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A Review on Drug-Drug Interactions Between Cancer Drugs

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ABSTRACT

Due to the limited therapeutic index and the intrinsic toxicity of anticancer drugs, drug reactions in oncology are of special concern. Interactions with other drugs could trigger slight differences in the chemotherapy agent's pharmacokinetics or pharmacodynamic, which may dramatically affect its effectiveness or toxicity. Although precise data is lacking, drug-drug interactions are thought to be more common in oncology than in most other diseases. The identification of potentially clinically important drug reactions has been made possible by advances in *in-vitro* approaches and early clinical research. Patients with cancer typically take a variety of drugs to control symptoms such as pain and nausea. The types of drug interactions that arise in oncology, the pathways causing these interactions and selected examples are illustrated.



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INTRODUCTION

A drug interaction is defined as the pharmacological or therapeutic response to the administration of a drug, or coexposure with another substance that influences the patient's response to the medicine. Medication interactions are thought to be responsible for 20-30% of all adverse drug responses. Adverse drug effects and drug-drug interactions (DDI) are critical public health concerns that cause significant morbidity and mortality worldwide. Drug-drug interactions are defined as a condition in which one medicine alters the pharmacological or clinical response to the other medication when at least two medications are administered together. Drug-food, drug-herbal medication, and vitamin interactions, on the other hand,

are common and should be mentioned [1]. Pharmacokinetic, pharmacodynamic, and pharmacological interactions are the three main types of drug-drug interactions. Drug-drug interactions can be the result of contact between medications at any step of active chemical in target tissues, and pharmacokinetics is the study of the components of absorption, transportation, delivery, digestion, and excretion. Many pharmacodynamic drug-drug interactions exist between medications with similar mechanisms of action, and these can be difficult to classify. Pharmaceutical drug-drug interactions are physical or chemical processes that have mostly antagonistic consequences, often known as pharmacological incompatibilities [2].

Increased risk of drug-drug interactions is associated with old age, poly-pharmacy, genetic factors and co-morbidities, such as reduced hepatic and renal function. In addition to anti-cancer therapy, additive care and prevention of co-morbid conditions contribute to poly-pharmacy as a whole. In the elderly and patients who take two or more drugs, drug-drug interactions occurrence increases. Cancer patients are especially at risk of drug complications as they may take several different drugs as part of their chemotherapy therapy or for other disease control. A total of one third of patients is confirmed to be facing drug-drug interactions due to

above mentioned reasons. Similarly, interactions between the drugs and adverse drug reactions in cancer patients account for 10% of hospital admissions [3].

Pharmacokinetic Drug Interactions

Absorption

Absorption has a vital impact on medications given orally. A pharmacological agent needs to meet its target in order to exert a therapeutic effect. Mostly anticancer agents are administered intravenously and, thus, their pharmacokinetics is little influenced by factors that influence absorption. However, for patient comfort and convenience of administration, oral delivery of anticancer medicines is gaining popularity in chronic therapy. Fortunately, after the Food and Drug Administration (FDA) licensed the first tyrosine kinase (TKI) inhibitor, Imatinib Mesylate, in 2001, hundreds of oral anti-cancer medications are now accessible for the therapy of different forms of cancer. For the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors, Imatinib is given orally [4]. Oral distribution involves close analysis of the different variables influencing the absorption of medications and reactions with other orally delivered compounds such as food can contribute to altered bioavailability. The pharmacokinetics of an orally administered drug will affect both food and co-administered drugs. By preventing gastric emptying, increasing hepatic blood flow and improving intestinal pH, food influences the absorption of the given drug. This can result in reduced bioavailability of some medications, such as inhibitors of Chlorambucil and tyrosine kinase (TKI) [5]. Meat, though, can not only limit a drug's bioavailability, but can also improve it. High fat meals, for example, can increase the absorption of lipophilic drugs such as Abiraterone Acetate and Levomalate Cabozantinib [6]. The net influence of food on the pharmacokinetics of an orally administered medicine is determined by the drug's chemical characteristics and composition, the gastrointestinal tract's physiology, and the amount and quantity of food consumed. Certain orally administered anticancer agents are prodrugs, which require metabolic activation for cytotoxic action by first-pass effects in the gastrointestinal tract and/or liver before entering systemic circulation. Anticancer medicines such as Capecitabine, Altretamine, Etoposide Phosphate, and Estramustine Phosphate Sodium² are employed and must be enabled in the treatment of numerous solid cancers (including breast, colorectal, ovarian, lung, prostate, and testicular). Factors that change the absorption of these drugs may, thus, have significant effects on

