Review Article

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Common Drug-Drug and Drug-Food Interactions in Antineoplastic Agents: A short update review

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ABSTRACT

Cancer treatment regimens often combine chemotherapeutics, supportive therapies, and medications for comorbidities, increasing the risk of drug-drug (DDIs) and drug-food interactions (DFIs). These interactions can alter the pharmacokinetics and pharmacodynamics of anticancer agents, potentially leading to treatment failure, severe adverse events, or hospitalization. Elderly patients, polypharmacy, and the narrow therapeutic index of many chemotherapeutics further compound these challenges. This review explores the mechanisms underlying DDIs and DFIs, focusing on absorption, metabolism, and transport protein modulation—key processes influencing drug bioavailability and toxicity in oncology. Clinically relevant examples are provided to illustrate these interactions. The review underscores the critical role of pharmacy services in identifying, preventing, and managing these interactions, offering actionable strategies to enhance patient safety and treatment efficacy. By addressing these interactions, healthcare providers can mitigate risks, improve therapeutic outcomes, and enhance the quality of life for cancer patients.

Keywords: Drug-Drug interaction, Food-Drug interaction, Oncology, Antineoplastics, Interactions

1. Introduction

Cancer treatment regimens are increasingly complex, incorporating a combination of chemotherapeutic agents, targeted therapies, immunotherapies, supportive medications, and medications for comorbid conditions [1]. In oncology, the efficacy and safety of cancer therapies are often compromised by DDIs and DFIs. Effective management of these interactions is essential for achieving favorable patient outcomes, given that many anticancer agents possess narrow therapeutic indices, where minor fluctuations in drug concentrations can result in significant toxicity or therapeutic failure [2,3].

The oncology population is particularly susceptible to DDIs and DFIs due to various factors, including polypharmacy, the narrow therapeutic index of anticancer agents, advanced age and comorbidities, altered pharmacokinetics, the use of dietary supplements and herbal products, enzyme and transporter interactions, immune system modulation, changes in nutritional status and food interactions, genetic variability, complex treatment regimens, the use of supportive care medications, and the presence of renal or hepatic impairment [4,5]. A significant proportion of cancer patients are elderly, making them more susceptible to comorbidities that necessitate concurrent medications. This situation often results in polypharmacy and an elevated risk of DDIs [4]. Chemotherapeutic agents, as well as newer targeted therapies and immunotherapies, often require specific metabolic pathways for activation or elimination. Interference in these pathways—whether due to other drugs, dietary components, or patient characteristics—can lead to altered drug levels. For example, interactions involving medications that inhibit cytochrome P450 enzymes (e.g., CYP3A4) or induce drug transport proteins (e.g., P-glycoprotein) are particularly critical in cancer care due to the limited margin for dosing errors [6]. Pharmacodynamic interactions can also significantly impact cancer treatment outcomes, encompassing therapeutic efficacy, patient survival, and overall quality of life [7]. The integration of particular cancer medicines with additional pharmaceuticals may heighten risks such as cardiotoxicity [8], immunosuppression [9], or gastrointestinal toxicity, resulting in dose reductions, treatment delays, or cessation of therapy. The simultaneous administration of anthracyclines and trastuzumab has been linked to heightened cardiotoxicity, perhaps requiring vigilant monitoring, dosage modifications, or the consideration of other treatments to avert serious cardiac problems [10].

Dietary supplements, often used by cancer patients for their perceived health benefits, further complicate the interaction landscape. The quality of these supplements can vary significantly due to differences in manufacturing processes, lack of standardization, and potential contamination [11]. For example, the concentration of active compounds in garlic or ginseng supplements may differ widely between brands, leading to unpredictable effects on drug metabolism. This variability underscores the need for healthcare providers to carefully evaluate the use of dietary supplements in cancer patients [12].

Given these challenges, managing drug interactions in oncology is crucial. Neglecting to recognize and address these interactions heightens the likelihood of adverse events and may undermine the efficacy of cancer treatments, thereby affecting patient survival and quality of life. Hospitals, clinics, and physicians utilize specialized drug interaction databases and clinical decision support systems (CDSS) to detect and manage drug-drug and drug-food interactions. Prominent systems encompass Lexicomp, Micromedex, and Stockley's medication Interactions, offering comprehensive medication interaction studies and evidence-based guidance for healthcare practitioners. Numerous electronic health record (EHR) systems incorporate tools such as First Databank (FDB) and Medi-Span to provide real-time notifications on potential interactions. Moreover, UpToDate and Epocrates provide extensive clinical guidelines in conjunction with drug interaction information, rendering them indispensable for medical decision-making. Databases like the FDA Drug Interactions Database, the European Medicines Agency (EMA) Guide, and the National Library of Medicine (NLM) Drug Portal offer regulatory and public health insights, granting access to official drug safety information and enabling clinicians to remain informed about emerging risks and guidelines [13]. This review examines the various drug-drug and drug-food interactions associated with chemotherapy, the mechanisms underlying these interactions, common examples, and clinical strategies for their prevention and management.

