T.R.N.C

NEAR EAST UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

Drug-drug interactions in Oncology department at Near East University Hospital in Northern Cyprus

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ABSTRACT

Introduction: Drug-drug interactions are one of the most important DRPs that occur in cancer patients and most DDIs can cause considerable adverse drug reaction.

Aim: This study aims to assess the frequency of DDIs, mechanism and severity of interaction in patients with cancer disease at Near East University Hospital.

Method: A retrospective observational study was conducted in hospitalized patients at Near East University Hospital (NEUH) in North Cyprus from 01 April 2017 to 01 April 2018, 87 patients with a cancer diagnosis who admitted to the oncology department at the hospital during the study period. Lexi-interact tool by Lexi-comp and Drugs.com database was used for identification of DDIs. Mann Whitney test and Chi-square were used to test for significant difference between the DDIs and age, gender and number of medications. A p-value <0.05 was assigned as statistically significant.

Result: According to Drugs.com, (87.4%) of DDIs were identified among 87 patients, (46.31%) of DDIs were a pharmacodynamic interaction and most DDIs were moderate in severity (68.85%). Also, according to Lexi-comp, (71.30%) of DDIs were identified among 87 patients, (52.30%) of DDIs were a pharmacodynamic interaction, risk rate C has been identified with the greatest number of DDIs (68.53%). There was a significant association between the presence of DDIs and number of medications (p-value <0.05)

Conclusion: We found that cancer patients have a high risk of occurrence Drug-drug interactions. The medical care community should pay attention to this issue and clinical pharmacists have an important responsibility to reduce the occurrence of DDIs.

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ABBREVIATIONS

Abbreviations	Explanation
DDIs	Drug-drug interactions
DRPs	Drug-Related Problems
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
CT scan	Computerized Tomography Scan
MRI Scan	Magnetic Resonance Imaging scan
PET Scan	Positron Emission Tomography Scan
IV	Intravenous
IP	Intraperitoneal
IA	Intra-Arterial
CNS	Central Nervous System
PNS	Peripheral Nervous System
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ACE inhibitor	Angiotensin-Converting-Enzyme Inhibitor
PH	Potential Hydrogen
CSF	Cerebrospinal Fluid
CYP	Cytochrome P450
ADR	Adverse Drug Reaction
GI	Gastrointestinal
S phase	Synthesis Phase
G phase	Gap 1 Phase
M phase	Mitotic Phase

Abbreviations	Explanation
MTX	Methotrexate
5-FU	5-Fluorouracil
NEUH	Near East University Hospital
PK	Pharmacokinetic
PD	Pharmacodynamic

1. Introduction

1.1 Drug Interaction

The drug interaction occurs when the side effects or effects of one drug are changed by the presence of another compound, which is drugs, food, drinks, herb, or environmental chemicals. Drug interaction is defined as the pharmacological or clinical response to the administration of a drug with another substance that alters the patient's response to the drug. The term 'drug interaction' is most often used to describe drug-drug interactions, but there are several substances and factors that can change the pharmacokinetics and/or pharmacodynamics of the drug. These include food, nutritional supplements, formulation excipients and environmental factors (such as cigarette smoking (Askari M. , 2013).

Drug interactions possibly are becoming more common in daily practice because of the increasing number of drugs coupled with the increased life expectancy of the general population. Interactions between two or more concomitantly administered drugs may rise or reduce therapeutic effect as well as undesired effects. Drug-drug interactions (DDIs) make patient safety at risk by leading to toxicity or a decreasing therapeutic benefit and may increase the mortality and morbidity, especially in elderly and frail patients like cancer patients.

Fatal adverse drug effects rank between the fourth and sixth major cause of death in the US, it is reported that 20–30% of all adverse reactions to drugs are caused by interactions between drugs. (Scripture, 2006).

DDIs can have three potential outcomes: increased therapeutic and/or adverse effects, decreased therapeutic and/or adverse effects or a unique reaction that does not occur with either agent alone (Blower, 2005), the outcome can be risky if the interaction causes an increase in the toxicity of the drug. for instance, there is a big increase in the risk of acute muscle damage if patients taking statins start taking azole (antifungals), a reduction in efficacy as a result of interaction can sometimes be just as harmful as an increase, for example, patients taking Warfarin who are given Rifampin needs more warfarin to maintain sufficient anticoagulation. (Preston, 2015).

Drug-drug interaction is divided into two main types of interaction: pharmacokinetic which include a change of absorption, distribution, metabolism, and elimination, and

the second type is pharmacodynamic there is a change in the pharmacological effect of a drug.

Drug interaction is also classified based on the severity:

1-Major (Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit)

2-Moderate (Moderately clinically significant. Usually avoid combinations; use it only under special circumstances)

3-Minor (Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan) (Qureshi, 2017)

1.2 The Incidence of Drug Interactions

The more drugs a patient takes the greater the probability that an adverse reaction will occur. In one hospital study found that the average was 7% in those taking 6 to 10 drugs but 40% of those taking 16 to 20 drugs, which appear a disproportionate increase. A possible explanation is that the drugs were interacting (Baxter, 2010).

In a prospective study of 639 elderly patients results showed 37% incidence of interactions. furthermore, another review of 236 geriatric patients found a 22% incidence of potentially serious and life-threatening interactions and 88% incidence of clinically significant interactions. A 4.1% incidence of drug interactions on prescriptions presented to community pharmacists in the US were found in a further survey (Baxter, 2010).

Another study was conducted in 2016 involving 331 patients who had received a total of 2,878 drugs, 89% of the patients were exposed to drug-drug interaction (Kannan, 2016).

Between 2002 and 2009, a study was conducted on 9644 patients in the intensive care unit,3892 had at least one drug-drug interaction (Askari M. E.-H., 2013).

1.3 Mechanism of Drug-drug Interactions

Knowledge of the mechanism by which a given drug interaction happens is sometimes clinically useful, it can help minimize side effects and undesirable effects by adjusting the dose or finding an alternative drug.

Drug interactions can be categorized as pharmaceutical, pharmacodynamic and/or pharmacokinetic

1.3.1 Pharmaceutical Drug Interactions

Pharmaceutical interactions occur before drugs are actually administered to the patient, it depends on the drug's properties and its pharmaceutical form. Mostly, perform incompatibilities of drugs administered by intravenous infusion. These incompatibilities apparent as an increase in measured haze or turbidity, particulates, and color changes. The final outcome of this type of interaction is not established but at the very least are presumed to increase the potential for vein irritation. There are some medications for example that should not be given (IV) like benzodiazepines, fentanyl, propofol and nalbuphine with any medication other than physiologic solutions. This is an important consideration during continuous propofol infusions because diazepam causes emulsion damage with free oil formation (Becker, 2011).

1.3.2 Pharmacodynamic Drug Interaction

Pharmacodynamic interactions can occur when the effects of one drug are changed by the presence of another drug that results in the same physiological outcome. These interactions are much less easy to classify than those of a pharmacokinetic type but in the pharmacodynamic interactions, itis not possible to explain a simple systematics as it is in pharmacokinetic interactions; instead, they require to be careful of the dose given to each drug that interferes with each other and which undesired effects, which can in turn, any potentiate or reduce in effect each other. (Jonathan G. Hardman, 2011)

Pharmacodynamic Interactions can be classified as:
Synergistic: (effect of two drugs is maximal than the sum of their individual effects)
Antagonistic (effect of two drugs is minimal than the sum of their individual effects)

Additive (effect of two drugs is just the sum of the effects of each)
Sequence-dependent (when the order in which two drugs are given governs their effects (Langford, 2007)

1.3.2.1 Additive or synergistic interactions

Additive or synergistic interactions occur when two drugs with similar pharmacological properties are given together. The synergistic effects can be of a pharmacological or physiological nature, pharmacological effects when two or more drug working directly on to the same target or system, for example, two CNS depressant. Physiological effects when two drugs working on the different physiological process but ultimately increase the risk of toxicity from one or both drug, for example, use Digoxin with Furosemide cardiac glycoside toxicity may be enhanced by the hypokalemic and hypomagnesemia effect of loop diuretics (Wang, 2010).

A common example is an ethanol combined with benzodiazepine anxiolytics or histamine H1-receptor antagonists used for travel sickness. Benzodiazepines alone have a high therapeutic index and while overdoses may cause prolonged sedation they are seldom fatal, but when a combination of benzodiazepine overdose with ethanol is often fatal (JPleuvry, 2005).

Coadministration of methotrexate with trimethoprim increases the risk of acute myelosuppression and megaloblastic anemia as a result of potential additive effects resulting from inhibition of dihydrofolate reductase by both drugs (Al-Quteimat, 2013). Also, use fluorouracil with folic acid lead to increase the toxicity of fluorouracil It is possible to cause diarrhea, and dehydration (Clippe, 2003).The serotonin syndrome can develop shortly after one serotonergic drug is added to another (Fluoxetine + Duloxetine) (Sternbach, 1991).

1.3.2.2 Antagonistic Interactions

The effect of two or more drugs is less than the sum of the effects produced by each drug separately. The pharmacological nature of the antagonistic interaction is a classic receptor antagonism for example (Naloxone and Morphine) naloxone is an antagonist that will reverse the actions of morphine (Gilman AG, 1999).

The physiological nature of the antagonistic interaction is opposing physiological

processes ,for example, patients who use (NSAIDs with ACEIs), the hypotensive effect of ACE inhibitors is decreased because of NSAID-induced inhibition of renal prostaglandin synthesis which can lead to Hypotension (Fournier, 2014).

Another example Coumarin interaction with dietary vitamin K as a competitive inhibition mechanism as a result coumarins prolong the blood clotting time (Violi, 2016).

Also, most Antidiabetics medication reduce their effect when taken concurrently with corticosteroids and can cause hyperglycemia, glucose intolerance (Hustak, 2011).

Table 1 : Examples of synergistic and antagonistic pharmacodynamic interaction (Cascorbi, 2012)

Drug A	**Drug B**	**Clinical Effects**
Synergistic Interaction		
NSAIDs	SSRIs, Preprohormone	Increase risk of bleeding
NSAIDs	Glucocorticoids	Increase risk of bleeding
ACEIs	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin Syndrome
Quinolones	Macrolides, citalopram	QT-Interval prolongation, torsade de points
Antagonistic Interactions		
Acetyl Salicylic Acid	Ibuprofen	Reduced effects
ACEIs	NSAIDs	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

1.3.3 Pharmacokinetic Interaction

Pharmacokinetics is defined as the time course of drug absorption, distribution, metabolism, and excretion.

Pharmacokinetic drug interactions can lead to dangerous adverse effect or decreased drug efficacy. Pharmacokinetic interactions are considered on the basis of knowledge of each drug and are identified by controlling the patient's clinical manifestations as well as the changes in serum drug concentrations (Palleria, 2013).

1.3.3.1 Drug Absorption Interactions

when the substances entered the body is uptake by the blood circulation; most drugs that are given orally are absorbed through the mucous membranes of the gastrointestinal tract.

The complexity of the gastrointestinal tract and the effects of different drugs with functional activity on the digestive system represent suitable conditions for the development of DDI that may modify or change the drug bioavailability (Mantia G, 2008).

Several factors can influence the mucosa absorption of a drug through the gastrointestinal mucosa. The most important factors (changes in gastrointestinal pH, chelation and other complexing mechanisms, Changes in gastrointestinal motility and Induction or inhibition of drug transporter proteins) (Palleria, 2013).

1.3.3.1.1 Effects of changes in gastrointestinal pH

Changes in PH balance have an influence on many aspects of the action of drugs. This is clearly appearing by the absorption of drugs from the stomach and intestine, in changes in the distribution of drugs between plasma and cells, and the effect of a change in urinary PH.

Drug absorption depends on being an ionized form or non-ionized form ,the non-ionized form of a drug is more lipid -soluble and this will improve absorption and make it more readily than the ionized form.

for example, H2 antagonists (ranitidine), antacids (aluminum hydroxide and sodium bicarbonate) and protein pump inhibitor (omeprazole, esomeprazole, pantoprazole) that increase the pH lead to a decrease in cefpodoxime bioavailability, but on the other hand, facilitate the absorption of beta-blockers and tolbutamide (Caglioti, 2013).

Antifungal agents (e.g., ketoconazole or itraconazole), need an acidic environment for being completely dissolved, So the combination between them and drugs able to increase gastric pH, may cause a decrease in both dissolution and absorption of antifungal drugs (Krishna G, 2009),So, antacid or PPI might be administered at least 2 hours after the administration of antifungal agents (Ogawa R, 2010).

1.3.3.1.2 Chelation or complexing mechanisms

Complexing is another factor that influences the drug absorption, in this case, drugs form non-soluble complexes between them and the metal ion, with this mechanism can affect the absorption of drugs given in therapeutic doses.

Tetracyclines (ex: doxycycline) combined with metal ions (ex: calcium, magnesium, aluminum, iron) in the digestive tract and form complexes poorly absorbed (Palleria, 2013),Therefore, any drug such as antacids who containing these metal ions can significantly reduce the tetracyclines absorption (Bokor-Bratić, 2000) ,separating the doses by 2 to 3 hours goes can reducing the effects of this type of interaction.

Cholestyramine, an anionic exchange resin prepared to bind bile acids and cholesterol metabolites in the gut, but also bind to a large number of drugs (digoxin, warfarin, acetylsalicylic acid , sulfonamides, levothyroxine) , thereby reducing their absorption (Scaldaferri F, 2011)

Antacids also interfere with this mechanism with fluoroquinolones and penicillin and form complexes that lead to a reduction of the effect of (fluoroquinolones and penicillin), In the agreement, was observed that antacids and fluoroquinolones should be administered at least 2 h apart or more (Seedher, 2010).

1.3.3.1.3 Changes in gastrointestinal motility

Most drugs are largely absorbed in the upper part of the small intestine, the absorption can influence when drugs change the rate at which the stomach empties. Drugs able to increase the gastric transit (ex: metoclopramide) can reduce the time of contact between the drug and mucosal area of absorption inducing a decrease of drug absorption (Lee, 2000).

For example, Antimuscarinic drugs can decrease the intestinal motility, thus the tricyclic antidepressants maybe alter the absorption of other drugs and increase them,

because they increase the time available for dissolution and absorption, but when it affects levodopa it can be reduced the absorption (Edwards, 1982).