their pharmacokinetics. Factors that alter these medications' absorption may thus have a substantial impact on their pharmacokinetics. When Estramustine Phosphate Sodium is added to food or milk, it causes a decrease in the rate and degree of absorption, as well as a 36% and 63% drop in bioavailability, respectively. It is also advised to take Sodium Estramustine Phosphate with water 1 hour before or 2 hours after a meal [7].

Distribution

Blood flow and plasma binding protein levels have a big impact on drug distribution. Anti-cancer medications and pharmaceuticals that are used to enhance treatment bind to plasma proteins in the vast majority of cases. Warfarin, an anticoagulant, binds to plasma proteins primarily, and competition between Warfarin and anti-cancer medications (Capecitabine) causes plasma proteins to bind to one another. The blood supply to the location and the drug's binding characteristics to plasma proteins determine how quickly medicines are delivered to the target site following absorption. Albumin, Alpha-Acid Glycoprotein, Lipoproteins, and Immunoglobulins are examples of anticancer drugs that can attach to a variety of blood components. The unbound chemical is known as the physiologically active fraction because it can affect the pharmacological target inside tissues. As a result, the drug's effect is inhibited when it binds to blood components. Warfarin has a narrow clinical index, which may be linked to enhanced DDIs and drug-food interactions, as well as drug-herbal medication. As a result, precise control of prothrombin duration and the international normalised ratio (INR) is critical for both preventing major bleeding and maintaining enough anticoagulation. Hundreds of drugs and foods have been connected to warfarin DDIs in the past [8]. In theory, highly protein-bound cytotoxic treatments like Paclitaxel and Etoposide could interact with other highly protein-bound medications like Warfarin, which is commonly used in cancer patients to prevent and cure thrombosis.

Metabolism

While certain drugs are metabolized at the absorption site, the liver is the main metabolism site. For most of the anticancer medications, the primary site of metabolism is the liver. CYP enzymes play an important part in a variety of DDIs, food-drug or herbal remedy-drug reactions that occur during phase I responses. CYP enzymes are responsible for the synthesis of more than half of all pharmaceuticals, and they can compete with one another