2. Antineoplastic Agents

Chemotherapeutic agents are essential in cancer treatment and often necessitate hospital adminis-

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tration due to their potency, complex preparation requirements, and the need for close monitoring to manage potential adverse effects [6]. These agents can be broadly categorized into conventional chemotherapy and newer targeted therapies and immunotherapies, each with distinct mechanisms of action, indications, and toxicity profiles.

Alkylating agents disrupt DNA replication by crosslinking strands and causing DNA breaks, effectively targeting rapidly dividing cells and debulking tumors to make resting cells susceptible to cell cycle-specific agents [14]. They are used in treating lymphomas, Hodgkin's disease, breast cancer, and multiple myeloma [15,16]. These drugs are typically administered intravenously in hospitals to control their high toxicity and interaction potential, particularly with other drugs that influence liver enzymes, such as CYP3A4 [17]. Hypersensitivity reactions to alkylating agents are well-documented, particularly with platinum-based compounds such as Carboplatin, Oxaliplatin, and Cisplatin, which can trigger IgE-mediated or delayed-type hypersensitivity reactions, especially after repeated exposure [18].

Antimetabolites act as false metabolites, disrupting DNA and RNA synthesis, primarily targeting the S phase of the cell cycle and proving effective against fast-growing tumors [9]. They mainly affect the hematopoietic and gastrointestinal systems, with examples including Methotrexate and 5-Fluorouracil. Hypomethylating agents, like 5-azacytidine, restore normal gene function in cell division [19]. While some antimetabolites can be taken orally (e.g., low-dose methotrexate), higher doses are typically administered intravenously under close supervision, as they can impair kidney function, reducing drug clearance and leading to rapid accumulation in serum and tissues, thereby increasing the risk of severe toxicity. Additionally, these effects can be exacerbated by interactions with nonsteroidal anti-inflammatory drugs and certain antibiotics, which may further reduce renal elimination and potentiate toxic effects [20].

Antitumor antibiotics, known as anthracyclines, interfere with RNA and DNA synthesis and exhibit cell-cycle non-specificity. Their primary effects impact the hematopoietic, gastrointestinal, cardiac, and reproductive systems, with a particularly high risk of cardiac toxicity in patients with preexisting heart conditions. Examples include Bleomycin, Daunorubicin, and Doxorubicin [21].

Topoisomerase I (TOP I) inhibitors, such as irinotecan and topotecan, function by preventing TOP I from disengaging from the cleavable complex, resulting in the formation of a ternary complex that halts relegation. Irinotecan is primarily prescribed for cancers like colorectal, cervical, esophageal, sarcoma, pancreatic, and lung [22], whereas topotecan is used in the treatment of cervical, ovarian, and small-cell lung cancers. Irinotecan's main toxicity is diarrhea, while topotecan's dose-limiting effects are neutropenia and thrombocytopenia [23].

Taxanes, including paclitaxel, docetaxel, and cabazitaxel, impair the balance between microtubule polymerization and depolymerization, disrupting cell function and replication and eventually inducing apoptosis [24]. These agents target microtubule assembly and act during the M phase of the cell cycle. Indications include breast, lung, prostate, ovarian, cervical cancers, and sarcoma for docetaxel; breast, lung, and ovarian cancers for paclitaxel [25] (including its protein-bound formulation, Abraxane); and prostate cancer for cabazitaxel. Common adverse effects include hypersensitivity, myelosuppression, and peripheral neuropathy [26].

Vinca alkaloids, such as vinblastine, vincristine, and vinorelbine, bind to tubulin, blocking microtubule assembly and causing cells to arrest in metaphase during the M phase. Vincristine is commonly used to treat acute lymphoblastic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, and small-cell lung cancer [27]. Peripheral neuropathy, affecting both motor and sensory functions, along with myelosuppression, are the primary toxicities associated with these agents [28].

