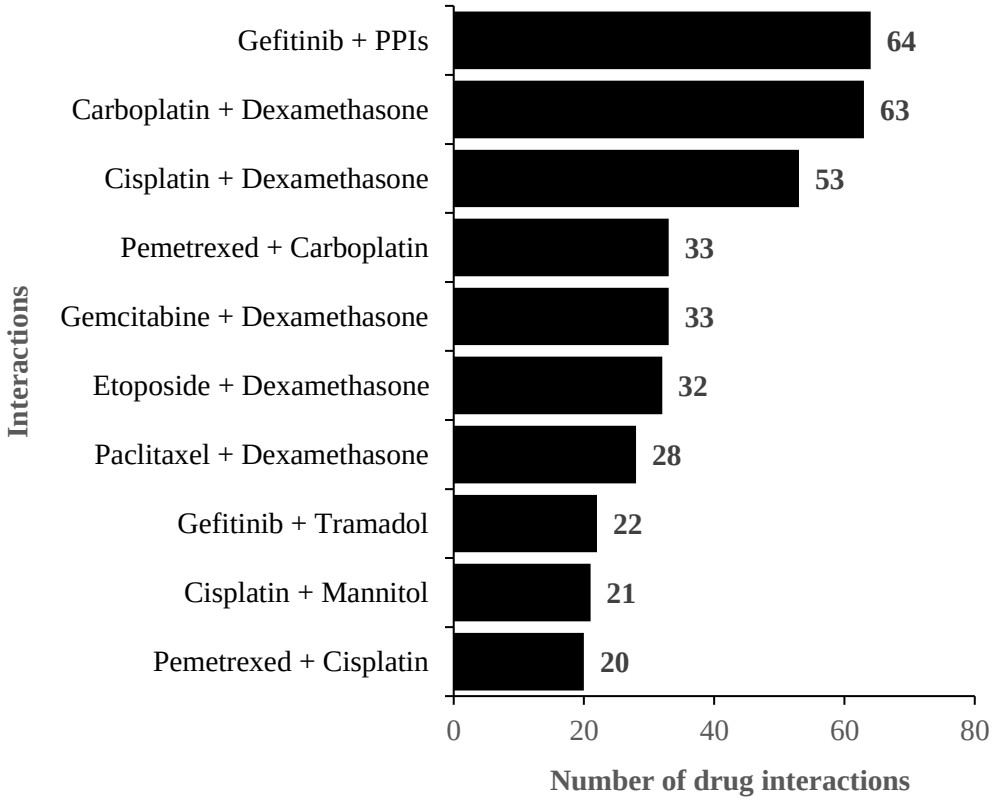

Figure 5. Frequency of the Top 10 Drug- Drug Interactions found in our study group of lung cancer patients.

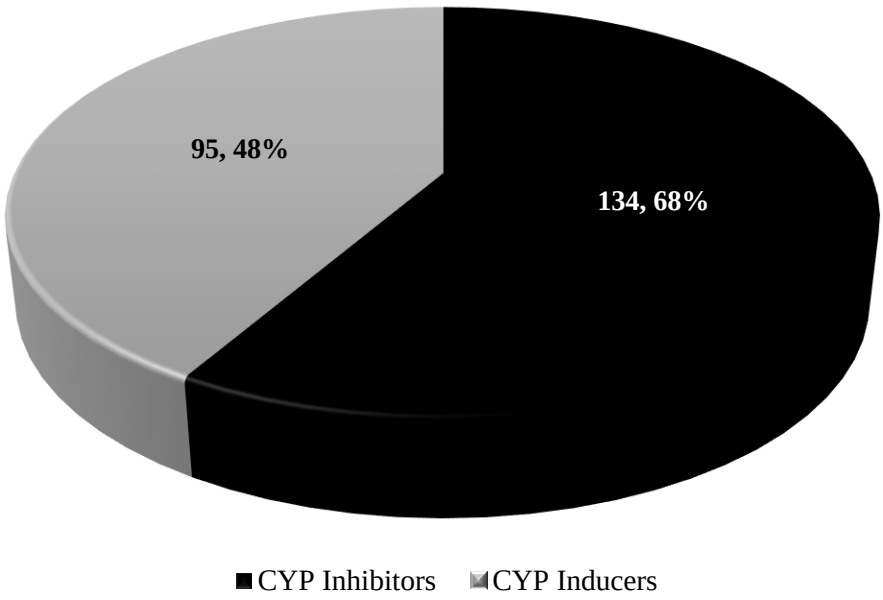

Figure 6. Frequency of lung cancer patients receiving atleast one CYP Inhibitor and CYP Inducer in our study group (n= 196). Some patients received more than one CYP inducer/ inhibitor.