Another example Metoclopramide can increase or decrease gastric emptying, it accelerates absorption of (alcohol, acetylsalicylic acid, acetaminophen, tetracycline and levodopa) and decreasing the absorption of digoxin and theophylline (Johnson, 1984).These examples explain that what actually happens is sometimes very unpredictable because the final outcome may be the result of several different mechanisms.

1.3.3.1.4 Inducing or inhibition of drug transporter proteins

Drug absorption can be highly dependent upon transport protein affinity. Transport proteins can be involved in the active absorptive influx of compounds, such as amino acids, monosaccharides, oligopeptides, bile acids, and several water-soluble vitamins, from the

lumen into the portal bloodstream (Ayrton, 2001). The oral bioavailability of some drugs is limited by the action of drug transporter proteins.

'P-glycoprotein is presently the most important drug transporter it's also known as multidrug resistance protein 1 (MDR1).

The pumping actions of P-glycoprotein may be induced or inhibited by some drugs, for example, The absorption of Digoxin in the intestines decreases when its interaction with rifampicin appears to be mainly due to induction of P-glycoprotein (Drescher, 2003). The serum digoxin levels increase with verapamil It has been indicated that P-glycoprotein may be involved (Verschraagen, 1999).Ketoconazole can inhibit the effect of P-glycoprotein, it is possible to lead to increasing the CSF levels of Ritonavir, probably by preventing the efflux of Ritonavir from the CNS (Crommentuyn, 2004).

It is necessary to note that this DDI could be also used in clinical management, documented that sildenafil inhibits the transporter function of P-glycoprotein, suggesting a possible strategy to enhance the distribution and increase the activity of some anticancer drugs. (Shi, 2011).

1.3.3.2 Drug Metabolism Interactions

One of the most important types of pharmacokinetic drug interactions is when two drugs are metabolized by the same enzyme and affect the metabolism of each other.

The CYP enzyme family plays a dominant role in the biotransformation of a wide number of drugs. In man, there are about 30 CYP isoforms, which are responsible for drug metabolism and these belong to families 1-4, but only 6 out of 30 isoforms belonging to families CYP1, 2 and 3 (i.e., CYP1A2, 3A4, 2C9, 2C19, 2D6 and 2E1) are mainly involved in the hepatic drug metabolism (Nelson, 1996).Although CYP genes are distributed widely throughout most tissues, the liver contains the greatest concentration of those CYP that oxidize drugs efficiently.

Drugs are metabolized by two major types of reaction. The first, called phase I reactions (involving oxidation, reduction or hydrolysis), which make drugs more polar compounds, while phase II reactions involve conjugation drugs with some other substance (e.g. glucuronic acid, known as glucuronidation) to make compounds that are usually inactive.

The wide range of drugs that undergo CYP mediated oxidative biotransformation is responsible for a large number of clinically significant drug interactions during multiple drug therapy. Many DDIs are related to the inhibition or induction of CYP enzymes.

1.3.3.2.1 Inhibition CYP Enzymes

CYP Enzyme is able to accommodate a large number of drug substrates which makes it more susceptible to inhibition by many agents, this results in the reduced metabolism of an affected drug, so that it may begin to accumulate within the body. The process of inhibition is usually short duration can occur within 2 to 3 days and includes minor disturbances that are not serious. As example Protease inhibitors (Saquinavir and Ritonavir) inhibit the activity of theCYP3A4, this affects the concentration of (Sildenafil, Tadalafil and Vardenafil) who metabolizes by CYP3A4 and leads to increase in their serum levels (Loulergue, 2011).

Also Carbamazepine and Valproate interaction in each other with this mechanism, carbamazepine increases the metabolism of valproate and it can form a hepatotoxic metabolite of valproic acid (2-propyl-4-pentenoic acid or 4-ene-VPA) (Huang, 2017).

Table 2: Example of Significant Cytochrome P450 Enzymes and Their Inhibitors, Inducers, and Substrates (TOM LYNCH, 2007)

Significant Cytochrome P450 Enzymes and Their Inhibitors, Inducers, and Substrates			
Enzyme	inhibitors	inducers	Substrates
CYP2C19	Fluvoxamine, isoniazid (INH), ritonavir	Carbamazepine, phenytoin, rifampin	Omeprazole, phenobarbital, phenytoin
CYP2C9	Amiodarone, fluconazole fluoxetine, metronidazole , ritonavir, trimethoprim/sulfamethoxazole	Carbamazepine, phenobarbital, phenytoin, rifampin	Carvedilol, celecoxib, irbesartan, losartan, glipizide, ibuprofen
CYP1A2	Amiodarone, cimetidine, ciprofloxacin, fluvoxamine	Carbamazepine, phenobarbital, rifampin, tobacco	Caffeine, clozapine, theophylline
CYP2D6	Amiodarone, cimetidine, diphenhydramine, fluoxetine, paroxetine	No significant inducers	Amitriptyline, carvedilol, codeine, donepezil, metoprolol, paroxetine, risperidone
CYP3A4 and CYP3A5	Clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone	Carbamazepine, Hypericumperforatum (St. John's wort), phenobarbital, phenytoin, rifampin	Alprazolam, amlodipine, atorvastatin, cyclosporine, diazepam, simvastatin, sildenafil, verapamil

1.3.3.3 Drug Distribution Interactions

Competition for binding sites on plasma proteins may lead to important drug interactions, this competition effects the distribution of the drug and leads to effect in the efficacy. There are many plasma proteins interacting with drugs, the most important are albumin, α1-acid glycoprotein, and lipoproteins (Hardman, 2011). Albumin represents the most prominent protein in plasma, it is synthesized in the liver and distributed in both plasma and extracellular fluids of skin, muscles and various tissues. Intestinal fluid albumin concentration is 60% of that in the plasma.

Basic drugs are usually bound to the α1-acid glycoprotein, lipoproteins, or both while acidic drugs are usually bound more extensively to albumin.

The unbound drug is effective when two drugs that are both highly bound to plasma proteins (> 90%) are combined in this case, one drug can displace the other from the protein binding sites and leading to increased efficacy and/or toxicity of the unbound drug. For example: increase the concentration of warfarin when interacting with erythromycin or amiodarone, because both are highly-bound drugs, and can be displaced warfarin from binding. (Kragh-Hansen U, 2002).

1.3.3.4 Drug Excretion Interactions

kidneys, liver, lungs, feces, sweat, saliva, milk these are organs responsible for the excretion (elimination) drugs and/or their metabolites. The excretion through saliva, sweat, and lungs (for volatile drugs e.g., inhaled general anesthetics), milk is important when the drugs can reach the baby during lactation. (Kapusta, 2007).

Drugs are excreted mainly through: renal tubular excretion (glomerular filtration, tubular reabsorption and active tubular secretion), biliary excretion. (Norte, 2011).The kidney is the main organ responsible for the elimination of drugs and their metabolites. Drug-drug interaction in excretion rates will affect the plasma concentration of drugs, the interaction may occur for a mechanism of competition at the level of active tubular secretion, where two or more drugs use the same transport system leading to increased concentration of one or more drugs in the plasma.

In some cases, this competition and interaction are of therapeutic benefits, such as when combined between Probenecid and penicillin or cephalosporin, probenecid contributes to delay renal excretion for penicillin or cephalosporin, thus increasing their serum concentration and saving in terms of dosage (Wu H, 2010).

Generally, only hydrophilic molecules are excreted effectively, lipophilic drugs must be bio transformed to hydrophilic drug metabolites to be excreted. Also, drugs that are highly protein bound are not filtered and small molecule drugs that are not protein bound are cleared rapidly.

The degree of ionization of the drug greatly influences the rate of excretion of acidic and basic drugs by ion trapping and reduced passive resorption, for example, if a weakly acidic drug (phenobarbital, salicylates) is excreted into an alkaline urine, the drug is highly ionized and therefore not lipid soluble.

Acidification of urine can be used to decrease reabsorption of weak bases by increasing the proportion of drug in the ionized form. Conversely, alkalization of urine can be used to increase the renal excretion of acidic drugs because a greater proportion of the drug is in the ionized form. (Jill E Maddison, 2008).

1.4 The role of pharmacist in managing drug Interactions

Drug interactions are the extremely important cause of adverse drug reactions (ADR) and This topic has received a great deal of care from the healthcare communities worldwide (Farkas D, 2008). There is an increase in the number of drugs are introduced every year and new interactions between drugs are increasingly reported. The most prescribed medicines for use in the in primary care practice are nonsteroidal anti-inflammatory drugs, antibiotics and, in particular, rifampin. Also, Drugs with a narrow therapeutic range or low therapeutic index are more likely to be the objects for serious drug interactions (Ament PW, 2000).

Pharmacists are key players for finding and preventing drug interactions in health care system in developed countries, it is his duty to ensure that the patient is aware of the drug interactions and possible side effects and how to deal with these harmful effects.

In a recent study it was at Norway in 2014, aimed to investigate the role of pharmacist in managing drug interactions in a public perspective and how much publicity is satisfied with this role and how the pharmacist can improve his presence and role as medicine expert in health care system. Study conducted on 150 patients and showed that 85.35 % patients are satisfied from the role of pharmacists in finding and informing patients about the drug interactions while rest of 14.65 % are not satisfied from the role of the pharmacist and they need the more professional engagement of the community pharmacist (Aziz, 2014).

1.4.1 Management options of drug interaction

Adjusting the dose of drugs: we can significantly reduce the interaction between drugs if we can adjust the dose without affecting the therapeutic benefit, example: Quinidine 100% increase serum concentration of Digoxin in at least 9 of 10 patients, and to prevent toxic effects of cardiac glycoside you should be aware of the need to reduce the dose of Digoxin by 25% to 50%. (Igel, 2007).

Avoiding the combination: in some drugs, the risk always outweighs the risk, and the combination should be avoided, for example, the combination between Nitroglycerin and Sildenafil lead to potentiate the hypotensive effects of nitrates and no safe interval between use of any PDE5 (phosphodiesterase 5) inhibitor and nitrate has been identified. (O'gara, 2013).

Spacing dosing times: some drug interaction involving binding in the GI tract, to minimize the can give the first drug at least 2 h before or 4 h after the second drug. In this way, the first drug can be absorbed into the circulation before the other drug appears. (Ansari, 2010).

Monitoring for early detection: In some cases, it is necessary to monitor the laboratory test and the clinical condition of the patient to avoid the effect of any drug-drug interaction on the patient, example: when a combination between two diabetes drugs, the patient should be advised to monitoring for the development of hypoglycemia.

1.5 Cancer overview

Globally, cancer is the second leading cause of death (WHO, 2018), about 90.5 million people had cancer and was responsible for 8.8 million deaths in 2015 (Theo Vos, 2016). According to annual statistics reporting from the American Cancer Society, cancer mortality rate decreases steadily over the past 2 decades in the US. As of 2015, the cancer death rate for men and women combined had fallen 26% from its peak in 1991, which means that about 2.4 million deaths have been avoided during this time period (Simon, 2018).

All cancers start in cells. The body made up of more than trillions of cells. Cancer starts with changes in one cell or a small group of cells then cells of an organ or tissue in the body become abnormal (Cancer Research UK, 2017). Cancer is the rapid being of abnormal cells that grow beyond their usual boundaries, and which can then invade local healthy tissues and spread to other organs, the latter process is referred to as metastasizing. Metastases are a major cause of death from cancer (WHO, 2018).

The most common types of cancer in males are lung cancer, prostate cancer, and stomach cancer. In females, the most common types are breast cancer, lung cancer, cervical cancer and colorectal cancer. In children, acute lymphoblastic leukemia and brain tumors are most common (WHO, World Cancer Report, 2014).

The most common symptoms in cancer patients are Lump, unexplained weight loss, abnormal bleeding, prolonged cough, change in bowel movements.

Early detection of cancer can improve the odds of successful treatment and survival. Imaging techniques such as X-rays, CT scans, MRI scans, PET scans, and ultrasound scans are used regularly in order to discover where a tumor is located.

Cancer treatment depends on the type of cancer, the stage of cancer (extent or degree of metastases), and patients' specific factor (Age, health status and additional personal characteristics)

Some factors contribute to the development of cancer such as ultraviolet, infections from certain viruses, bacteria, parasites, and components of tobacco smoke. Cells exposed to these factors may become abnormal due to DNA damage.

Often normal cells with damaged DNA are dying. However, these abnormal cells with DNA damaged to continue to grow and replicated themselves and these abnormal cells can invade tissues and organ.

cancer treating considers challenging for health care provider because cancer patient receives a high number of drugs concomitantly, including cytotoxic agents, hormonal agents, targeted agents, and supportive care agents among the medication prescribed to treat comorbidities. Drug–drug interactions are one of the most important DRPs that occur in cancer patients and most drug–drug interactions can cause considerable adverse drug reaction (Van Leeuwen D. H., 2013).

A clinical pharmacist has an important role in minimizing the risk of drug drug interactions through knowledge of type and severity of DDIs and possible side effects of any medication taken by the patient.

1.6 Anticancer Drugs

Pharmaceutical therapy is one of the methods used to treat cancer as well as surgery and radiation therapy. Usually, a combination of treatment is used. Also, important factors that determine the successful response to treatment such as the tumor type and extent of disease.

Use of anticancer drugs produces a high average of cure of disease. On the other hand, without chemotherapy, resulting in high mortality rates (ex, testicular cancer, acute lymphocytic leukemia in children, and Hodgkin's lymphoma). Also, the anticancer drugs are more toxic than any other pharmaceutic agents, and therefore their benefits and risks must be evaluated to improve their therapeutic benefits and minimize unwanted side effects and risks. The essential goal in cancer chemotherapy is to develop the medication that selectively targets specific cancer cells through the use of advances in cell biology. A few such agents are in clinical use, and many more are in development. (Anthony J. Trevor, 2013).

Anticancer drug, also called antineoplastic drug, any drug that is effective in the treatment of malignant, or cancerous disease. Anticancer medication can be broadly chracterized as Cytotoxic chemotherapy (antimetabolites, antimicrotubles, alkylating agents , antibiotics) , Biologic targeted (monoclonal antibodies , tyrosine kinase

inhibitor) and Hormonal therapy(antiestrogens , aromatase inhibitor). (Kourtney Laplant, 2015).

İn the upcoming sections, we will highlight the most important anticancer drugs and their mechanisms of action , pharmacokinetics, therapeutic benefits and the side effects.