Table 1: Examples of DDI's of Anti-Cancer Drugs

Cancer Drug	Other Drug	Interaction
5-Fluorouracil	Leucovorin	Leucovorin potentiates the antitoxic effects of 5-FU ([9]. page 563)
6-Mercaptopurine	Allopurinol	6-Mercaptopurine is metabolized by xanthine oxidase. Allopurinol inhibits the enzyme xanthine oxidase and thus prolongs the action of 6-MP. When both drugs are given concurrently, the dose of 6-MP should be reduced by 50-70%. ([9]. page 561, [10]. page 863, [11]. Page 828) decreases the inactivation of 6-Mercaptopurine ([11]. page 818)
Antiandrogen (Flutamide and Bicalutamide)	Combination with orchietomy or GnRH analogues	Flutamide and Bicalutamide enhance testosterone levels through antiandrogenic activity in the pituitary gland ([10]. page 872).
Arsenic trioxide	Corticosteroid treatment	Nausea, dizziness, malaise, weariness, sensory abnormalities, effusions, dyspnea, hyperglycemia, Q-T prolongation, and A-V block ([10]. page 869) are some of the negative consequences of arsenic.
Busulfan	Anticonvulsants Phenytoin	Busulfan stimulates the metabolism of phenytoin, which protects against acute CNS toxicities such as tonic-clonic convulsions ([12]. page 1686) (1686, page 26)
Camptothecins	Atropine	Excessive salivation, abdominal cramps, mitosis, bradycardia and sweating respond to treatment with atropine ([9]. page 565)
Cisplatin	Adequate hydration and diuretics like Manitol/Furosemide 5-HT ₃ antagonist like Ondansetron Aluminium	Reduce nephrotoxic effect ([9]. page 558 and 576, 25. Page 825) Vomiting gets well controlled ([9]. page 559) Reacts with and inactivates cisplatin ([12]. page 1689)
	Amifostine	Prophylaxis of Cisplatin Prophylaxis for Cisplatin-induced neuro/nephrotoxicity and xerostomia caused by irradiation ([9]. page 876, [12]. Page 1689)
	Aminoglycosides	Aggravate Renal toxicity ([11]. page 825)
Cyclophosphamide and Ifosphamide	Mesna(sodium-2-mercaptoethane sulfonate) and irrigating the bladder with Acetylcysteine	Mesna, a -SH molecule secreted in urine - binds and inactivates the vasicotoxic metabolites of Ifosphamide and Cyclophosphamide, preventing the dose-limiting toxicity of Ifosphamide, haemorrhagic cystitis ([9]. Page 557, [10]. page 860 and 876, [11]. Page 815)
Docetaxel	Formulated in Polysorbate medium	Produces less acute hypersensitivity reactions ([10]. page 866)
Doxorubicin (anthracycline antibiotic)	Dexrazoxan (an iron chelating agent)	Reduce the risk of cumulative total dose related cardiotoxicity ([10]. page 876)

Continued on next page

Table 1 continued

Cancer Drug	Other Drug	Interaction
Gefitinib	CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, barbiturates, St. John's wort) and inhibitors (e.g., itraconazole, ketoconazole)	Decrease Gefitinib plasma concentrations and efficacy ([10]. page 870, [12]. Page 1735) Increase plasma concentrations of Gefitinib. ([12]. page 1735)
	Drugs that produce a long-term increase in gastric pH	Co-administration reduce mean Gefitinib AUC by 47% ([12]. page 1735)
Glucocorticoids	Ondansetron/ Metoclopramide	Potentiate the anti-emetic action ([10]. page 872)
Imatinib	Warfarin Intraconazole/ Erythromycin Single dose of Ketoconazole	Increases the maximal Imatinib concentration in plasma and its plasma AUC by 26% and 40%, respectively, by increasing the serum concentration of Warfarin ([11]. page 826) and increasing the plasma concentration of Imatinib ([11]. page 826) ([12]. page 1733)
	Rifampin	Co-administration lowers the plasma Imatinib AUC by 70% ([12]. page 1733)
Irinotecan	Prior Atropinisation	Suppresses cholinergic effects ([10]. page 867)
Mercaptopurine	Oral antibiotics or food	Decrease absorption ([12]. page 1702)
	High dose Methotrexate	Oral bioavailability increases ([12]. Page 1702)
Methotrexate	Folinic acid THF and Thymidine Folic acid (administered IV or IM 8-24h after initiation of Methotrexate) Folic acid (folic acid rescue)	Rapidly reverses the toxic effects of Methotrexate ([9]. Page 560, [10]. page 862, [11]. Page 818) Permits much higher doses of Mtx and has enlarged its scope to many difficult-to-treat neoplasms ([10]. page 863 and 876)
	Salicylates, Sulfonamides, Penicillin, Aspirin and Probenecid	Inhibit the renal tubular secretion of methotrexate from plasma protein binding sites ([9]. page 560)
	Ketoprofen and other NSAID	Prolonged and striking elevation of plasma Methotrexate level ([11]. page 818)

for substrates including drugs, food, and herbal supplements. Inducers and inhibitors of CYP enzymes can modify the action of specific substrates for these enzymes [13]. Drug interactions with metabolising enzymes can be either activation or inhibitory reactions. As a result, combining an enzyme-inducing product with a substrate for the same enzyme mechanism leads to an increase in metabolism and, as a result, a decrease in blood levels. Substances that interfere with CYP metabolism raise serum concentrations of the enzyme substrates that are inhibited. Furthermore, because both medications are substrates of the same enzyme, they will reversibly inhibit each other [14]. The probable interaction of Warfarin and Tamoxifen via CYP3A4 is a good example of pharmacokinetic drug interactions at the level of metabolism. Imatinib, which is a CYP3A4 enzyme inhibitor, has been documented to increase the levels of simvastatin. Imatinib has also been shown to increase metoprolol AUC levels through the inhibition of the enzyme CYP2D6. Likewise, Gefitinib can also increase metoprolol and other CYP2D6 substrates plasma AUC levels [15].