Given below is the list of inducers and inhibitors of the CYP450 system of isoenzymes along with their substrates (Table 4). The strength of enzyme activity is categorised as weak, moderate, and strong. It was found that 95 (48.5%) patients were prescribed atleast one CYP isoenzyme inducer while 134 (68.4%) patients took atleast one CYP isoenzyme inhibitor, as shown above in Figure 6. The medications used in both groups include those prescribed as supportive care agents and to treat the clinically significant associated comorbidities. The CYP isoenzyme inducers and inhibitors most commonly taken by patients in our study group included antacids, anti- emetics, anti- hypertensives, anti-fungals, and corticosteroids.

Table 4. List of CYP 450 isoenzymes in our study group: Substrates, Inhibitors and Inducers

CYP Substrates					
CYP3A4	**CYP3A5**	**CYP2C8**	**CYP2D6**	**CYP2D6**	**CYP2E1**
Pantoprazole	Gefitinib	Domperidone	Tramadol	Metoclopramide	Etoposide
Gefitinib	Crizotinib	Erlotinib	Phenytoin	Ondansetron	
Crizotinib	Etoposide	Atorvastatin	Codeine	Atenolol	**CYP1A2**
Erlotinib	Paclitaxel	Paclitaxel	Domperidone	Nebivolol	Pemetrexed
Etoposide	Docetaxel		Diphenhydramine	Theophyline	
Paclitaxel	Cyclophosphamide		Dextromethorphan	Zolpidem	
Docetaxel	Vincristine	**CYP2C9**	Chlorpheniramine	Tamsulosin	
Doxorubicin		Cyclophosphamide	Tapentadol	Amiodarone	
Cyclophosphamide			Acetaminophen	Quetiapine	
Vinorelbine		**CYP2C19**	Loperamide	Sildenafil	
Everolimus		Pantoprazole	Gefitinib	Formoterol	
Vincristine		Cyclophosphamide	Olanzapine		
CYP Inhibitors					
CYP3A4	**CYP3A5**	**CYP2C8**	**CYP2D6**		**CYP2E1**
Acetaminophen +	Fluconazole +	Erlotinib +	Gefitinib +		Etoricoxib +
Dexamethasone +	Amlodipine +	Amoxicillin +	Amitriptyline +		
Ranitidine +		Amitriptyline ++	Etoricoxib +		
Mirtazepine +		Ondansetron ++	Amiodarone +		
Olanzapine +			Isoniazid +		
Octreotide +		**CYP2C9**	Rabeprazole +		
Clindamycin ++		Aprepitant +	Verapamil +		
Fluconazole ++			Vinorelbine +		
Aprepitant ++		**CYP2C19**	Clotrimazole ++		
Isoniazid ++		Aprepitant +	Clobazam ++		
Milnacipran ++		Etoricoxib +	Metoprolol ++		
Itraconazole +++					
Efavirenz +++					
Loperamide +++					
CYP Inducers					
CYP3A4	**CYP3A5**	**CYP2C8/ 2C9/ 2C19**	**CYP2D6**		**CYP2E1**
Warfarin +	Budesonide ++	Nil	Nil		Etoricoxib +
Clobazam +	Dexamethasone ++				
Dexamethasone ++/+++					
Rifampicin +++					
Rifaximin +++					

Weak: +; Moderate: ++; Strong: +++

Prevalence of treatment with the CYP 450 inducers and inhibitors is shown in Table 5. As depicted, CYP3A4 was found to be the majorly involved CYP isoenzymes.

As mentioned earlier, one of the most common pharmacokinetic interactions involved gefitinib and pantoprazole. Though the frequency of interaction seemed to be higher, considering the enzymes involved in the CYP pathway, gefitinib appears to be a CYP 3A4 inhibitor of pantoprazole of an unestablished strength. However, being a major pharmacokinetic interaction, it is recommended that more studies be conducted to establish its strength so as to aid in clinical decision making.