1.6.1 Antimetabolites

Antimetabolites are the most widely used and most effective group of anticancer medication. Also, antimetabolites are the oldest rationally designed anticancer drugs. They are folic acid, pyrimidine or purine analogs. They interfere with nucleic acid (DNA and RNA) synthesis. (Peters, 2014)

Antimetabolites affect cancer cell replication through its ability to induce cell death during the S phase of cell growth when incorporated into RNA and DNA or inhibit enzymes needed for nucleic acid production and therefore cell division and tumor growth (van der Wilt CL, 2000).

These agents are applied for a variety of cancer treatment, including leukemia, breast, pancreatic, ovarian, and gastrointestinal cancers. Examples of cancer drug antimetabolites include, but are not limited to the following: Methotrexate, 5-Fluorouracil, 6-Mercaptopurine, Capecitabine, Cytarabine, Floxuridine.

A. Methotrexate

Folic acid is a necessary compound for the metabolic reaction and play an essential role in a production of nucleotides**,** Methotrexate (MTX) are antifolate agents.

1.mechanism of action*:* methotrexate competitively inhibits dihydrofolate reductase (DHFR), the enzyme that converts folic acid to dihydrofolate (DHF) and tetrahydrofolate (THF). The inhibition by MTX results in decreased protein and DNA methylation in addition to impaired DNA formation and repair (Nicole Hagner, 2010).

2.Therapeutic uses: methotrexate is used to treat certain types of cancer, is effective against acute lymphoblastic leukemia, breast cancer, head and neck cancer, lung cancer and high dose methotrexate is given in combination with doxorubicin and a platinum agent in most osteosarcoma protocols (Holmboe, 2012).Methotrexate remains one of the most widely used in psoriasis and first-line therapy for the treatment of rheumatoid arthritis (Lopez-Olivo MA, 2014).

3. Pharmacokinetics: In the GI tract, MTX is absorbed through active transport mediated by the reduced folate carrier. Also, the bioavailability of MTX after oral dosing may be affected by ABC transporters which can move MTX out of the enterocytes and back into the intestinal tract or into the blood (Qiu A, 2006).Methotrexate distributes to synovial fluid, and to different tissues such as kidney, liver, joint tissues and low concentration distributed to the skin. Clearance of MTX primarily through renal glomerular filtration. The drug mainly excreted by the kidney regardless of the route of administration and only a small portion of the MTX is excreted into the bile duct via ABCC2 and ABCB1 transporters (Vlaming ML, 2009).

4.adverse effects: common side effects including: anorexia, nausea, vomiting, abdominal pain, diarrhea, itching, anemia, headache, fatigue and drowsiness.

B. 5-Fluorouracil

Fluorouracil is also known as FU or 5-FU, a pyrimidine analog. It’s one of the most commonly used drugs to treat cancer and according to the World Health Organization's List of Essential Medicines (WHO, 2016) 5-FU is one of the most effective and safe drugs needed in a health system.

1. mechanism of action*:* 5FU interfering with DNA synthesis and mRNA translation by inhibition Thymidylate synthase (TS), which is an enzyme that catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Thymidine is a nucleoside required for DNA replication. 5FU increased levels of dUMP which lead to decrease DNA synthesis and imbalanced cell growth (Álvarez P, 2012).

2.Therapeutic uses: systemically is given to treat breast, colorectal, stomach and pancreatic cancer. Is also available in a topical form for actinic keratosis and basal cell carcinoma.

3. Pharmacokinetics: 5-FU is commonly given IV because more than 80% of it is metabolized in the liver and its severe toxicity to the GI tract, it can give topically for skin cancer patients. There are several routes for metabolism of 5-FU, some of which lead to activation of the drug. Dihydropyrimidine dehydrogenase (DPD)is an enzyme that contributes to pyrimidine degradation and it is also involved in the degradation of the 5-FU. Deficiency in enzymes DPD leads to increase concentration of 5-FU which can lead to severe and even fatal 5-FU toxicity (van Kuilenburg AB, 2003). limited oral bioavailability because gut mucosa has high concentrations of dihydropyridine dehydrogenase .80% of the drug is eliminated by hepatic metabolism and 20% by renal excretion.

4. adverse effects: fluorouracil may cause some unwanted effects such as diarrhea, heartburn and sores in the mouth and on lips.

1.6.2 Antimicrotubules

Microtubules are important cellular targets for anticancer therapy because of their role in mitosis. Antimicrotubule agents such as taxanes, vinca alkaloids these drugs have mechanisms of cytotoxic action and unique spectra of antitumor activity. the primary effect is to disrupt the organization and dynamics of the mitotic spindle, preventing the M phase transit and cell division and eventually leading to apoptotic cell death (Risinger AL, 2009).The therapeutic effects of antimicrotubule drugs for cancer therapy has been impaired by different adverse effects such as notably neurological and hematological toxicities (Zhou J, 2005).

A. Paclitaxel and Docetaxel

Paclitaxel and its semisynthetic analog docetaxel were among the most important new additions to the chemotherapeutic drugs. Paclitaxel and docetaxel share many structural features, but there is a differ in pharmacology and pharmacokinetics, in some patients, solid tumors have been shown to be sensitive to docetaxel but resistance to paclitaxel.

Paclitaxel shown good activity against ovarian cancer and breast cancer, Docetaxel is commonly used in the prostate, GI cancer and non-small lung cancers (Jordan, 2004).

1. Mechanism of action: Texan drugs are active in the G/M phases of the cell cycle, they inhibit microtubule assembly and stabilizes the microtubule polymer and protects it from disassembly. Paclitaxel and Docetaxel block the progression of mitosis and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division (Brito, 2008).

2. Pharmacokinetics: both drugs given as an injection or infusion into the vein (intravenous, IV). Primarily metabolized in the liver and their primary route of elimination of the parent drug and hydroxylated metabolite is through biliary excretion via feces. Both are metabolized by CYP3A4, also paclitaxel metabolized by CYP2C8 and docetaxel metabolized by CYP3A5 (Cresteil, 2003).
The dose should be reduced in patients with hepatic dysfunction.

3.Adverse effects: include the common side effects of other cytotoxic drugs, but it can also cause nail destruction, bradycardia (first 3 h of infusion), and mild elevation of liver enzymes.

B. Vincristine and Vinblastine

Vinblastine and Vincristine are alkaloids derived from the periwinkle plant, vinca rosea

1. Mechanism of action: vinca alkaloids have cell cycle-specific activity in the M phase, they work slightly by binding to the tubulin protein, stopping the cell from separating its chromosomes during the metaphase leading cell to death.

2.Therapeutic uses: both are similar structurally, but they differ in the type of tumors, so they are administrating in combination with other drugs. Vinblastine is indicated in the treatment of patients with Hodgkin's and non-Hodgkin's lymphomas, it is also combination with bleomycin and cisplatin to treat testicular carcinoma. Vincristine is more widely used for the treatment of patients with myeloma, acute lymphocytic leukemia (Thirumaran, 2007).

3. Pharmacokinetics: vinca alkaloids are lower than for other chemotherapy drugs in clinical pharmacokinetics. These drugs have a large total distribution volume, rapid total plasma clearance and a long terminal half-life (Rahmani, 1995).They are concentrated and metabolized in the liver by cytochrome P-450 3A and eliminated in bill and faces.

4.Adverse effects: In addition to the typical side effects of cytotoxic chemotherapeutics, vincristine causes peripheral neuropathy, hyponatremia, constipation, hair loss and vinblastine may cause loss of white blood cells and blood platelets, gastrointestinal problems, high blood pressure.

1.6.3 Alkylating agents

Alkylating agents are the oldest class of anticancer agents, alkylation of DNA is maybe the crucial cytotoxic reaction that lethal to the tumor cells, the alkyl group is attached to the guanine base of DNA.

These alkylating agents were nitrogen mustards, sulfur mustard and alkyl sulfonates. We also have drugs do not have an alkyl group but act like the alkylating agent and it causes damage DNA, so they are sometimes described as "alkylating-like" (Pourquier, 2011). They are used in combination with other drugs to treat a variety lymphatic and solid cancer.

A. Cyclophosphamide

Cyclophosphamide is a prodrug that requires hepatic transformation by cytochrome P450- to form active form 4 hydroxy cyclophosphamide, which then breaks down to form the ultimate alkylating agent. Cyclophosphamide is a synthetic alkylating agent and a descendant of the more toxic nitrogen mustard.

1. Mechanism of action: Cyclophosphamide is converted to the active metabolites phosphoramide mustard and aldophosphamide in the liver, which binds to DNA, in this way inhibiting DNA replication and initiating cell death.

2.Therapeutic uses: Cyclophosphamide is used for patients with Hodgkin's and non-Hodgkin's lymphoma, chronic lymphocytic leukemia, lung cancer and breast cancer. It may also be used to treat other cancers.

3. Pharmacokinetics: Cyclophosphamide is usually given through a vein by injection or infusion (intravenous, IV) or by mouth in tablet form. It's metabolized in the liver by the hepatic cytochrome P450 (CYP) isozymes CYP2B6, 2C9 and 3A4 to active and inactive metabolites, the main active metabolite is 4-hydroxycyclophosphamide, its highly protein bound and distributed to all tissues. Cyclophosphamide metabolites are primarily excreted in the urine, drug dosing should be adjusted in patients with renal dysfunction (Haubitz M, 2002).

4.Adverse effects: hemorrhagic cystitis may occur in up to 40% of patients (especially children) on long term or high dose cyclophosphamide therapy (McEvoy, 2006), also common side effect included severe nausea or vomiting, loss of appetite, stomach pain or upset, temporary hair loss and changes in skin color or changes in nails.

B. Alkylating-like (Cisplatin, Carboplatin and Oxaliplatin)

Cisplatin, Carboplatin, and Oxaliplatin are coordination complexes of platinum. Approximately half of all patients who receive chemotherapy drugs are treated with a platinum drug (Johnstone, 2014). Cisplatin was the first drug discovered, but because of its toxicity to both the CNS and PNS, Carboplatin and Oxaliplatin were developed.

1. Mechanism of action: Platinum analogs antineoplastic agents are a similar alkylating agent and due to similar effects but they do not have an alkyl group. These drugs have the ability to crosslink with the purine bases on the DNA, these interfering with DNA causes destroys cancerous cells, and preventing cell division and growth (Dasari, 2014).

2.Therapeutic uses: Cisplatin, Carboplatin, and Oxaliplatin are used for the treatment of specific cancers, Cisplatin treat testicular carcinoma in combination with bleomycin and treat ovarian cancer with cyclophosphamide. Oxaliplatin used in the setting of colorectal cancer. Also, they are used to treat lung, bladder, and head and neck cancers.

3. Pharmacokinetics: These drugs are administered via IV infusion. Also, Cisplatin and Carboplatin can administer via IP and IA. They diffuse rapidly into tissues and rapidly distributed into pleural effusions, the highest concentrations found in the liver, prostate, and kidney. Excreted through urine.

4.Adverse effects: The dose-limiting side effect of cisplatin is nephrotoxicity, for carboplatin it is myelosuppression, and for oxaliplatin it is neurotoxicity. Other common side effects include thrombocytopenia, and anemia, hepatotoxicity, ototoxicity, nausea and vomiting, diarrhea, pain, anorexia (Oun, 2018).

1.6.4 Antibiotics

Antibiotic drugs kill malignant cells by fragmenting the DNA in the cell nucleus and by oxidizing critical compounds the cells need. Antitumor antibiotics have abilities to inhibit topoisomerases and produce free radical that plays a main role in their cytotoxic effects. They are not cell-cycle specific. Antibiotics are used against leukemia, testicular cancer, and sarcomas.
There are many antitumor antibiotics, including anthracyclines, bleomycin.

A. Anthracyclines: Doxorubicin, daunorubicin, idarubicin and mitoxantrone

Anthracyclines are a class of drugs used in cancer chemotherapy extracted from Streptomyces bacterium. The anthracyclines are among the most effective anticancer treatments ever developed and are effective versus more types of cancer than any other class of chemotherapeutic agents.

1. Mechanism of action: Anthracyclines have many mechanisms of action. For example, preventing the replication of rapidly growing cancer cells through inhibition of DNA and RNA synthesis and they cause damage DNA and cell membrane by the generation of free oxygen radicals. Also, one of the mechanisms is inhibition of topoisomerase II enzyme which leads to blocking DNA transcription and replication (Pommier, 2010).

2.Therapeutic uses: Doxorubicin and its derivative are used in breast and lung cancers and soft tissue sarcomas, Daunorubicin is used to treat acute lymphoblastic or myeloblastic leukemias, and its derivative, Idarubicin is used in multiple myeloma, non-Hodgkin's lymphomas, and breast cancer.

3. Pharmacokinetics: all these drugs not stable in gastric acids and not absorbed from GI tract so we must be administrated IV. They widely distributed in plasma and in tissues and metabolize in the liver and other tissues. Predominantly excretion in biliary route.

4.Adverse effects: the most dangerous side effect of Anthracyclines is cardiotoxicity (early or late effects), other common and potential side effect include nausea, vomiting, alopecia, and coloration of urine.

1.6.5 Hormonal therapy

Hormone therapy is one of the main ways to treat various types of cancers. Hormonal therapy involves altering or modifying the endocrine system through the exogenous or external administration of specific hormones such as steroid hormones (Prednisone), or medications act as hormone receptor antagonists (Tamoxifen, Bicalutamide), or medications are considered as inhibitors of hormone synthesis (Anastrozole, Leuprorelin). Endocrine therapy can cause some cancers to stop growing, or even undergo cell death.
Hormone therapy may involve surgically removing endocrine organs that are making the hormones such as orchiectomy and oophorectomy.

A. Tamoxifen

Tamoxifen itself is a prodrug, it's an estrogen antagonist and it's classified as a selective estrogen receptor modulators (SERMs).

1. Mechanism of action: Tamoxifen is a competitive inhibitor of estrogen binding to estrogen receptors (ERs), inducing a conformational change in the receptor. The prolonged binding of tamoxifen leading to reduced DNA polymerase activity, blockade of estradiol uptake, and decreased estrogen response.

2.Therapeutic uses: Tamoxifen has been prescribed to millions of females for breast cancer prevention or treatment breast cancer in women and men, it is used to decrease the chance of invasive breast cancer in patients who have had surgery and radiation therapy for ductal carcinoma in situ (DCIS).