Hydroxyurea targets ribonucleoside diphosphate reductase and exerts its effects during the S phase of the cell cycle. It is indicated for acute myeloid leukemia, chronic myeloid leukemia, and sickle cell disease, with key toxicities including myelosuppression and dermatologic reactions [29]. Tretinoin, a derivative of vitamin A, activates the RAR-α receptor to promote cell differentiation and is utilized in acute promyelocytic leukemia (APL) treatment. APL differentiation syndrome, characterized by fever and cardiopulmonary complications, is a notable toxicity of tretinoin [30]. Arsenic trioxide facilitates cell differentiation and is also used to treat APL. Its associated toxicities include QT prolongation, necessitating regular EKG monitoring, electrolyte replace-

ment (potassium and magnesium), and management of APL differentiation syndrome [31]. Proteasome inhibitors, such as bortezomib, are used to treat multiple myeloma, with peripheral neuropathy being a primary adverse effect [32].

In recent years, the development of targeted therapies and immunotherapies has revolutionized cancer treatment [33]. These agents are designed to specifically target molecular pathways involved in cancer growth or to harness the immune system to fight cancer, offering improved efficacy and reduced toxicity compared to conventional chemotherapy [34].

Targeted therapies include small-molecule inhibitors and monoclonal antibodies that interfere with specific molecules involved in tumor growth and progression [35].

Tyrosine kinase inhibitors (TKIs), are a class of targeted cancer therapies that specifically inhibit the activity of tyrosine kinases, including receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases. These enzymes play a critical role in cell signaling pathways that regulate growth, survival, and metabolism. In cancer, tyrosine kinases are often dysregulated due to mutations, overexpression, or amplification, leading to uncontrolled cell proliferation and survival. TKIs block these aberrant signaling pathways, making them effective in treating various cancers [36]. Agents like imatinib, erlotinib, and osimertinib target specific tyrosine kinases involved in cancer cell signaling. For instance, imatinib is used in chronic myeloid leukemia, while osimertinib is effective in non-small cell lung cancer with EGFR mutations [37].

Monoclonal Antibodies (mAbs) Against RTKs, are highly specific biologic agents that target RTKs on the cell surface, preventing ligand binding and receptor activation. By blocking RTK signaling, these antibodies inhibit tumor growth and progression. Additionally, some mAbs can trigger immune-mediated destruction of cancer cells through antibody-dependent cellular cytotoxicity [36]. For instance, trastuzumab (Herceptin) targets HER2 in HER2-positive breast and gastric cancers, disrupting downstream signaling and promoting tumor cell apoptosis [38]. Similarly, cetuximab (Erbitux) inhibits EGFR activity in colorectal and head & neck cancers, reducing tumor proliferation [39]. Another key mAb, bevacizumab (Avastin), functions by neutralizing vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis and limiting the tumor's ability to establish a blood supply [40]. These targeted therapies offer a more precise approach to cancer treatment, reducing systemic toxicity compared to traditional chemotherapy.

Antibody-drug conjugates (ADCs) represent an innovative therapeutic approach that combines the specificity of monoclonal antibodies with the cytotoxic power of chemotherapy. ADCs are designed to selectively deliver chemotherapy agents to cancer cells expressing RTKs, thereby maximizing drug efficacy while minimizing systemic side effects [41]. A prime example is trastuzumab deruxtecan (Enhertu), an ADC that targets HER2-positive tumors and delivers a potent chemotherapy payload directly to the cancer cells [42]. Similarly, brentuximab vedotin is used to treat Hodgkin's lymphoma by binding to CD30 on lymphoma cells and releasing its cytotoxic agent upon internalization [43]. By selectively targeting tumor cells, ADCs improve treatment precision, reduce off-target toxicity, and are particularly effective in patients with resistance to traditional monoclonal antibody therapies [41].

Poly ADP-Ribose Polymerase inhibitors (PARP): are a class of targeted cancer therapies that exploit the concept of synthetic lethality to selectively kill cancer cells with defects in DNA repair mechanisms, particularly those with mutations in the BRCA1 or BRCA2 genes PARP is an enzyme involved in the repair of single-strand DNA breaks (SSBs) through the base excision repair (BER) pathway [44].. Drugs like olaparib and rucaparib are used in cancers with BRCA mutations, such as ovarian and breast cancer, by inhibiting DNA repair mechanisms in cancer cells [45,46].