Excretion

In addition to its function in the absorption of intestinal drugs, ABCB1 also plays a major role in the kidney during excretion. Because ABCB1 is involved in tubular filtration of drug metabolites in proximal renal tubules, inhibition or activation of ABCB1 can affect the excretion of pharmaceuticals that are ABCB1 substrates [16]. ATP-binding cassette subfamily G member 2 (ABCG2), also known as Breast Cancer Resistance Protein (BCRP) and CDw338, is a membrane-associated protein that transports various chemicals across cell membranes. ABCG2 inhibitors and activators are also linked to DDIs. Drug absorption and efflux require transport systems in the stomach, liver, and kidney. The transport mechanism relies on organic anion transport transporters (OAT) and organic anion transport polypeptides (OATP). OAT1 is a transmembrane protein present in proximal renal tubular cells and other organs. It is essential for the transfer of renal organic anion, which is a crucial step in the renal excretion of a wide range of drugs. On the other hand, OATPs have a similar role in the liver. Furthermore, OATPs are found in a variety of tissues and interact with anti-cancer drugs such as TKIs, Chlorambucil, Mitoxantrone, Vinblastine, Vincristine, Paclitaxel, and Etoposid [17]. In specific, Pazopanib and Nilotinib are inhibited by the hepatic OATP-1B1 transporter protein system. Therefore, the concomitant use of these TKIs with compounds such as Cilostazol and Digitalis [18]. Non-steroidal anti-inflammatory drugs (NSAIDs) such

as Acetylsalicylic Acid, Ibuprofen, Ketoprofen and Indomethacin may reduce methotrexate excretion by inhibiting OAT-mediated proximal renal tubule transport, which may further increase the risk of DDIs and life-threatening toxicities associated with Methotrexate [19].

Pharmacodynamic Drug Interactions

Pharmacodynamic interactions can occur when two or more drugs have mechanisms of action that result in the same physiological outcome. Pharmacodynamic interactions are classified as synergistic (when the effect of two medicines is greater than the sum of their individual effects), antagonistic (when the effect of two medicines is less than the sum of their individual effects), additive (when the effect of two medicines is simply the sum of their individual effects), and sequence-dependent (if the order in which two medicines are administered). While pharmacodynamic interactions are fairly common in clinical practice, adverse effects can generally be minimised if the interactions are predicted and adequate countermeasures are taken.

Synergistic Interactions

For years, pharmacodynamic interactions for medicinal advantage in oncology (combination chemotherapy) have been used. Increased cytotoxic activity may result in synergistic effects and result in better clinical reaction. Leucovorin, for example, is well known for increasing 5-FU activity in the treatment of colorectal cancer by stabilising the 5-FU and thymidylate synthase (TS) complexes [20]. However, it is important to remember that synergistic interactions can amplify negative effects. Although leucovorin is often used as a modulator to boost the anti-tumor activity of 5-FU, it may also increase 5-FU toxicity.

Antagonistic Interactions

When corticosteroids and interleukin 2 are given together, they have an antagonistic association (IL2). Clinical investigations examining the use of the corticosteroid dexamethasone in patients receiving IL2 immunotherapy discovered that they could tolerate a higher dose of IL2, but the toxicity was significantly reduced. In addition, animal studies have shown that the in vivo anti-tumor activity of IL22 has been abrogated by providing steroids to tumor bearing mice [21]. Corticosteroids and interleukin 2 have an antagonistic relationship when taken jointly (IL2). Clinical trials exploring the use of the corticosteroid dexamethasone in patients receiving IL2 immunotherapy revealed that they were able to tolerate a larger dose of IL2 while experiencing much less toxicity.