3. Pharmacokinetics: Tamoxifen is extensively metabolized after oral administration, metabolized by hepatic cytochrome P450 (CYP) 3A4. Fecal excretion is the primary route of elimination,65% of the tamoxifen excreted by fecal and 13% by urine (Aubert, 2009).

4.Adverse effects: increased tumor or bone pain, hot flashes, vaginal bleeding, nausea, fatigue, depression.

2.Methodology

A retrospective observational study was conducted in hospitalized patients at Near East University Hospital (NEUH) in North Cyprus from 01 April 2017 to 01 April 2018. The data was collected for male and female with Cancer diagnosis admitted to the oncology department of the hospital. We analyzed and evaluated patient's data based on the latest update of patient files in the oncology department archives.

Drug-drugs interactions were screened using Lexi-Interact tool of Lexicomp and Drugs.com databases. The focus was only at drug-drug interactions regardless of the interaction between drug and complementary, herbal or food.

2.1 Inclusion criteria

1.Patients hospitalized at Near East University Hospital during 01 April 2017 to 01 April 2018.

2.Cancer patients who have medical file in the oncology department archives.

3.Patients using at least one chemotherapy drug and one other medication.

4.Patients who are adult (age≥24) and older.

2.2 Exclusion criteria

1. Patients who using only other drugs without any cancer medication.
2. Patients who died during the study.
3. Patients who didn't have complete medical files.
4. Patients who take only one medication.

2.3 Drug-drug interaction identification and categorization

The data collected was analyzed using Lexi-interact tool of Lexicomp (copyright 2018, Wolters Kluwer Clinical Drug Information, Inc) and Drugs.com database. Mechanisms of DDI in both (Lexicomp and Drugs.com) were categorized to Pharmacodynamic, Pharmacokinetic and Unknown. Based on Lexicomp classification interaction level into 5 categories (A, B, C, D and X), interaction level of X, D and C were Very important clinically and need to modify the medications and dosages or avoid combination [Table 3].

In Drugs.com database DDIs are classified according to the severity of interaction into major, moderate, minor [Table 4]

Table 3: Interaction levels categories by Lexicomp (Wolters Kluwer Clinical Drug Information, Inc)

Interaction Levels	Action	Description
X	Avoid combination	The risks associated with concomitant use of these agent usually outweigh the benefits
D	Consider therapy modification	patient-specifics assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risk
C	Monitor therapy	Data demonstrate that the specific agent may interact with each other in a clinically significant manner. the benefits of concomitant use of these two medications usually outweigh the risk
B	No action needed	Data demonstrate that the specific agent may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interaction between the specified agents

Table 4: Drug Interaction Classification according severity in Drugs.com database

Severity	Action	Description
Major	Avoid combination	Highly clinically significant, the risk of the interaction outweighs the benefit
Moderate	Usually avoid combinations	Moderately clinically significant, use it only under special circumstances.
Minor	No action need	Minimally clinically significant, assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

2.4 Statistical analysis

The collected and analyzed data were conducted using Microsoft Excel 2016 and statistical package for the Social Sciences (SPSS), software version 18.0 we used descriptive statistic to analyzed continuous data and used crosstab and correlation test for categorical data. The continuous data have presented by mean ± Std Deviation, median and ranges. Mann Whitney test was used to test for significant difference between the DDIs and age, gender and number of medications. While absolute information will be presented as frequency and percentage

2.5 Ethical Consideration

Privacy of the patient was assured during the study. The study was approved by the Near East Institutional Review Board (IRB) of Near East University Hospital that assigned this research as being just an observational study. Private patient data were not recorded. Only the age of patient, type of cancer, and gender were used during the study.

The medical record and patient's profile approved to be obtained from the NEU oncology department archives.

3. Results

3.1 Characteristic of the patients

There were 97 patients in oncology department in NEUH during 01 April 2017 to 01 April 2018,
97 oncology patients were hospitalized during the period of study, 87 patients were included in for analysis. 33 (37.9%) were male and 54 (62.1%) were female patients. 10 patients who were taking only one medication were excluded.

Related to patient's distribution according to age groups, according Development Through Life: A Psychosocial Approach we divide the age of patients into four sections: early Adulthood between 24 to 34 Years (2 patients 2.3%), Middle Adulthood between 34 to 60 Years (36 patients 41.4%). Later Adulthood between 60 to 75 Years (39 patients 44.8%). Elderhood ≥ 75 (10 patients 11.5%). The median age was 62 (mean age 59.70 ±12.7 years).

87 cancer patients used 410 drugs with mean 4.8(±2.7) medication per patient and rang 16 medication. 27 different chemotherapy drugs (mean 2.44 ±1.1 drugs per patients) and 83 nonchemotherapy drugs (mean 2.24 ±2.45 drugs per patients). Most of patients were taking 1 to 3 chemotherapy drugs 70(80.5%) and 25(28.7%) of patients didn't take any nonchemotherapy drugs. 46(52.8%) were taking 1 to 3 nonchemotherapy drugs. [Table 5]

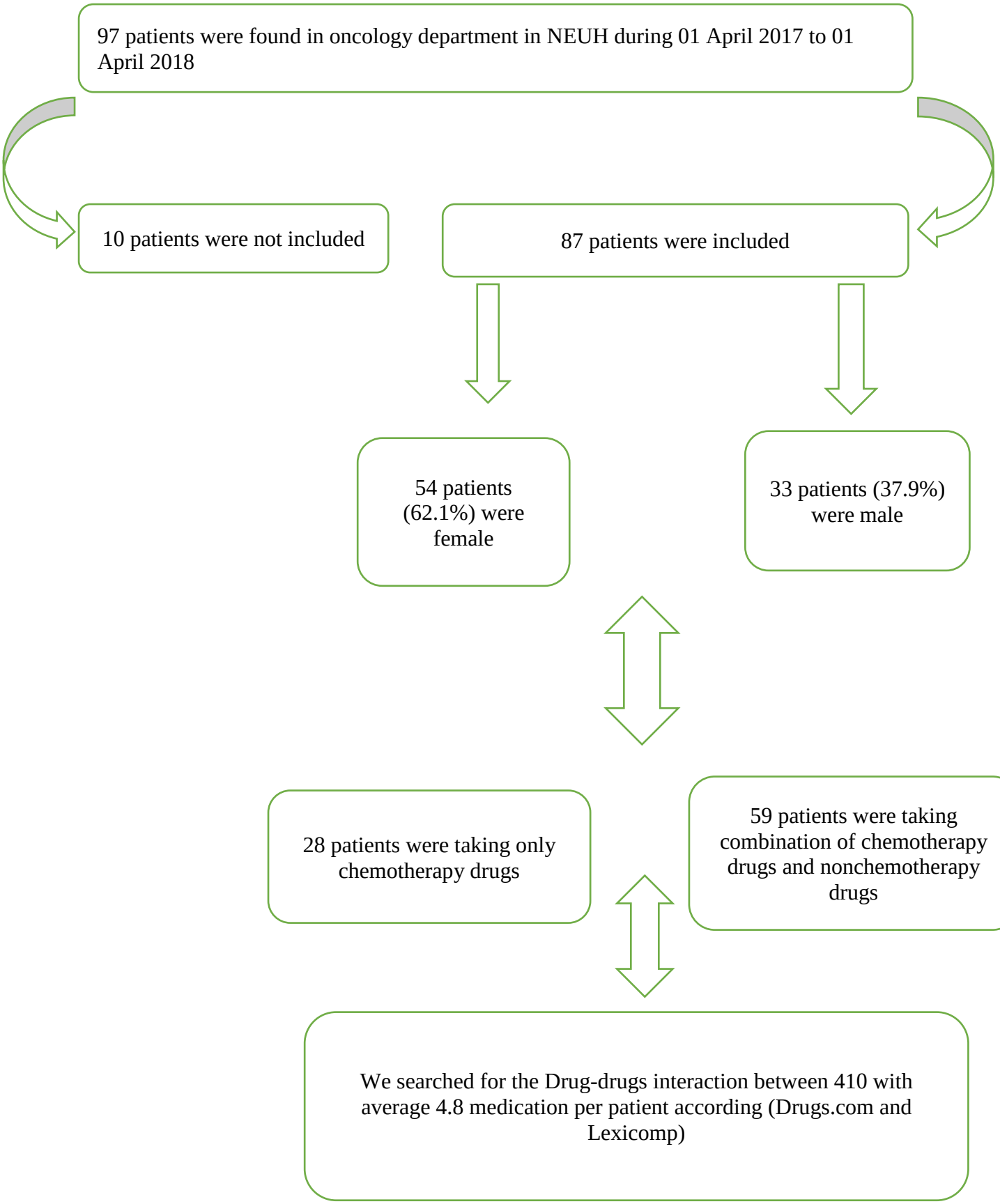

97 patients were found in oncology department in NEUH during 01 April 2017 to 01 April 2018
10 patients were not included
87 patients were included
54 patients (62.1%) were female
33 patients (37.9%) were male
28 patients were taking only chemotherapy drugs
59 patients were taking combination of chemotherapy drugs and nonchemotherapy drugs
We searched for the Drug-drugs interaction between 410 with average 4.8 medication per patient according (Drugs.com and Lexicomp)

Table 5: Characteristics of the patients and number of drugs per patient

Characteristic	*Frequency*	*Percent %*
Gender		
Male	33	37.90%
Female	54	62.10%
Age		
24 to 34 Years	2	2.30%
34 to 60 Years	36	41.40%
60 to 75 Years	39	44.80%
≥ 75	10	11.50%
No of chemotherapy drugs per patient		
1	18	20.70%
2	34	39.10%
3	18	20.70%
4	12	13.80%
5	5	5.70%
No of nonchemotherapy drugs per patient		
0	25	28.70%
1	12	13.80%
2	17	19.50%
3	17	19.50%
4 to 6	10	11.70%
>6	6	6.80%

3.2 Polypharmacy effects on drug-drug interactions

Out of 87 patients ,76 had drug-drug interaction. The largest number of DDIs were in patients who taking more than 5 drugs. 39(44.8%) of patients taking 5 medication or more and 38(97.4%) of them had DDIs.48(55.2%) of patients taking between 2 to 4 medication and 38(79%) of them had DDIs.

There is a significant association between number of medication and presence DDIs ($P<0.05$) [Figure 1]

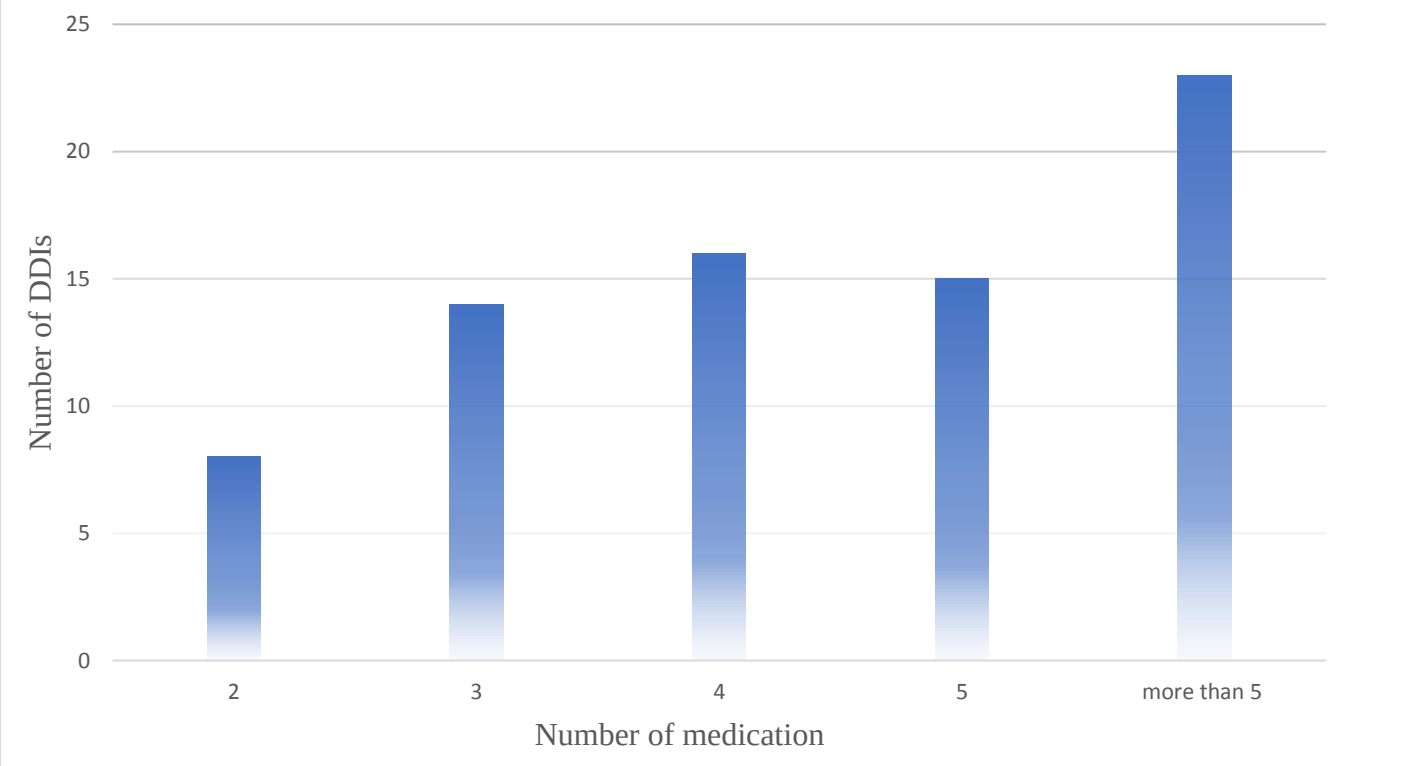


Figure 1: The frequency of DDIs with number of medications

3.3 Drug-drug interaction according to Drugs.com

Out of 87 patients,76 (87.4%) patients had DDIs [Table 6], there are 244 interactions with a mean (2.8) DDIs for each patient. Among the 87 patients with 244 DDIs, 28(36.8%) patients were male whereas 48(63.2%) were female. [Table 7].