Table 5. Prevalence of Treatment with CYP isoenzymes Inducers and Inhibitors (n= 196)

CYP Isoenzyme	No. treated with CYP Inducer			No. treated with CYP Inhibitor		
	Weak	**Moderate**	**Strong**	**Weak**	**Moderate**	**Strong**
3A4	5	78	83	114	53	7
3A5	×	88	3	25	1	×
2C8	×	×	×	5	3	×
2C9	×	×	×	2	×	×
2C19	×	×	×	2	×	×
2D6	×	×	×	69	5	×
2E1	3	×	×	3	×	×

× Not applicable

DISCUSSION

DISCUSSION

In order to present the data in a qualitative manner, the common DDIs are summarised in Table 6 along with the mechanism of the interacting drug and their resulting effects.

It was found that 185 patients out of 196 patients undergoing chemotherapy were prone to experiencing atleast one potential DDI. Polypharmacy was observed among patients with, as well as without metastatic tumours. Many patients were found to be taking medications having a significant potential for pharmacodynamic DDIs as well as CYP isoenzyme- mediated pharmacokinetic DDIs.

Upon classifying the DDIs based on the mechanism of action in Micromedex and Epocrates, there exists an evident difference in the type of interactions found between the two drug sources. As shown in Figure 4, Micromedex describes DDIs mainly based on pharmacokinetic interactions, whereas Epocrates describes them mainly based on pharmacodynamic interactions. However, both sources are user- friendly and are accurate in terms of their sensitivity and specificity.

Oral drug delivery appears to possess unique considerations, and thus it is essential for oncologists to understand the potential DDIs it may relate to. Interactions involving oral anticancer drugs can result in intensifying the toxic profile of the drug or a substantial decrease in efficacy if not managed properly. The oncologist and clinical pharmacist must jointly manage these patients by conducting an open discussion with the patients. These drugs should be prescribed only after thoroughly reviewing the concomitantly administered medications, to address the potential DDIs, if any. Patients must also be counselled on proper administration of such medications to ensure optimal absorption and minimize toxicity.

In order to avoid interactions between PPIs and TKIs, PPIs must be preferably switched to H2RAs, or the interaction can also be minimised by administering H2RAs at night, approximately 12 hours apart from the drug, i.e., erlotinib and gefitinib. Moreover, over-the-counter acid- lowering agents such as antacids, if needed, can be administered, provided that a dosing interval of 2 hours before or after the administration of these oral chemotherapeutic agents is maintained.

Certain TKIs can result in profound toxicity if administered with strong inhibitors of CYP3A4. On the other hand, strong inducers of CYP3A4 could significantly decrease the activity of the

TKIs. Thus, in cases where concurrent administration of erlotinib, a TKI and a strong CYP3A4 inducer is required, an alteration in the dose by 50 mg daily must be deemed necessary, whereas when given along with CYP3A4 inhibitors, dose must be augmented by 50 mg, and patients must be monitored carefully.[17]

Stopping gastric acid suppressants such as PPIs can be difficult, however in a study conducted by Van Leeuwen et al, researchers reported that it may be possible to neutralise the decreased absorption of TKIs by using an acidic beverage such as cola during drug administration. When tested with erlotinib, it showed to increase the bioavailability of erlotinib by approximately 40%, and may help minimise the associated drug interaction.[43].

In patients initiating oral chemotherapeutic drugs that may be likely to increase vulnerability to warfarin toxicity, INR must be carefully monitored until stabilization is attained. Additionally, patients should also be counselled regarding the signs and symptoms of bleeding.

In addition to PPIs, several interactions were also found between gefitinib and tramadol. The combination is known to inhibit the hepatic metabolism of tramadol, thereby preventing its conversion into its active metabolite. This can increase the likelihood of various ADRs including CNS depression and respiratory depression, as well as QT prolongation that could lead to cardiac arrythmias. Periodic monitoring of RR and ECGs must be carried out.[44]

Dexamethasone, a supportive care agent for the mitigation of nausea and vomiting in anticancer therapy, has found to be one of the most frequently administered co-medications. Among the DDIs found in our study group, we noticed that dexamethasone was the most common interacting co-medication. It mainly showed to interact with cytotoxic agents like carboplatin and cisplatin. When administered concurrently, it causes an additive effect through an unknown mechanism, thereby increasing chances of hypokalemia and serious infection. Potassium levels in these patients must be kept under a constant check and any signs of infection must be treated at the earliest.