Additive Interactions

There have been numerous additive pharmacodynamic interactions mentioned. Simultaneous administration of Trastuzumab and Doxorubicin has been reported in clinical trials to raise the risk of heart toxicity in patients with metastatic breast cancer as compared with Trastuzumab alone. Increased renal toxicity has been found when cisplatin is used with other nephrotoxic drugs such as aminoglycosides, Amphotericin B, and Rituximab. Vinorelbine has been related to new or worsening neuropathy in patients who have had or are currently receiving paclitaxel, while the underlying additive impact that causes neuropathy is unknown. These data point to the likelihood of combination vinorelbine and paclitaxel neurotoxicity. Paclitaxel treatment can cause latent neuronal damage, which is only clinically apparent after vinorelbine therapy [22].

Sequence- or Schedule-Dependent Interactions

When paclitaxel is injected before carboplatin, an advantageous sequence-dependent pharmacodynamic association has been found that results in reduced thrombocytopenia relative to carboplatin alone. The immediate influence of paclitaxel on platelets is a proposed hypothesis. Paclitaxel specifically binds to tubulin and is abundant in platelets high in tubulin. Inhibition of tubulin mediated paclitaxel platelet activation or compromised clearance via the reticuloendothelial system will extend platelet lifespan. Paclitaxel can reduce the toxicity of carboplatin to megakaryocytic or megakaryocytic precursors in the bone marrow. Paclitaxel appears to be safe for colony-forming megakaryocytic units in vitro [23].

Clinical research suggests that when Paclitaxel is delivered before an Anthracycline, a sequenced and schedule-dependent mixed pharmacokinetic and pharmacodynamic association is observed and this could impact the cardio toxicity of the mixture. The pharmacokinetics and pharmacodynamic of paclitaxel while used in conjunction with Doxorubicin have also been tested in many trials [24]. However, these studies regularly show a rise in the peak concentration of Doxorubicin with no impact on the pharmacokinetics of paclitaxel, irrespective of the sequence of administration or length of infusion. Taken together, they form the base of existing clinical guidelines for Doxorubicin administration.

Pharmaceutical Drug Interaction

This occurs before the drug is administered into the body when chemically incompatible drugs are mixed together leading to change in physiochemical property of the drug which may cause inactivation of

active-ingredient or increase the toxicity and reducing the efficacy of the drugs. Phenobarbital when mixed with opioid analgesics results in inactivation of the drugs. This is a good example of incompatibility reaction [25, 26].

DISCUSSION

Many medications exhibit clinically important medication interactions for the researcher, clinician and patient, which pose a therapeutic risk. In consideration of the high incidence of use and possible risks that may arise from concomitant administration of anticancer agents, physicians may include an evaluation of the use of herbal remedies before taking drug histories. This is especially significant because many people don't think it's necessary to tell their doctor about their usage of over-the-counter medications and herbal supplements. Multiple cytotoxic drugs, medicine to minimize side effects, and medicine for co-morbid disorders (such as cardiovascular disease, gastrointestinal diseases, diabetes, and respiratory disease) are all available to cancer patients as part of their treatment. Because cytotoxic medicines have a narrow therapeutic index, even a little increase or decrease in cytotoxic activity produced by a drug interaction could result in increased toxicity or reduced efficacy. The majority of the time, this merely entails monitoring biological or clinical indicators. The prescribing physician may benefit from working with a clinical pharmacist. Via improved understanding of the potential for drug reactions, by administering adequate drugs and screening for signs of an interaction, clinicians can mitigate these threats. Examples of DDI'S of anticancer drugs were listed in Table 1.

CONCLUSION

Drug interaction knowledge must be transmitted to physicians, consultants, and other health-care workers via print and electronic media. Medical education courses should be held on a regular basis. Clinical investigations are required to know the actual consequence of the DDIs. Our ability to utilize the information from DDIs to cancer therapies has lacked significantly. Pharmacists must be in charge of monitoring for drug interactions and informing physicians and patients of any potential issues. There are still many issues to be investigated about real impact of DDI s in oncology. For that large representative studies are required.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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