Patients aged between 60 to 75 years old had the highest number of interactions (46.07%) followed by patients between 34 to 60 years (38.15%), followed by patients older than 75 years (13.15%) and patients aged between 24 to 34 years old had the lowest number of interaction (2.63%).
[Table 8]

Out of 244 DDIs, there are 61(25%) pharmacokinetic interaction, 113(46.31%) pharmacodynamic interaction and 70(28.69%) with unknown mechanism of interaction. According to severity, most DDIs were moderate 168 (68.85%), 32 (13.11%) were major and 44(18.03%) were minor
[Table 9]

Table 6: Frequency and percent of DDIs among the patients according Drugs.com

Presence of DDIs		
	Frequency	Percent
Have interaction	76	87.40%
No interaction	11	12.60%
Total	87	100%

Table 7: DDIs according to gender according Drugs.com

			DDIs		
			Have Interaction	No Interaction	Total
Gender	Male	Count	28	5	33
		% within DDIs	36.8%	45.5%	37.9%
	Female	Count	48	6	54
		% within DDIs	63.2%	54.5%	62.1%
Total		Count	76	11	87
		% within DDIs	100.0%	100.0%	100.0%

P>0.05, 95% confidence interval, 0.73 to 0.75, P -value = 0.58, according Drugs.com there is No statistically significant association between gender and presence DDIs in patients with cancer

Table 8: DDIs according to age according Drugs.com

			DDIs		
			Have Interaction	No Interaction	Total
Age	24 to 34 Years	Count	2	0	2
		% within DDIs	2.6%	0.0%	2.3%
	34 to 60 Years	Count	29	7	36
		% within DDIs	38.2%	63.6%	41.4%
	60 to 75 Years	Count	35	4	39
		% within DDIs	46.1%	36.4%	44.8%
	75 Until Death	Count	10	0	10
		% within DDIs	13.2%	0.0%	11.5%
Total		Count	76	11	87
		% within DDIs	100.0%	100.0%	100.0%

P>0.05, 95% confidence interval, 0.16 to 0.18, P -value = 0.32, according Drugs.com there is No statistically significant association between age and presence DDIs in patients with cancer

Table 9: Number of DDIs according Types of DDIs and severity and type of drug according Drugs.com

Number of DDIs according Drugs.com	Frequency *n*	Percent %
According to the mechanism of interaction		
Pharmacokinetic	61	25%
Pharmacodynamic	113	46.31%
Unknown	70	28.69%
According to the severity		
Major	32	13.11%
Moderate	168	68.85%
Minor	44	18.04%
According to type of Drug		
Between chemotherapy and nonchemotherapy drugs	41	16.81%
Between chemotherapy drugs	97	39.75%
Between nonchemotherapy drugs	106	43.44%

3.3.1 DDIs between chemotherapy and nonchemotherapy drugs according to types and severity of interaction (Drugs.com)

Out of 87 patients,59 of them were have therapeutic protocols contain chemotherapy drugs and nonchemotherapy drugs., 24 (40.68%) were have DDIs and 35 (59.32%) of these patients didn't have any DDIs. We found 41 DDIs most of them were moderate severity 35 (85.36%), major 2 (4.88%) and minor 4 (9.76%). [Table 10]

Table 10: Frequency and percent of DDIs between chemotherapy and nonchemotherapy drugs according Drugs.com

Number of interactions between chemotherapy and nonchemotherapy drugs according to severity of interaction (Drugs.com)							
NO. of Drugs	No of patients	No of patients have interaction	No of patients didn't have interaction	No. interaction	Major	Moderate	Minor
2	4	0	4 (100%)	0	0	0	0
3	7	1 (14.29%)	6 (85.71%)	1	0	1(100%)	0
4	15	5 (33.33%)	10 (66.67%)	7	0	6 (85.71%)	1 (14.29%)
5	10	3 (30%)	7 (70%)	6	0	6 (100%)	0
6	8	5 (62.50%)	3 (37.50%)	9	1 (11.11%)	7 (77.78%)	1 (11.11%)
7 to 10	11	7 (63.64%)	4 (36.36%)	10	0	9 (90%)	1 (10%)
more than 10	4	3 (75%)	1 (25%)	8	1 (12.5%)	6 (75%)	1 (12.5%)
Total	59	24 (40.68%)	35 (59.32%)	41	2 (4.88%)	35 (85.36%)	4 (9.76%)

3.3.2 DDIs between chemotherapy drugs according to types and severity of interaction (Drugs.com)

Out of 87 patients, 67 of them taking at least two chemotherapy drugs regardless of any other drugs, 61 (91.04%) were have DDIs and 6 (8.96%) of these patients didn't have any DDIs. we found 97 DDIs most of them were moderate severity 55 (56.70%), major 19 (19.59%) and minor 23 (23.71%). [Table 11]

Table 11: Frequency and percent of DDIs between chemotherapy drugs according Drugs.com

Number of interactions between chemotherapy drugs according to severity of interactions (Drugs.com)							
NO. Anticancer Drugs	No of patients	No of patients have interaction	No of patients didn't have interaction	No. interactions	Major	Moderate	Minor
2	34	29 (85.29%)	5 (14.71%)	29	1 (3.45%)	20 (68.97%)	8 (27.59%)
3	16	15 (93.75%)	1 (6.25%)	27	6 (22.22%)	17 (62.96%)	4 (14.81%)
4	12	12 (100%)	0	30	11 (36.67%)	16 (53.33%)	3 (10%)
5	5	5 (100%)	0	11	1 (9.09%)	2 (18.18%)	8 (72.73%)
Total	67	61 (91.04%)	6 (8.96%)	97	19 (19.59%)	55 (56.70%)	23 (23.71%)

3.3.3 DDIs between nonchemotherapeutic drugs according to types and severity of interaction (Drugs.com)

Out of 87 patients, 49 of them were taking at least two nonchemotherapy drugs without consideration chemotherapy drugs, 30 (61.22%) were have DDIs and 19 (38.78%) of these patients didn't have any DDIs. we found 106 DDIs most of them were moderate severity 78 (73.58%), major 11 (10.38%) and minor 17 (16.04%). [Table 12]

Table 12: Frequency and percent of DDIs between nonchemotherapy drugs according Drugs.com

Number of interactions between nonchemotherapy drugs according to severity of interactions (Drugs.com)							
NO. nonchemotherapy Drugs	No of patients	No of patients have interaction	No of patients didn't have interaction	No. interactions	Major	Moderate	Minor
2	17	4 (23.53%)	13 (76.47%)	4	1 (25%)	2 (50%)	1 (25%)
3	17	13 (76.47%)	4 (23.53%)	22	0	17 (77.27%)	5 (22.73)
4	6	4 (66.67%)	2 (33.33%)	7	3 (42.86%)	3 (42.86%)	1 (14.29%)
5	3	3 (100%)	0	13	0	11 (84.62%)	2 (15.38)
6	1	1 (100%)	0	5	0	5 (100%)	0
from 7 to 10	4	4 (100%)	0	33	2 (6.06%)	28 (84.85%)	3 (9.09%)
more than 10	1	1 (100%)	0	22	5 (22.73%)	12 (54.55%)	5 (22.73%)
Total	49	30 (61.22%)	19 (38.78%)	106	11 (10.38%)	78 (73.58%)	17 (16.04%)

3.4 Drug-drug interaction according to Lexi-interact by Lexicomp

Out of 87 patients,62 (71.30%) patients were have DDIs and 25(28.70%) patients with no DDIs [Table 13], there are 197 interactions with mean 2.2 DDIs for each patient had interaction. Among the 87 patients with 197 DDIs 20(32.3%) patients were male whereas 42(67.7%) were female. [Table 14].

Patients were between 60 to 75 years old of age showed the highest number of patients have interaction 28(45.2%), two patients (3.2%) have interaction between 24 to 34 years, 25(40.3%) have DDIs between 34 to 60 years and 7(11.3%) patients have DDIs were older than 75 years
.[Table 15].

Out of 197 DDIs, there are 46(23.4%) pharmacokinetic interaction, 103(52.3%) pharmacodynamic interaction and 48(24.3%) unknow interaction. According risk rating of interaction, most DDIs were C level 135(68.53%),33(16.76%) were D level ,28(14.21%) were B level and only one patient have X interaction level (0.50%). [Table 16]

Table 13: Frequency and percent of DDIs among the patients according Lexicomp

Presence of DDIs		
	Frequency *n*	Percent %
Have interaction	62	71.30%
No interaction	25	28.70%
Total	87	100%

Table 14: DDIs according to gender according Lexicomp

			DDIs		
			Have Interaction	No Interaction	Total
Gender	Male	Count	20	13	33
		% within DDIs	32.3%	52%	37.9%
	Female	Count	42	12	54
		% within DDIs	67.7%	48%	62.1%
Total		Count	62	25	87
		% within DDIs	100.0%	100.0%	100.0%

P>0.05, 95% confidence interval, 0.08 to 0.09, P -value = 0.08, according Lexicomp there is No statistically significant association between gender and presence DDIs in patients with cancer

Table 15: DDIs according to age according Lexicomp

			DDIs		
			Have Interaction	No Interaction	Total
Age	24 to 34 Years	Count	2	0	2
		% within DDIs	3.2%	0.0%	2.3%
	34 to 60 Years	Count	25	11	36
		% within DDIs	40.3%	44%%	41.4%
	60 to 75 Years	Count	28	11	39
		% within DDIs	45.2%	44%	44.8%
	75 Until Death	Count	7	3	10
		% within DDIs	11.3%	12%	11.5%
Total		Count	62	25	87
		% within DDIs	100.0%	100.0%	100.0%

P>0.05, 95% confidence interval, 0.86 to 0.87, P -value = 0.83, according Lexicomp there is No statistically significant association between age and presence DDIs in patients with cancer

Table 16: Types of DDIs and severity according Lexicomp

Types of DDIs according Lexicomp	Frequency *n*	Percent %
According to the mechanism of interaction		
Pharmacokinetic	46	23.4%
Pharmacodynamic	103	52.3%
Unknown	48	24.3%
Risk rating of interaction		
A	0	0%
B	28	14.21%
C	135	68.53%
D	33	16.76%
X	1	0.5%
According to the severity		
Major	75	38%
Moderate	95	48.2%
Minor	27	13.8%
According to type of Drug		
Between chemotherapy and nonchemotherapy drugs	30	15.2%
Between chemotherapy drugs	86	43.7%
Between nonchemotherapy drugs	81	41.1%

3.4.1 DDIs between chemotherapy and nonchemotherapy drugs according to types and risk rating of interaction (Lexicomp)

Out of 87 patients, 59 of them were have therapeutic protocols contain chemotherapy drugs and nonchemotherapy drugs., 13 (22%) were have DDIs and 46 (78%) of these patients didn't have any DDIs. we found 30 DDIs most of them according risk rating of interaction were C 24 (80%), B level 3 (10%) and D level 3 (10%). [Table 17]

Table 17: Frequency and percent of DDIs between chemotherapy and nonchemotherapy drugs according Lexicomp

Number of interactions between chemotherapy and nonchemotherapy drugs according to severity of interaction (Lexicomp)									
NO. of Drugs	No of patients	No of patients have interactions	No of patients don't have interactions	No. interaction	Interaction Levels				
					X	D	C	B	A
2	4	1	3	1	0	0	1	0	0
3	7	1	6	1	0	0	1	0	0
4	14	3	11	5	0	0	5	0	0
5	12	1	11	2	0	1	1	0	0
6	6	2	4	3	0	0	1	2	0
7 to 10	12	3	9	5	0	0	5	0	0
more than 10	4	2	2	13	0	2	10	1	0
Total	59	13(22%)	46(78%)	30	0	3(10%)	24(80%)	3(10%)	0

3.4.2 DDIs between chemotherapy drugs according to types and risk rating of interaction (Lexicomp)

Out of 87 patients, 67 of them taking at least two chemotherapy drugs regardless of any other drugs, 53(79.2%) were have DDIs and 14(20.8%) of these patients didn't have any DDIs. we found 86 DDIs most of them according risk rating of interaction were level C 48 (55.8%), B level 17 (19.78%) and D level 21 (24.4%) [Table 18]

Table 18: Frequency and percent of DDIs between chemotherapy drugs according Lexicomp

Number of interactions between chemotherapy drugs according to severity of interaction (Lexicomp)									
NO. Anticancer Drugs	No of patients	No of patients have interactions	No of patients didn't have interactions	No. interaction	Interaction Levels				
					X	D	C	B	A
2	33	22	11	22	0	6	12	4	0
3	17	14	3	29	0	7	15	7	0
4	13	13	0	29	0	8	16	5	0
5	4	4	0	6	0	0	5	1	0
Total	67	53(79.2%)	14(20.8%)	86	0	21(24.4%)	48(55.8%)	17(19.78%)	0

3.4.3 DDIs between nonchemotherapy drugs according to types and risk rating of interaction (Lexicomp)

Out of 87 patients, 49 of them were taking at least two nonchemotherapy drugs without consideration chemotherapy drugs, 21(42.9%) were have DDIs and 28(57.14%) of these patients didn't have any DDIs. we found 81 DDIs most of them according risk rating of interaction were level C 63(77.8%), B level 8(9.9%) and D level 9(11.1%) [Table 19]

Table19: Frequency and percent of DDIs between nonchemotherapy drugs according Lexicomp

Number of interactions between nonchemotherapy drugs according to severity of interaction (Lexicomp)									
NO. nonchemotherapy Drugs	No of patients	No of patients have interaction	No of patients don't have interaction	No. interaction	Interaction Levels				
					X	D	C	B	A
2	16	3	13	3	0	1	2	0	0
3	15	3	12	5	0	0	5	0	0
4	8	5	3	10	0	2	7	1	0
5	4	4	0	13	0	1	11	1	0
6	0	0	0	0	0	0	0	0	0
from 7 to 10	5	5	0	33	1	1	28	3	0
more than 10	1	1	0	17	0	4	10	3	0
Total	49	21(42.9%)	28(57.1%)	81	1(1.2 %)	9(11.1 %)	63(77.8%)	8(9.9%	0

3.5 Comparison between Drugs.com and Lexicomp according to the number, mechanism and severity of the interactions

Table 20: Comparison between Drugs.com and Lexicomp according to the number, mechanism and severity of the interactions

Name of Database	No of patients have interactions	No of interactions	According to the mechanism of interaction			According to the severity		
			PK	PD	Unknow	Major	Moderate	Minor
Drugs.com	76	244	61	113	70	32	168	44
Lexicomp	62	179	46	103	48	75	95	27