Combination of cisplatin and mannitol is known to increase cisplatin levels, thereby causing myelosuppression and nephrotoxicity. A phase II clinical trial involving cisplatin and mannitol in patients with advanced lung cancer, led by *Jager DR et.al* revealed that renal toxicity was observed in 9.9% (8 out of 81 patients) of the patients, with a peak S.Cr. (serum creatinine) >2.5 mg/100 ml, as well as 1 death due to toxicity. Mild myelosuppression was also observed.[45] Patients taking such combinations must be monitored for CBC, sodium levels,

renal function, and ototoxicity. In view of reducing the risk of developing nephrotoxicity, magnesium supplements can be administered along with cisplatin therapy.[46]

Pharmacist's role

Proficient pharmacists can play a major role in improving patient care. As clinical pharmacists, we can contribute by screening the medications prescribed to the patients along with the chemotherapeutic drugs, examining the plausibility of DDIs, and managing them by closely monitoring them, endorsing modifications in dose, or providing alternate treatment options. This can help improve effectiveness of the anti-cancer drugs, thereby curtailing its toxicity. Pharmacists can also counsel patients regarding the likelihood of DDIs, and advise them to consult their oncologists or pharmacists before using any OTC acid- lowering medications.

Table 6. Characteristics of the Commonly Interacting Drugs.

Anticancer agent	Interacting Drug	Mechanism	Frequency (n)	Possible Mechanism and Severity	Recommendation/ Management	Source
Gefitinib	PPIs[a]	PK	64	Major- Absorption of gefitinib decreased at higher gastric pH.	Administer gefitinib 12 hours after the last dose or 12 hours before the next dose of the proton pump inhibitor	Micromedex/ Epocrates
	H_2RA[b]/ Antacids[c]	PK	9	Major- Absorption of gefitinib decreased at higher gastric pH.	Administer gefitinib 6 hours after or 6 hours before a H2RA or antacid	Micromedex/ Epocrates
	Warfarin	PK/ PD	2	Moderate- May increase prothrombin time and INR and risk of bleeding.	Monitor for changes in prothrombin time (PT) or INR, during first 2 weeks following warfarin initiation. Warfarin dose adjustment may be needed.	Micromedex/ Epocrates
	Tramadol	PK	22	Hepatic metabolism inhibited; Decreased conversion of tramadol to active metabolite.	Use alternative or monitor RR, ECG and withdrawal syndrome	Epocrates
	Calcium Carbonate	PK	10	Major- Absorption of gefitinib decreased at higher gastric pH.	Separate administration by 6 hours	Micromedex/ Epocrates
	Phenytoin	PK	1	Major- Induction of CYP3A4 mediated metabolism of gefitinib.	Monitor Phenytoin levels: Increase gefitinib dose to 500 mg during and x7 days after phenytoin	Micromedex/ Epocrates
	Itraconazole	PK	1	Hepatic metabolism of gefitinib is inhibited	Caution advised	Epocrates
	Rifampin	PK	1	Major- Induction of CYP3A4 mediated metabolism of gefitinib	Inc. gefitinib dose to 500 mg during and x7 days after rifampin	Micromedex/ Epocrates

[a] PPIs- Pantoprazole, Rabeprazole, Esomeprazole
[b] H_2RAs- Ranitidine
[c] Antacids- Magnesium Hydroxide