Angiogenesis inhibitors: are a class of drugs that target the formation of new blood vessels (angiogenesis), which is essential for tumor growth and metastasis [47]. Tumors require a blood supply to deliver oxygen and nutrients, and angiogenesis inhibitors disrupt this process, effectively "starving" the tumor. Bevacizumab, a monoclonal antibody targeting VEGF, is used in colorectal, lung, and renal cancers to inhibit tumor blood supply [48].

Immune checkpoint inhibitors: are a groundbreaking class of cancer immunotherapy drugs that enhance the body's immune response against tumors. They work by blocking immune checkpoint proteins, which are molecules that regulate the immune sys-

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tem and prevent it from attacking normal cells [49]. Cancer cells often exploit these checkpoints to evade immune detection. By inhibiting these checkpoints, immune checkpoint inhibitors "release the brakes" on the immune system, allowing it to recognize and destroy cancer cells [50]. Agents like pembrolizumab and nivolumab block immune checkpoint proteins (e.g., PD-1, CTLA-4), enabling T cells to recognize and attack cancer cells. These drugs are used in melanoma, lung cancer, and other malignancies [51].

Chimeric antigen receptors (CAR) -T cell therapy: A form of adoptive cell therapy where T cells are genetically engineered to express CARs targeting specific cancer antigens [52]. CAR-T therapy has shown remarkable success in hematologic malignancies like acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) [53].

While targeted therapies and immunotherapies offer significant advantages, they are not without risks. Targeted therapies can cause off-target effects, such as skin rashes, hypertension, or cardiac toxicity [54], while immunotherapies may lead to immune-related adverse events, including colitis, hepatitis, and pneumonitis [55].

Chemotherapy agents can be administered orally, intravenously, subcutaneously, intramuscularly, or intrathecally, with intravenously administration being the most common due to its 100% absorption rate [6]. Some drugs, such as paclitaxel, have poor solubility and require solvents like cremophor to enhance absorption [56]. Chemotherapeutics are primarily metabolized and excreted by the liver or kidneys, with some drugs posing toxicity risks to these organs [57]. In liver or kidney dysfunction cases, dose adjustments are critical to prevent toxic accumulation, as with capecitabine in renal disease [58]. Most chemotherapy dosing is based on body surface area, and DDIs are common. Body surface area (BSA) is used in chemotherapy dosing because it provides a more consistent measure of drug metabolism and toxicity across species and individuals compared to body weight (BW). Early studies found that BSA correlates with physiological parameters like basal metabolic rate, blood volume, and renal function, making it a practical metric for drug dosing. Research by Pinkel and Freireich demonstrated that cytotoxic drug doses, when adjusted for BSA, showed similar toxicity levels across mammals, whereas doses based on BW varied widely [59]. Although BSA dosing has limitations—such as inaccuracies in BSA estimation, lack of accounting for individual variability, and challenges in obese or cachectic patients—it became a standard approach due to its historical validation and simplicity. However, modern insights suggest that BSA may not be the optimal dosing strategy today, as it fails to account for many factors influencing drug disposition, prompting the exploration of alternative methods for dose individualization [60].

3. Drug-Food Interactions

Foods, beverages, and dietary supplements can significantly influence the pharmacokinetics and pharmacodynamics of anticancer medications, leading to altered drug absorption, metabolism, distribution, and excretion [61]. These interactions, known as DFIs, can compromise the efficacy and safety of chemotherapy, particularly given the narrow therapeutic index of many anticancer agents [62]. Pharmacokinetic interactions, the most common type of DFIs, primarily occur through mechanisms such as enzyme inhibition or induction, where certain foods or supplements can inhibit or induce CYP450 enzymes (e.g., CYP3A4) or drug transporters (e.g., P-glycoprotein), altering drug metabolism and bioavailability [63]. Additionally, foods can affect gastric pH, motility, or the solubility of drugs, influencing their absorption [64]. For example, high-fat meals can increase the absorption of oral tyrosine kinase inhibitors like lapatinib, while acidic beverages may alter the solubility of certain drugs [65]. Furthermore, components of food or supplements may compete with drugs for binding sites on plasma proteins or transporters, affecting drug distribution. These changes can critically impact drug bioavailability, which is essential in chemotherapy as sustained exposure to cytotoxic agents is necessary for their antineoplastic action [63].

Responses to DFIs vary widely among patients due to genetic differences in enzyme systems, dietary habits, and the quality of dietary supplements. While approximately 40% of DFIs show low or no severity, 50% are moderate, and fewer than 10% are severe [66]. The variability in dietary supplement quality—due to differences in manufacturing processes, lack of standardization, and potential contamination—further complicates the prediction and management of DFIs [11].