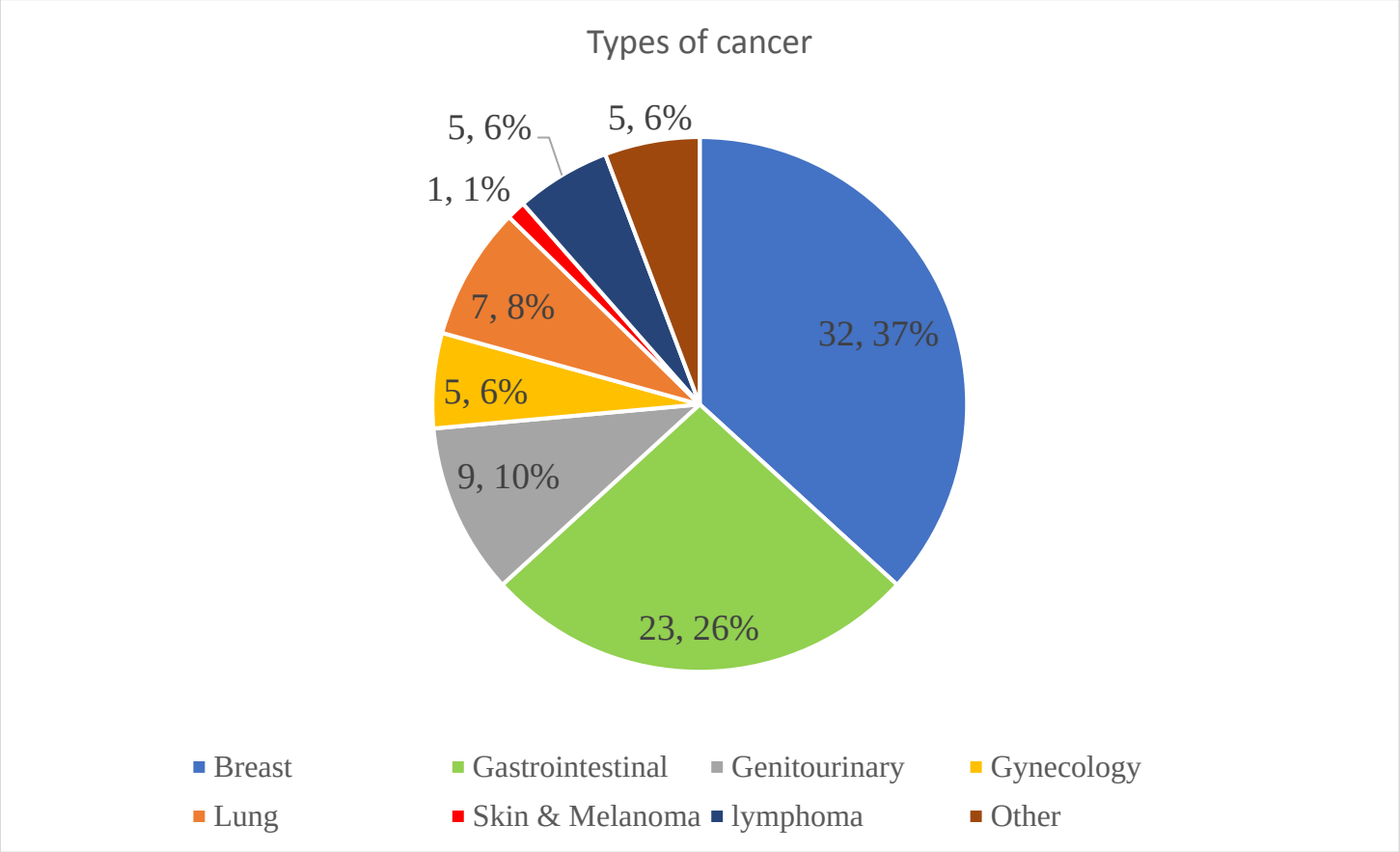
* PK: Pharmacokinetic, PD: Pharmacodynamic

Number of Major interactions according to Lexicomp having **** $p<0.0001$, were considered statically significant having when compared to Drugs.com.

Number of Moderate interactions according to Drugs.com having **<0.01, were considered statically significant having when compared to Lexicomp.

3.6 Drug-drug interaction according types of cancer

Out of 87 patients, 32 (36.8 %) of patients had breast cancer, and in these patients, we found 62 drug-drug interactions. 23 (26.4%) of patients had gastrointestinal cancer, and they have 39 drug -drug interactions. [Figure 2]



[Figure 2]: Number of patients according to the type of cancer

Table 21: Number of DDIs according types of cancer

Types of cancer	*Number of patients*	*Number of DDIs*
Breast	32	62
Gastrointestinal	23	39
Genitourinary	9	20
Gynecology	5	31
Lung	7	5
Skin & Melanoma	1	19
lymphoma	5	17
Other	5	4

P > 0.05, there is No statistically significant association between types of cancer and number of DDIs in patients.

Drug interactions , severity ,clinical significance and recommendation between chemotherapeutic drugs (Drugs.com)

Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Fluorouracil	Leucovorin	pharmacodynamic	Major	increases toxicity of fluorouracil	TDM	17
Carboplatin	Paclitaxel	Unknow	Moderate	Increases risk of peripheral neuropathy during combination	Monitored closely for symptoms of neuropathy	8
Capecitabine	Oxaliplatin	pharmacodynamic	Moderate	Additive toxicities	Monitoring for hematologic and nonhematologic toxicities	5
Cisplatin	Gemcitabine	Unknow	Minor	Synergistic effect may increase toxicity	No need action	3
Fluorouracil	Cyclophosphamide	pharmacodynamic	Moderate	Additive toxicities	Monitoring for hematologic and nonhematologic toxicities	1
Fluorouracil	Methotrexate	pharmacodynamic	Moderate	Additive toxicities	Monitoring for hematologic and	1
Cyclophosphamide	Doxorubicin	Unknow	Minor	Doxorubicin may enhance the risk of hemorrhagic cystitis associated with cyclophosphamide.	No need action	17
Doxorubicin	Vincristine	pharmacokinetics	Minor	Increased severity of side effects	No need action	4
Carboplatin	Etoposide	pharmacokinetics	Moderate	Increase the systemic exposure of etoposide	Observed for potentially increased toxicity of etoposide	3
Carboplatin	Gemcitabine	pharmacodynamic	Moderate	Additive toxicities	Monitoring for hematologic and nonhematologic toxicities -Dosing adjustments	2

Drug interactions , severity ,clinical significance and recommendation between chemotherapeutic drugs (Drugs.com)						
Drug A	**Drug B**	**Mechanisms of interaction**	**Severity**	**clinical significance**	**Recommendation**	**frequency of this interaction**
Fluorouracil	Docetaxel	pharmacodynamic	Moderate	Additive toxicities	Monitoring for hematologic and nonhematologic toxicities -Dosing adjustments	3
Fluorouracil	Oxaliplatin	pharmacodynamic	Moderate	Additive toxicities	Monitoring for hematologic and nonhematologic toxicities -Dosing adjustments	10
Docetaxel	Oxaliplatin	Unknow	Moderate	Increase risk of peripheral neuropathy	monitored closely for symptoms of neuropathy such as burning, tingling	2
Doxorubicin	Paclitaxel	pharmacokinetics	Moderate	Increases levels of doxorubicin by decreasing renal clearance.	Monitor for doxorubicin-induced cardiovascular toxicity	7
Irinotecan	Oxaliplatin	Unknow	Moderate	Oxaliplatin may increase the incidence and/or severity of irinotecan-induced cholinergic syndrome	Monitored for cholinergic symptoms	3
Doxorubicin	Trastuzumab	pharmacodynamic	Major	Trastuzumab and anthracyclines in combination has been associated with a high risk of cardiotoxicity	Cardiac function should be closely monitored.	2
Paclitaxel	Trastuzumab	Unknow	Moderate	Non-human studies have demonstrated that paclitaxel can significantly increase the serum levels and decrease the clearance of trastuzumab	Monitored closely for signs of trastuzumab toxicity	4
Paclitaxel	Oxaliplatin	Unknow	Moderate	Increase risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling	1
Carboplatin	Docetaxel	Unknow	Moderate	Increase risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling	2
Prednisone	Docetaxel	pharmacokinetics	Minor	Decrease the level or effect of docetaxel by affecting hepatic/intestinal enzyme CYP3A4 metabolism	No need action	1
Cisplatin	Vinorelbine	Unknow	Moderate	Increase risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling	1
Filgrastim	Rituximab	Unknow	Moderate	growth factors such as colony-stimulating factors (G-CSF and GM-CSF) and stem cell factors (SCF) given simultaneously with cancerchemotherapy hav e not been established	growth factors should not be used within 24 hours before or 24 hours after administration of antineoplastic agents	1

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Alprazolam	Bisoprolol	Pharmacodynamic	Moderate	may result in additive effects on blood pressure and orthostasis	Monitoring for development of hypotension	1
Alprazolam	Bisoprolol	Pharmacodynamic	Minor	Decrease in beta-blocking effectiveness is possible.	No action need	1
Alprazolam	Estradiol	Pharmacodynamic	Moderate	Estrogens may increase serum thyrotropin concentration / increase serum thyroid-binding globulin concentration in a dose-dependent manner	Serum thyrotropin should be measured approximately 12 weeks after estrogen therapy is initiated	1
Amiodarone	Metoprolol	pharmacokinetic	Minor	Increase aspirin absorption	Monitored for altered antihypertensive response	5
Amiodarone	Insulin aspart	Pharmacodynamic	Moderate	Hypoglycemia	TDM	3
Amiodarone	Insulin glargine	Pharmacodynamic	Moderate	Hypoglycemia	TDM	2
Amiodarone	Acetaminophen	Unknown	Minor	potentiate the hepatotoxicity of acetaminophen,	No action need	1
Amlodipine	Glipizide	Pharmacodynamic	Moderate	Hypoglycemia	Cardioselective beta-blockers are considered safer than noncardioselective agents	1
Amlodipine	Insulin	Pharmacodynamic	Moderate	Hypoglycemia	Cardioselective beta-blockers are considered safer than noncardioselective agents	1
Amlodipine	Glipizide	Pharmacodynamic	Moderate	Hypoglycemia	TDM	2

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Aspirin	Citalopram	pharmacokinetic	Moderate	Bradycardia, Hypotension	TDM	2
Aspirin	Glipizide	Pharmacodynamic	Moderate	Hypoglycemia	TDM	1
Aspirin	Insulin	Pharmacodynamic	Moderate	Hypoglycemia	TDM	1
Aspirin	Furosemide	Pharmacodynamic	Major	Prolongation of the QT interval - Hypoglycemia - Hypomagnesemia	Avoid Combination	1
Aspirin	Citalopram	Pharmacodynamic	Major	Prolongation of the QT interval- Ventricular arrhythmias including torsade de pointes	Avoid Combination	1
Aspirin	Metoprolol	Pharmacodynamic	Moderate	Bradycardia - Cardiac arrest- Ventricular fibrillation -	Monitoring of patient hemodynamic status	1
Aspirin	Spironolactone	Unknown	Moderate	Hyponatremia	Use SSRIs or SNRIs with caution	1
Aspirin	Aspirin	Pharmacodynamic	Moderate	Risk of bleeding	Use SSRIs or SNRIs with caution	1
Atenolol	Furosemide	Unknown	Moderate	Hyponatremia	Use SSRIs or SNRIs with caution	1
Atenolol	Atorvastatin	pharmacokinetic	Moderate	Increase the plasma concentrations of Atorvastatin	TDM	2

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Atenolol	Furosemide	Unknown	Moderate	Hyponatremia	Use SSRIs or SNRIs with caution	1
Atenolol	Atorvastatin	pharmacokinetic	Moderate	Increase the plasma concentrations of Atorvastatin	TDM	2
Atorvastatin	Furosemide	Unknown	Moderate	Hyperglycemia - Hypertriglyceridemia -Risk of QT interval prolongation- Arrhythmias	Monitoring of serum potassium levels, blood pressure, and blood glucose	1
Atorvastatin	Spironolactone	Unknown	Moderate	Hyperglycemia - Hypertriglyceridemia -Risk of QT interval prolongation- Arrhythmias	Monitoring of serum potassium levels, blood pressure, and blood glucose	1
Atorvastatin	Furosemide	Pharmacodynamic	Minor	Blunt the diuretic and natriuretic response to loop diuretics.	No action need	1
Calcium carbonate	Spironolactone	pharmacokinetic	Minor	Inhibit the natriuretic properties of spironolactone	Discontinuing the salicylate - TDM	1
Calcium carbonate	Diclofenac	Pharmacodynamic	Moderate	Attenuate the antihypertensive effects	Monitoring for altered blood pressure control	1
Calcium carbonate	Diclofenac	Pharmacodynamic	Moderate	Increase the risk of bleeding	Close clinical and laboratory observation for hematologic complications	1
Candesartan	Diclofenac	Pharmacodynamic	Moderate	Risk of GI bleeding	Observation for increased NSAID toxicity	1
Candesartan	Clopidogrel	Pharmacodynamic	Moderate	Increase the risk of bleeding	Close clinical and laboratory observation for hematologic complications	1
Candesartan	Diclofenac	Pharmacodynamic	Moderate	Attenuate the antihypertensive effects	Monitoring for altered blood pressure control	1
Candesartan	Ramipril	Unknown	Moderate	Enhance the vasodilatory and hypotensive effects	This combination is used to clinical advantage	1
Captopril	Trimeprazine	Unknown	Moderate	Syncope associated with vasodilation	Monitoring for development of hypotension is recommended - TDM	1
Captopril	Trimeprazine	Unknown	Moderate	Enhance the vasodilatory and hypotensive effects	Monitoring for development of hypotension is recommended - TDM	1