Erlotinib	Pantoprazole	PK	4	Major- Absorption decreased at higher gastric pH	Avoid combination	Micromedex/ Epocrates
	Calcium Carbonate	PK	1	Major- Absorption of erlotinib decreased at higher gastric pH	Separate administration by 2 hours	Micromedex/ Epocrates
Crizotinib	Fluconazole	PK/ PD	1	Contraindicated- May result in QT prolongation and cardiac arrythmias- Hepatic metabolism inhibited & Additive effects	Use alternative or monitor ECG, electrolytes	Micromedex/ Epocrates
Carboplatin	Dexamethasone	PD	70	Additive effect- Risk of hypokalemia and serious infection	Monitor Potassium	Epocrates
	Hydrocortisone	PD	6	Additive effect- Risk of hypokalemia and serious infection	Monitor Potassium	Epocrates
	Formoterol/ Terbutaline	PD	5	Additive effect- Risk of hypokalemia	Monitor potassium	Epocrates
	Telmisartan	PD	7	Additive effect- Risk of infection, myelosuppression, nephrotoxicity.	Monitor CBC, renal function and ototoxicity	Epocrates
	Mannitol	PD	2	Additive effect- Risk of infection, myelosuppression, nephrotoxicity.	Use alternative or monitor CBC, renal function and ototoxicity	Epocrates
	Furosemide	PD	1	Additive effect- Risk of infection, myelosuppression, nephrotoxicity and hypokalemia	Use alternative or monitor CBC, renal function and potassium	Epocrates
	Naproxen/ Ibuprofen/ Diclofenac	PD	7	Additive effect- Risk of serious infection, myelosuppression, nephrotoxicity.	Monitor CBC, renal function and ototoxicity	Epocrates
	Warfarin	PD	1	Major- Risk for elevated INR and subsequent bleeding	Monitor INR and monitor for signs of bleeding. May require warfarin doage adjustment.	Micromedex

Cisplatin	Dexamethasone	PD	61	Additive effect- Risk of hypokalemia and serious infection	Monitor Potassium	Epocrates
	Terbutaline	PD	3	Additive effect- Risk of hypokalemia	Monitor potassium	Epocrates
	Mannitol	PD	27	Additive effect- Risk of infection, myelosuppression, nephrotoxicity.	Use alternative or monitor CBC, renal function and ototoxicity	Epocrates
	Hydrochlorothiazide	PD	3	Additive effect- Risk of infection, myelosuppression, nephrotoxicity, hypokalemia, SIADH and hyponatremia	Monitor CBC, renal function, ototoxicity and electrolytes	Epocrates
	Naproxen/ Diclofenac	PD	8	Additive effect- Risk of serious infection, myelosuppression, nephrotoxicity, SIADH and hyponatremia	Monitor CBC, renal function and sodium levels	Epocrates
	Warfarin	PK/ PD	1	Moderate- Increased INR (Unknown mechanism)	Monitor INR while starting and stopping warfarin, or consider changing the dosage of Cisplatin.	Micromedex
Paclitaxel	Dexamethasone	PD	29	Additive effect- Risk of serious infection	Caution advised	Epocrates
Docetaxel	Dexamethasone	PD	6	Additive effect- Risk of serious infection	Caution advised	Epocrates
Etoposide	Dexamethasone	PD	38	Additive effect- Risk of serious infection	Caution advised	Epocrates
Gemcitabine	Dexamethasone	PD	33	Additive effect- Risk of serious infection	Caution advised	Epocrates
	Warfarin	PK/ PD	3	Major- Increased risk of bleeding due to reduced warfarin metabolism and decreased hepatic synthesis of clotting factors	Monitor INR. May require warfarin dose reduction.	Micromedex

Pemetrexed	Carboplatin	PD	33	Additive effect- Risk of serious infection, myelosuppression, nephrotoxicity and auditory adverse effects.	Monitor CBC, renal function and ototoxicity	Epocrates
	Cisplatin	PD	20	Additive effect- Risk of serious infection, myelosuppression, nephrotoxicity and auditory adverse effects.	Monitor CBC, renal function and ototoxicity	Epocrates
	Naproxen	PK/ PD	2	Major- Additive effect- Decreased clearance of pemetrexed may result in risk of myelosuppression, nephrotoxicity and GI toxicity.	Monitor CBC and renal function	Micromedex/ Epocrates
Nivolumab	Dexamethasone	PD	4	Additive effect- Risk of serious infection	Caution advised	Epocrates
	Prednisolone/ Hydrocortisone	PD	4	Additive effect- Risk of serious infection	Caution advised	Epocrates
Bevacizumab	Dexamethasone	PD	4	Additive effect- Risk of hypertension	Monitor BP	Epocrates

LIMITATIONS

LIMITATIONS

1. The study conducted was single- centered and not a multi-centre study.

2. A larger sample size would have been desired.

3. Clinical impact of DDIs were not evaluated due to the study being retrospective.

4. Cost of therapy was unaffordable to many patients as they were from a low to average-income based category. Hence, they refused treatment and requested for discharge against medical advice (DAMA).