The study of DFIs was revolutionized by the accidental discovery of the grapefruit juice-felodipine interaction in the early 1990s. This interaction led to a 2.8-fold increase in the oral bioavailability of felodipine, a calcium channel blocker, due to grapefruit juice's inhibition of CYP3A4 in the small intestine [67]. This landmark finding highlighted the potential for common foods to significantly alter drug metabolism and spurred further research into DFIs. Grapefruit juice has since become one of the most well-studied examples of DFIs, known for its ability to inhibit both CYP3A4 and organic anion-transporting polypeptides, leading to increased plasma concentrations of drugs metabolized by these pathways [68]. For instance, a study involving 21 healthy volunteers demonstrated that grapefruit juice raised the peak concentration of nilotinib (a tyrosine kinase inhibitor) by 60% and its area under the curve by 29% [69]. Similarly, a case report described a patient with esophageal squamous cell carcinoma who experienced slower docetaxel clearance when consuming grapefruit juice, with plasma clearance rates dropping from 36.7 L/h to 13.2 L/h. After discontinuing grapefruit juice, docetaxel's AUC increased by 60%, and its half-life decreased by 10% [70]. These findings underscore the profound impact of grapefruit juice on drug pharmacokinetics and its clinical relevance in cancer therapy.

Garlic, commonly used for its antimicrobial and immune-stimulating properties, can interact with chemotherapy drugs. High-dose garlic supplements (rather than dietary garlic) are more likely to cause interactions [71]. For instance: In a study of women with metastatic breast cancer, 12-day garlic supplementation reduced docetaxel clearance by 36%, potentially increasing toxicity risks due to drug accumulation.Garlic has been shown to inhibit CYP2E1 and CYP3A4 in vitro, though its effects on intestinal P-glycoprotein are less consistent [72].

Panax ginseng, often used by cancer patients for its immune-boosting properties, has been reported to both inhibit and induce CYP enzymes (e.g., CYP3A4, CYP2C19) and P-glycoprotein, leading to variable effects on drug metabolism [73]. A notable case involved a chronic myeloid leukemia patient on imatinib who developed hepatotoxicity after consuming a ginseng-based energy drink for three months. Upon discontinuation of ginseng, liver enzyme levels normalized, suggesting a CYP3A4-mediated interaction, though the potential for enzyme induction in long-term users remains a concern [74]. Additionally, ginseng has been associated with an increased bleeding risk due to its effects on platelet aggregation and thromboxane formation. This effect is particularly concerning in cancer patients receiving anticoagulants or antiplatelet therapy, where concurrent ginseng use could potentiate hemorrhagic complications [75]. Given the variability in ginsenoside content across different commercial preparations of ginseng, interaction potential may differ between formulations. More clinical studies are needed to establish standardized recommendations for ginseng use in oncology patients.

Echinacea, commonly used among cancer patients as an immunomodulatory supplement, has significant herb-drug interactions due to its dual ability to inhibit and induce CYP3A4 and P-glycoprotein, leading to variable effects on drug metabolism [76]. While some studies indicate that echinacea can increase drug clearance, others suggest minimal or no impact on certain chemotherapeutics [67]. For instance, echinacea increased midazolam clearance by 34%, indicating a potential inductive effect on CYP enzymes [77], yet in a study of 10 cancer patients, no significant pharmacokinetic alterations were observed with docetaxel. However, a case report highlighted a clinically significant interaction with etoposide, where echinacea-induced CYP inhibition led to drug accumulation and severe thrombocytopenia, requiring a platelet transfusion [78]. The variability in echinacea's pharmacological effects may stem from differences in species (e.g., Echinacea purpurea vs. Echinacea angustifolia), plant extracts, and patient-specific metabolism. Given these unpredictable effects, caution is warranted when using echinacea alongside anticancer drugs, particularly those with narrow therapeutic indices or significant hematologic toxicities [78].

St. John's wort is a potent inducer of CYP3A4, CYP2C19, and P-glycoprotein, significantly reducing the plasma concentrations of many drugs, including chemotherapeutic agents [79]. This induction accelerates drug metabolism, leading to lower systemic exposure and reduced efficacy of anticancer treatments. In a study involving 10 cancer patients, St. John's wort decreased the area under the curve of docetaxel by 12% and increased its clearance by 14%, suggesting a potential reduction in therapeutic effectiveness [80]. Similarly, in another study, St. John's wort reduced the active metabolite of irinotecan (SN-38) by

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42%, which lowered myelosuppressive effects but also raised concerns about compromised anticancer activity [81]. These interactions are clinically significant, as they may lead to suboptimal chemotherapy outcomes and increase the risk of treatment failure. Given its strong enzyme-inducing properties, St. John's wort should be avoided in cancer patients undergoing chemotherapy, particularly those receiving irinotecan, taxanes, or tyrosine kinase inhibitors [82], where maintaining precise drug levels is critical for therapeutic success.