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Citalopram	Diclofenac	Pharmacodynamic	Moderate	Attenuate the antihypertensive effects	Monitoring for altered blood pressure control	1
Citalopram	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM	2
Citalopram	Aspirin	Pharmacodynamic	Moderate	Attenuate the antihypertensive effects	Monitoring for altered blood pressure control	3
Citalopram	Metoprolol	Unknown	Moderate	Unfavorable outcomes on morbidity and mortality in heart failure patients	Avoid Combination	2
Citalopram	Fentanyl	pharmacokinetic	Major	Risk of serotonin syndrome	Avoid Combination	1
Clopidogrel	Tramadol	pharmacokinetic	Major	Risk of serotonin syndrome	Avoid Combination	1
Doxazosin	Fentanyl	Pharmacodynamic	Major	Sedation- Respiratory depression - Coma and death	Avoid Combination - Minimum dosage if required	1
Doxazosin	Duloxetine	pharmacokinetic	Major	Risk of serotonin syndrome	Avoid Combination	1
Duloxetine	Duloxetine	pharmacokinetic	Major	Risk of serotonin syndrome	Avoid Combination	1
Duloxetine	Tramadol	pharmacokinetic	Major	Risk of serotonin syndrome	Avoid Combination	1
Enalapril	Tramadol	Unknown	Major	Sedation- Respiratory depression - Coma and death	Avoid Combination - Minimum dosage if required	1
Enalapril	Candesartan	Pharmacodynamic	Major	Hyperkalemia- Hypotension - Syncope- Renal dysfunction	Monitoring Serum electrolytes, blood pressure, and renal function	1
Famotidine	Lorazepam	Pharmacodynamic	Moderate	Hypotension	Monitoring for development of hypotension	1
Fluoxetine	Insulin aspart	Pharmacodynamic	Moderate	Hypoglycemia	monitoring for the development of hypoglycemia	1
Fluoxetine	Insulin aspart	Pharmacodynamic	Moderate	Hypoglycemia	monitoring for the development of hypoglycemia	1
Fluoxetine	Insulin aspart	Pharmacodynamic	Moderate	Hypoglycemia	monitoring for the development of hypoglycemia	1
Fluoxetine	Lorazepam	Unknown	Moderate	respiratory-depressant effects	Monitored for potentially excessive or prolonged CNS and respiratory depression.	1

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Isosorbide mononitrate	Insulin glargine	Pharmacodynamic	Moderate	Hypotension	Monitoring for development of hypotension	1
Isosorbide mononitrate	Insulin glargine	Pharmacodynamic	Moderate	Hypotension	Monitoring for development of hypotension	1
Levothyroxine	Insulin glargine	Pharmacodynamic	Moderate	Hypotension	Monitoring for development of hypotension	1
Levothyroxine	Lorazepam	Unknown	Moderate	Hypotension	Monitoring for development of hypotension	1
Levothyroxine	Metformin	Unknown	Moderate	Hypoglycemia	Monitoring for the development of hypoglycemia	1
Levothyroxine	Lorazepam	Unknown	Minor	Delay the gastrointestinal absorption and reduce the peak plasma concentration (Cmax) of Lorazepam	Administration times of benzodiazepines and Calcium carbonate	1
Lorazepam	Captopril	Pharmacodynamic	Minor	Decrease the oral bioavailability of captopril	No action need	1
losartan	Duloxetine	Unknown	Minor	Earlier release of duloxetine from the formulation	No action need	1
Metformin	Pantoprazole	Unknown	Minor	Reducing gastric acid secretion	No action need	1
Metformin	Pantoprazole	Unknown	Minor	Earlier release of duloxetine from the formulation	No action need	1
Metformin	Prednisolone	pharmacokinetic	Moderate	Inducing sodium and fluid retention- Antagonize the effects of antihypertensive medications	TDM of Atenolol	1
Metformin	Amlodipine	pharmacokinetic	Moderate	Congestive heart failure- Severe hypotension- angina	TDM	1
Metformin	Prednisolone	pharmacokinetic	Moderate	Inducing sodium and fluid retention- Antagonize the effects of antihypertensive medications	TDM of Amlodipine	1

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Metformin	Prednisolone	pharmacokinetic	Moderate	Inducing sodium and fluid retention- Antagonize the effects of antihypertensive medications	TDM of Doxazosin	1
Metformin	Atenolo	Pharmacodynamic	Moderate	reflex tachycardia - Hypotension	TDM of Doxazosin	1
Metformin	Glipizide	Pharmacodynamic	Moderate	Hypoglycemia	Monitoring for the development of hypoglycemia	1
Metoprolol	Alprazolam	Pharmacodynamic	Moderate	Increase hypotensive effects	Monitoring for development of hypotension	1
Metoprolol	Metformin	Unknown	Moderate	Hypoglycemia	Monitoring for the development of hypoglycemia	1
Metoprolol	Repaglinide	Pharmacodynamic	Moderate	Hypoglycemia	TDM of Repaglinde	1
Metoprolol	Ramipril	Pharmacodynamic	Moderate	Attenuate the antihypertensive effects	TDM of Aspirin	1
Metoprolol	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM	1
Metoprolol	Trandolapril	Pharmacodynamic	Minor	Hypotension	Monitoring of the systemic blood pressure	1
Metoprolol	Metformin	pharmacokinetic	Moderate	Hypoglycemia	TDM of Metformin	2
Metoprolol	Losartan	Pharmacodynamic	Moderate	Attenuate the antihypertensive effects	Monitoring for altered blood pressure control	2
Nateglinide	Glimepiride	Pharmacodynamic	Moderate	Hypoglycemia	Cardioselective beta-blockers are considered safer than noncardioselective agents	1
Nifedipine	Glimepiride	Pharmacodynamic	Moderate	Hypoglycemia	TDM of Glimeiride	1
Pantoprazole	Glimepiride	Pharmacodynamic	Moderate	Hypoglycemia	TDM of Glimeiride	1

Drug interactions , severity ,clinical significance and recommendation between nonchemotherapeutic drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency of this interaction
Perindopril	Atenolo	pharmacokinetic	Minor	Increase aspirin absorption	Monitored for altered antihypertensive response	1
Ramipril	Hydrochlorothiazide	Unknown	Moderate	Hyperglycemia-Glucose intolerance - Risk of lactic acidosis -	Monitoring of glycemic control	1
Ramipril	Leuprolide	Pharmacodynamic	Moderate	Hyperglycemia -Glucose intolerance	Monitoring of glycemic control	1
Ramipril	Clopidogrel	pharmacokinetic	Moderate	Reduce the metabolic activation of Clopidogrel	Monitoring for altered efficacy of clopidogrel	2
Ranitidine	Clopidogrel	Pharmacodynamic	Moderate	Risk of GI bleeding	Use with caution	1
Sertraline	Hydrochlorothiazide	Unknown	Moderate	Hypotension	Monitoring for development of hypotension	1
Sertraline	Hydrochlorothiazide	Unknown	Moderate	Hypotension	Monitoring for development of hypotension	1
Sertraline	Omeprazole	pharmacokinetic	Moderate	increase the pharmacologic effects and serum levels of Alprazolam-Increased sedation	TDM of Alprazolam	1
Sertraline	Omeprazole	pharmacokinetic	Moderate	risk of Myopathy	Monitoring for symptoms of Muscle pain	1
Tramadol	Calcium carbonate	pharmacokinetic	Moderate	Decrease the oral bioavailability of levothyroxine	Separating the times of administration of levothyroxine and calcium-containing preparations by at least 4 hours - Monitoring of serum TSH levels	1
Tramadol	Vit B12	Unknown	Minor	Reducing gastric acid secretion	No action need	1
Valsartan	Simvastatin	pharmacokinetic	Major	Risk of myopathy	Simvastatin dosage should not exceed 20 mg daily	1
Valsartan	Clopidogrel	pharmacokinetic	Moderate	Reduced therapeutic efficacy of Clopidogrel	Monitor the therapeutic efficacy of clopidogrel	1
Verapamil	Pantoprazole	pharmacokinetic	Moderate	risk of Myopathy	Monitoring for symptoms of Muscle pain	1
Vit B12	Ramipril	Pharmacodynamic	Minor	Hypotension	Monitoring of the systemic blood pressure	1

Drug interactions , severity ,clinical significance and recommendation between chemotherapy and nonchemotherapy drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency
Bortezomib	Furosemide	Unknow	Moderate	Risk of ototoxicity.	Monitor auditory function	1
Bortezomib	levofloxacin	PK	Minor	Reduce the plasma concentrations of levofloxacin	No action need	1
Bortezomib	Omeprazole	Unknow	Moderate	Hypomagnesemia	Monitoring of serum magnesium levels	1
Carboplatin	Simvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	1
Carboplatin	Atorvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	2
Carboplatin	Aspirin	PK	Moderate	Potentially nephrotoxicity	Monitored Renal function	2
Carboplatin	Diclofenac	PK	Moderate	Potentially nephrotoxicity	Monitored Renal function	1
Cisplatin	Loperamide	PD	Moderate	Risk of ventricular arrhythmias including torsade de pointes and sudden death	Monitoring Cardiac function /TDM of Loperamide	1
Cyclophosphamide	Lactulose	PD	Moderate	Risk of torsade de pointes ventricular arrhythmia /Electrolyte loss	Monitored periodically for electrolyte imbalance if patients use Lactulose more than six month	1
Cyclophosphamide	prochlorperazine	PD	Moderate	Risk of ventricular arrhythmias including torsade de pointes and sudden death	Monitoring Cardiac function	1
Cyclophosphamide	Acetaminophen	Unknow	Moderate	Risk of liver injury	Monitoring of hepatic function	1
Cyclophosphamide	Citalopram	PD	Major	Risk of ventricular arrhythmias including torsade de pointes and sudden death	Monitoring Cardiac function	1
Cyclophosphamide	Aprepitant	PK	Moderate	Increase the plasma concentrations of Doxorubicin	Use with Caution	1

Drug interactions , severity ,clinical significance and recommendation between chemotherapy and nonchemotherapy drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency
Docetaxel	Rosuvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	2
Docetaxel	Glipizide	PK	Moderate	Hypoglycemia	Monitoring for the development of hypoglycemia	1
Docetaxel	Glimepiride	PK	Moderate	Hypoglycemia	Monitoring for the development of hypoglycemia	1
Doxorubicin	Hydrochlorothiazide	Unknow	Moderate	Blood dyscrasias	Alternative antihypertensive therapy	1
Doxorubicin	Repaglinide	PK	Moderate	Hypoglycemia	Monitoring for the development of hypoglycemia	1
Etoposide	Aprepitant	PK	Moderate	Increase the plasma concentrations of Cyclophosphamide	Use with Caution	1
Fluorouracil	Rosuvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	2
Fluorouracil	Atorvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM OF Bortezomib	1
Irinotecan	Amiodarone	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM OF Bortezomib	1
Methotrexate	Citalopram	PK	Minor	Unkown	No action need	1

Drug interactions , severity ,clinical significance and recommendation between chemotherapy and nonchemotherapy drugs (Drugs.com)						
Drug A	Drug B	Mechanisms of interaction	Severity	clinical significance	Recommendation	frequency
Oxaliplatin	Dexamethasone	PK	Minor	Unkown	No action need	1
Oxaliplatin	Atorvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	1
Oxaliplatin	Prednisone	PK	Minor	Unkown	No action need	2
Oxaliplatin	Atorvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	1
Oxaliplatin	Verapamil	PK	Moderate	Increase the plasma concentrations of paclitaxel : diarrhea, mucositis, myelosuppression, and peripheral neuropathy.	Monitor for evidence of dose-related toxicities of paclitaxel	1
Oxaliplatin	Aprepitant	PK	Moderate	Increase the plasma concentrations of Paclitaxel	Use with Caution	1
Paclitaxel	Rosuvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	1
Paclitaxel	Atorvastatin	PD	Moderate	Risk of peripheral neuropathy	Monitored closely for symptoms of neuropathy such as burning, tingling, pain / TDM	1
Paclitaxel	Clopidogrel	PK	Moderate	increase the plasma concentrations of paclitaxel,	TDM of Paclitaxel	1
Paclitaxel	Multivitamin	Unknow	Major	Deaths from severe enterocolitis, diarrhea, and dehydration	Monitored closely for potential toxicities of Fluorouracil	1
Paclitaxel	Hydrochlorothiazide	Unknow	Moderate	Blood dyscrasias	Alternative antihypertensive therapy	1
Vincristine	Lactulose	PD	Moderate	Sever diarrhea	TDM	1

Drug interactions , severity ,clinical significance and recommendation between chemotherapeutic drugs (Lexicomp)

Drug A	Drug B	Mechanisms of interaction	Severity	Interaction Levels	clinical significance	Recommendation	frequency
Bortezomib	Dexamethasone	PK	Minor	B	Decrease the serum concentration of Bortezomib	No need action	1
Capecitabine	Oxaliplatin	PD	Minor	B	Enhance QTc -prolonging effect	No need action	5
Carboplatin	Paclitaxel	PK	Major	D	Enhance the myelosuppressive effect of Paclitaxel	Administer Paclitaxel befor Carboplatin	8
Carboplatin	Trastuzumab	PD	Major	C	Enhance the neutropenic effect of Carboplatin	Monitor for neutropenia and /or anemia	2
Cyclophosphamide	Filgrastim	Unknow	Major	C	Enhance the adverse/toxic effect of Cyclophosphamide (pulmonary toxicity)	Monitoring for enhance pulmonary toxicity	1
Cyclophosphamide	Trastuzumab	PD	Major	C	Enhance the neutropenic effect of Cyclophosphamide	Monitor for neutropenia and /or anemia	2
Docetaxel	Oxaliplatin	PK	Major	D	Enhance the myelosuppressive effect of Oxaliplatin	Administer Oxaliplatinl befor Docetaxel	2
Docetaxel	Carboplatin	PD	Major	D	Enhance effect of Docetaxel	Administer Docetaxel befor Carboplatin	2
Docetaxel	Trastuzumab	PD	Major	C	Enhance the neutropenic effect of Docetaxel	Monitor for neutropenia and /or anemia	2
Doxorubicin	Cyclophosphamide	PD	Major	C	Synergistic effect may increase cardiotoxic effect	Monitor cardiac function	18
Doxorubicin	Paclitaxel	PK	Major	D	Risk of Doxorubicin Toxicity (CHF)	Use Docetaxel instead of Paclitaxel	8
Doxorubicin	Trastuzumab	Unknow	Major	D	Cardiotoxic effect of Doxorubicin	Monitor for signs and symptoms of cardic dysfunction	2
Fluorouracil	Leucovorin	PD	Major	C	increases toxicity of fluorouracil	Monitor closely for Fluorouracil toxicity including diarrhea and neutropenia	16
Fluorouracil	Oxaliplatin	Unknow	Minor	B	Enhance the QTC-prolonging effect(Torsades de pointes ,Ventrical tachyarrhythmias)	No action need	11
Navelbine	Cisplatin	Unknow	Moderate	C	Enhance the adverse/toxic effect of Navelbine (granulocytopnia)	Monitor of rate of granulocytopenia	1
Paclitaxel	Trastuzumab	PK	Moderate	C	Decrease the serum concentration of Paclitaxel	Monitor closely for adverse effects and response to therapy	4
Paclitaxel	Oxaliplatin	PD	Major	D	Enhance effect of Paclitaxel	Administer Paclitaxel befor Oxaliplatin	1