5. Confounding results between the two drug databases used in the study.

6. Inexplainable comparisons between significance levels of these two databases.

CONCLUSION

CONCLUSION

Numerous drug- drug interactions were found in patients admitted to Kasturba Hospital, Manipal. Physicians must be alerted of the potential adverse events that may be caused due to these drug- drug interactions. Medication therapy review is not commonly practiced in our hospital. This suggests a strong need for clinical pharmacists, who with their clinical knowledge can help minimise the number of drug- drug interactions by regularly reviewing the medication therapies. Collaboration of oncologists and clinical pharmacists can prove to resolve the current issue.

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APPENDICES

APPENDIX- I

KASTURBA HOSPITAL
MANIPAL
(An associate Hospital of MAHE, Manipal)

Kasturba Medical College and Kasturba Hospital
Institutional Ethics Committee
(Registration No. ECR/146/Inst/KA/2013/RR-16)

Communication of the decision of the Institutional Ethics Committee

Wednesday 14th August 2019 **IEC : 545/2019**

Project title	:	Drug Utilisation Review of Anti-cancer Drugs with Other Medications in Lung Cancer Patients.
Principal Investigator	:	Miss. Rosella Ayesha Pinto
Guide/ Co Guide/ Co Investigators	:	Dr. Mahadev Rao, Arpita Roy, Dr. Karthik Udupa
Name & Address of Institution	:	Department of Pharmacy Practice, MCOPS, MAHE, Manipal, Department of Medical Oncology, KMC, Manipal.
Status of review	:	New
Date of review	:	13.08.2019
Decision of the IEC	:	Approved for the study period from 13.08.2019 to 12.08.2021.
Endorsement of continuation of approval : (due date 12.08.2020)	:	Signature and Seal

- The PI and all members of the project shall ensure compliance to current regulatory provisions (as per Schedule Y of Drugs and Cosmetics Act and ICH-GCP), Ethical Guidelines for Biomedical Research on Human Participants by ICMR, and the SOP of IEC including timely submission of Interim Annual Report and Final Closure Report
- Participant Information Sheet and a copy of signed Informed Consent shall be given to every research participant
- Inform IEC in case of any proposed amendments (change in protocol / procedure, site / Investigator etc)
- Inform IEC immediately in case of any Adverse Events and Serious Adverse Events.
- Members of IEC have the right to monitor any project with prior intimation.

Dr. Rajeshkrishna Bhandary P
MEMBER SECRETARY - IEC

ETHICS COMMITTEE APPROVED KASTURBA HOSPITAL, MANIPAL

IEC Secretariat, Room No. 22, Ground Floor, Faculty Room Complex, Kasturba Medical College Premises,
Kasturba Medical College, Manipal - 576104, Karnataka, India. Phone : +91 - 0820 - 2933522, Fax : +91 - 0820 - 2571927. Email : iec.kmc@manipal.edu

APPENDIX- II

CRF FORM

I.P. No:	**H.P. No:**	**Co-morbidities:**
Age:	**Sex: M ● F ●**	
Date of Admission:		
BMI:		
Smoking status:		**Classification /Grade / Stage:**
Surgery:		

ANTI- CANCER DRUGS				**OTHER DRUGS**			
Generic Name	**Brand Name**	**Dose**	**Time**	**Generic Name**	**Brand Name**	**Dose**	**Time**

CRF FORM

Cycle	Total DDIs Found ( )

CHARACTERISTIC OF INTERACTION		
MECHANISM OF DRUG-DRUG INTERACTION	**PHARMACODYNAMIC:**	**PHARMACOKINETIC:**

SIGNIFICANCE	**Acc to Micromedex:**	**Acc to Epocrates:**
	Mild:	Monitor/ Modify Treatment:
	Moderate:	Avoid/ Use alternative:
	Severe:	Contraindicated:
	Contraindicated:	Caution advised:

ADVERSE CONSEQUENCES	1. Increase in toxicity of both the drugs
	2. Increase in toxicity of anticancer drugs
	3. Increase in toxicity of co-medication drugs
	4. Decrease in efficiency of anticancer drugs
	5. Decrease in efficiency of co-medication

Thesis

ORIGINALITY REPORT

%1	%1	%0	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.science.gov Internet Source	<%1
2	www.clostridiumdifficile.fi Internet Source	<%1

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