Drug interactions , severity ,clinical significance and recommendation between chemotherapy and nonchemotherapy drugs (Lexicomp)							
Drug A	**Drug B**	**Mechanisms of interaction**	**severity**	**Interaction Levels**	**clinical significance**	**Recommendation**	**frequency**
Bortezomib	Amiodarone	Unknow	Moderate	D	Enhance the QTC-prolonging effect(Torsades de pointes ,Ventrical	Combination should onaly be undertaken with caution	1
Bortezomib	Citalopram	Unknow	Moderate	D	Enhance the QTC-prolonging effect(Torsades de pointes ,Ventrical tachyarrhythmias)	Combination should onaly be undertaken with caution	1
Bortezomib	Spironolactone	PD	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	1
Bortezomib	Isosorbride Dinitrate	PD	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	1
Bortezomib	Furosemide	PD	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	2
Bortezomib	Metoprolol	PD	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	2
Cyclophosphamide	Amiodarone	PD	Moderate	C	Risk of pulmonary toxicity	Monitored closely for toxic effect of Amiodarone	1
Cyclophosphamide	Losartan/Hydrochlorot iazide	Unknow	Moderate	C	Enhance the adverse/toxic effect of Cyclophosphamide (granulocytopnia)	Monitor of rate of granulocytopenia	1
Dexamrthasone	Amiodarone	PK	Moderate	C	Decrease the level or effect of amiodarone	No action need	1
Dexamrthasone	Aspirin	PD	Moderate	C	Gastrointestinal ulceration - Bleeding	Monitor for gastrointestinal irritation	1
Dexamrthasone	Furosemide	PK	Moderate	C	Hypokalemia	Monitor closely serum potassium	1
Doxorubicin	Emend	PK	Major	D	increase effect of Doxorubicin	Alternatives Emend to anther agent - Avoid combination	1
Fluorouracil	Loperamide	PD	Minor	B	Enhance the QTC-prolonging effect(Torsades de pointes ,Ventrical tachyarrhythmias)	No action need	1
Fluorouracil	Trazodone	PD	Minor	B	Enhance the QTC-prolonging effect(Torsades de pointes ,Ventrical tachyarrhythmias)	No action need	1

Drug interactions , severity ,clinical significance and recommendation between chemotherapy and nonchemotherapy drugs (Lexicomp)							
Drug A	**Drug B**	**Mechanisms of interaction**	**severity**	**Interaction Levels**	**clinical significance**	**Recommendation**	**frequency**
Oxaliplatin	Loperamide	PD	Minor	B	Enhance the QTC-prolonging effect(Torsades de pointes , Ventrical tachyarrhythmias)	No action need	1
Paclitaxel	Furosemide	Unknow	Moderate	C	Hypotension	Monitor for additive hupotensive effects	1
Paclitaxel	Tamsulosin	PK	Moderate	C	Hypotension	TDM	1
Paclitaxel	Trandolapril	Unknow	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	1
Paclitaxel	Verapamil	PK	Moderate	C	Increase effect of Paclitaxel	Monitor for increase effects of Paclitaxel	1
Paclitaxel	Atenolol	Unknow	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	1
Paclitaxel	Losartan	Unknow	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	1
Paclitaxel	Bisoprolol	Unknow	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	1
Paclitaxel	Emend	PK	Moderate	C	Increase effect of Paclitaxel	Monitor for increase effects of Paclitaxel	1
Paclitaxel	Amlodipine	Unknow	Moderate	C	Hypotension	Monitor closely for additive hypotensive effects	2
Paclitaxel	Clopidogrel	PK	Moderate	C	Increase the serum concentration of Paclitaxel	Monitor for sever neuropathy or neutropenia	1
Paclitaxel	Ramipril	Unknow	Moderate	C	Increase the serum concentration of Paclitaxel	Monitor for sever neuropathy or neutropenia	1
Prednisolone	Aspirin	Unknow	Moderate	C	Gastrointestinal ulceration - Bleeding	Monitor for gastrointestinal irritation	1

4. Discussion

Cancer treating considers challenging for health care provider. Also, they are more prone to drug interaction because cancer patient receives a high number of drugs concomitantly including cytotoxic agents, hormonal agents and targeted agents and usually present comorbid conditions and cancer-related syndromes such as pain, depression, and seizures. In addition, most chemotherapy drugs are potent and toxic drugs with a narrow therapeutic index. Remarkably, in most countries, cancer patients are not routinely checked for DDIs. In cancer patients, drug interactions increase adverse events or decrease/inactivation of the antitumor effects and may enhance drug toxicity and indirectly compromise treatment outcomes and adherence. Physicians and clinical pharmacists should be more aware of these potential interactions. We have assessed the prevalence of potential drug interactions, frequency, mechanisms of action, and severity among cancer patients. Several studies have evaluated drug interactions, the frequency of DDIs, and the potential risks for patient's safety in general medicine, but only a few have addressed this subject in cancer patients.

In clinical practice, DDIs can be classified as pharmaceutical, pharmacokinetic, and pharmacodynamic interactions. Pharmaceutical DDIs occur when two chemically or physically incompatible drugs are combined. Pharmacokinetic interactions mean any influence on the time course of drug absorption, distribution, metabolism, and excretion of the drug itself or a combination of drugs, prevalent pharmacokinetic interaction which happens on a level of metabolism by the cytochrome P450 (CYP) enzymes, many of antineoplastic medication are metabolized by CYP3A such as paclitaxel, vinca alkaloids, cyclophosphamide and 5-fluorouracil.Pharmacodynamic drug interactions occur when two or more drugs have a similar mechanism of action and the same physiological outcome. The effect can be synergistic, additive, or antagonistic. Also, this interaction can be beneficial in therapeutic effect for example fluorouracil and leucovorin can be enhanced pharmacologic effects and use as effective adjuvant chemotherapy.

In a retrospective study conducted in Norway, 18% of 732 deaths were directly or indirectly associated with drug interactions, 4 %of the cancer related-deaths were considered to be associated with drug interactions. (Buajordet, 2001)

A number of studies have been shown the occurrence of DDIs in cancer patients was high, more than half of the patient group are with at least one DDIs. A cross-sectional study conducted on 405 oncology patients showed that 27% of patients had at least one potential

drug interaction (Riechelmann, 2016). Riechelmann through used Drug Interaction Facts software found 180 DDIs in 63 patients, 63% presented at least one potential drug interaction (Riechelmann R. P., 2005). Another study in three Dutch centers identified 1359 DDIs in 426 patients 46 %, by using electronic (Drug Interaction Fact software) and manual screening methods (Van Leeuwen, 2013). Also, a cross-sectional study included 138 patients with cancer showed a high percentage of DDIs 83(62.88 %) (Hadjibabaie, 2013). Like most previous studies our study showed a high percentage of DDIs in cancer patients, we found 244 drug-drug interaction in 87 patients and 76 (87.4%) of patients presented at least one potential drug interaction, this result is by using Drugs.com database, many studies support this high rate of DDIs in patients with cancer. There is no significant difference in result when used Lexi-comp tools and the remaining high percentage of present DDIs 62 (71.30%) of patients were had DDIs and we found 197 interaction in all patients.

At the level of a mechanism of action in our study, DDIs have been categorized according to Drugs.com database and Lexi-comp tool as: pharmacodynamic, pharmacokinetic and unknown. In both cases, pharmacodynamic caused the greatest number of DDIs among patients, in Drugs.com pharmacodynamic interaction causes 113(46.31%) while pharmacokinetic interaction caused 61(25%) and 70(28.69%) with an unknown mechanism of interaction. In Lexi-comp pharmacodynamic interaction causes 103(52.3%) while pharmacokinetic interaction caused 46(23.4%) and 48(24.3%) with an unknown mechanism of interaction. The results of the other studies were similar to the results of our study at the mechanism level and showed the pharmacodynamic caused the greatest number of DDIs in cancer patients. A retrospective study conducted on 426 patients showed that 86% of DDIs of total 1359 DDIs were caused by pharmacodynamic interaction while pharmacokinetic interaction 14% (Van Leeuwen, 2013). On the other hand, a cross-sectional study surveyed 405 patients with different types of cancer who were receiving anticancer drugs, out of 276 interaction more than half 55% were a pharmacokinetic interaction (Riechelmann R. P., 2007).

According to the severity of drug-drug interactions, in our study the most DDIs in 244 interaction found were moderate 168 (68.85%) followed by minor 44(18.03%), major 32 (13.11%). A retrospective search over a period of 12 months, showed a close comparison to our study, 83% in total DDIs were classified as moderate severity and 15% were major (Van Leeuwen D. H., 2013).Another study found 180 potential drug interactions in 63 hospitalized cancer patients,102(56.7%) were moderate, 45(25%) were minor, and 32(18.3%) were severe (Riechelmann R. P., 2005). Also, Riechelmann and, Tannock they did a cross-sectional study in ambulatory adult patients with solid tumors showed,77% of potential drug interactions were of moderate severity,14% of minor severity and 9 % of major severity (Riechelmann R. P., 2007).The moderate DDIs are usually accompanied by probable side effect such as GI disturbances, rashes, muscle tremor, headaches and dizziness. The moderate severity of DDIs is not life-threatening but may result in exacerbation of the patient's condition. Clinical pharmacists should suggest changing treatment, add treatment, and hospitalization.

According Lexi-comp, DDIs are classified by risk rating of interaction into five level A, B, C, D, X.A retrospective study on 149 elderly cancer patients found 458 DDIs, the most DDIs according to risk rating is C interaction 386(84.2%) followed by D interaction 70 (15.2%) and X interaction 2 (0.8%) (Pottel, 2012).The results of our study similar previous study, more than half of 197 DDIs were level C interaction 135(68.53%) followed by D interaction33 (16.76%), D interaction 28 (14.21%) and X interaction 1 (0.5%). No need to worry when medications have interaction on level C, usually the benefits of concomitant two drugs outweigh the risks. An appropriate monitoring plan must be applied to avoid possible adverse effects. Dosage adjustments of one or both drugs may be necessary for patients. Also, a prospective study found 37 DDIs in 26 cancer patients by using Lexi-comp, 29.7% of this interaction were considered a high risk of interaction level D (Ramos-Esquivel, 2016).

Gender, age and an increasing number of medications are a risk factor for potential drug interactions, but not all of them have a statistically significant association with DDIs.
In our study, age was not associated with a higher number of DDIs (P=0.333), we divided patients into four groups, the median age of patients was 62 years, the highest number of DDIs were in patients between 60 to 75 years. This result is similar to the results in other studies that have linked age to DDIs, in a study published in 2013 on 278 ambulatory cancer patients showed age was not associated with a higher number

of PDIs (P-value =0.223) (Van Leeuwen, 2013). Also, another study on 405 patients with median 58 years old found no statistically significant association between age and drug interaction (Riechelmann R. P., 2007). Conversely, a retrospective study showed patients who are older than 67 years have significant associated with increased odds for potential drug interactions (P-value =0.004) (Riechelmann R. P., 2005).
This difference between this study and the results of previous studies or our study and maybe because they divided the age of patients into two groups only older or younger than 67 years.

Gender like age there is no significant difference between males and females by increasing the number of DDIs. In our study were included 33 (37.9%) male and 54 (62.1%) were female patients. Female patients had a higher number of DDIs 48(63.2%), but there's no statistically significant association between gender and presence DDIs in patients with cancer (P-value =0.86). Similarly, several studies showed that there is no relationship between gender of patients and the increasing number of drug-drug interactions, (P-value=0.381) (Hadjibabaie, 2013), (P-value=0.890) (Riechelmann R. &., 2016).

Several studies have been shown that the occurrence of DDIs in cancer patients increased significantly with the increased number of drugs. A study by Hadjibabaie on 132 patients during a 6-month, patients take between (5-30) medication with a mean (14.2 ± 4.92), (P-value = 0.002) this result shows that the increasing number of administered medications during hematology-oncology ward stay was considered as a risk factor for developing a DDIs (Hadjibabaie, 2013). In another study,268 cancer patients used nine (range 2–22) drugs per patient, showed the increasing number of drugs was associated with a higher number of DDIs (Van Leeuwen R. W., 2011). Also, a study on 409 patients, the median number of medications per patient was 5 (range 0 – 23), Proved that the increase in the number of drugs has a statistically significant association with the increasing number of potential drug interactions (P-value<0.001) (Riechelmann R. P., 2007). A study designed to evaluate the potential for drug interactions in hospitalized cancer patients showed the increasing number of medications related to increasing number of DDIs, the median of medication taken by the patient was 8 and range between 1-20 drugs, (P-value =0.001) (Riechelmann R. P., 2005). These results are similar to ours, we divided patients by the number of their medications into five groups (2,3,4,5 and more than 5 drugs), 87 cancer patients used

410 drugs with mean 4.8(±2.7) medication per patient. The largest number of DDIs were in patients who take more than 5 drugs, 39(44.8%) of patients taking 5 medication or more and 38(97.4%) of them had DDIs. Like previous studies, we found a significant association between a number of medication and the presence of DDIs (P-value<0.05).

It's not easy to reduce polypharmacy in cancer patients because the management of cancer itself may result in the addition of more medications to reduce the adverse effects of chemotherapy drugs. Proposed measures to reduce polypharmacy thus reducing the incidence of DDIs, first of all, the assessment that all medical conditions are properly treated, the avoidance of drug interactions, and of drugs that may affect the outcome of anticancer drugs and the choice of drugs with the lowest risk of complications in cancer patients.

5.Conclusion

Drug interactions considered important issue in oncology, DDIs are common among patients treated for a cancer disease, with approximately more than half of cancer patients being at risk of DDIs. In our study, the number of prescribed drugs is the only factor that leads to an increase in the incidence of drug interactions. Screening for possible interactions should take place routinely before administering anticancer drugs.

A multidisciplinary approach is required to identify and avoid potentially harmful DDIs. Health care providers should be more aware of these potential interactions. The clinical pharmacist should have sufficient information about the types of drug interactions and potential side effects of these interactions to try to prevent them or to inform the patients if have any of these undesirable effects.

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