Milk thistle, widely used among cancer patients for its purported hepatoprotective and anticancer properties, contains silymarin, a bioactive compound known to interact with drug-metabolizing enzymes [83]. Silymarin and its active component, silibinin, are reported to inhibit CYP enzymes, particularly CYP2C9, which can reduce the metabolism of drugs such as losartan, potentially leading to increased drug concentrations and prolonged effects [84]. However, the clinical significance of these interactions remains variable. A study in six cancer patients found that 12-day milk thistle supplementation had no significant impact on irinotecan's pharmacokinetics, a CYP3A4 substrate, suggesting that at typical doses, its interaction potential with chemotherapy may be weak. Despite this, concerns remain due to significant variations in the composition of commercial milk thistle supplements, which may affect their pharmacological properties and interaction potential [83]. Given this variability, cancer patients taking milk thistle alongside CYP2C9-metabolized drugs (such as certain anticoagulants, NSAIDs, and chemotherapeutics) should exercise caution and consult healthcare providers to avoid potential alterations in drug efficacy and toxicity.

The variability in dietary supplement quality—due to differences in manufacturing processes, lack of standardization, and potential contamination—poses significant challenges in predicting and managing DFIs. For example, the concentration of active compounds in garlic or ginseng supplements can vary widely between brands, leading to unpredictable effects on drug metabolism. Healthcare providers should; educate patients about the risks of consuming certain foods or supplements during chemotherapy, monitor patients for signs of DFIs, such as unexpected toxicity or reduced drug efficacy and consider the source and quality of supplements when assessing potential interactions.

4. Drug-Drug Interactions

In oncology, DDIs occur when one drug affects the pharmacokinetics or pharmacodynamics of another concurrently administered drug, leading to modified therapeutic effects, increased toxicity, or reduced efficacy [85]. Chemotherapy patients are particularly susceptible to DDIs due to the extensive range of prescribed medications, including supportive agents (e.g., antiemetics, corticosteroids) and treatments for comorbidities (e.g., anticoagulants, antihypertensives) [4]. A recent study by Koni et al. [3] highlighted the high prevalence of DDIs, with 88.1% of oncology patients experiencing at least one potential interaction. Most DDIs were moderate in severity, with 11.1% requiring therapy adjustments, and a smaller subset (2.6%) classified as high-risk, such as the combination of aprepitant and doxorubicin, which should be avoided due to significant toxicity risks.

Absorption-related DDIs are particularly relevant for orally administered anticancer drugs. Acid-reducing agents, such as proton pump inhibitors, increase stomach pH, reducing the solubility and bioavailability of certain drugs, especially TKIs. For example, the oral bioavailability of erlotinib, gefitinib, and dasatinib is significantly reduced when co-administered with PPIs or H2-antagonists [86]. Inhibition of drug transporters (e.g., P-glycoprotein) and intestinal enzymes (e.g., CYP3A4) can also alter systemic drug exposure, impacting therapeutic effectiveness [87].

Distribution-related DDIs occur when multiple highly plasma protein-bound drugs are used simultaneously, leading to the displacement of one drug from its binding site (e.g., albumin). This increases the pharmacologically active unbound fraction of the displaced drug. However, clinically significant DDIs from protein-binding displacement remain rare in oncology [88].

Metabolism-related DDIs are the most common in cancer therapy due to the role of the CYP450 enzyme system in drug metabolism. Drugs like rifampicin can accelerate the metabolism of anticancer agents, reducing their plasma concentrations and efficacy. For instance, rifampicin reduces the exposure of imatinib, potentially compromising its therapeutic effect [89]. However, drugs like ketoconazole can inhibit CYP enzymes, increasing the plasma concentrations of certain anticancer drugs and raising tox-

icity risks. For example, ketoconazole increases the exposure of vincristine, leading to an elevated risk of neurotoxicity [90]. Some anticancer drugs, such as tamoxifen, require CYP-mediated activation. CYP inhibition (e.g., by paroxetine) can impair this activation, reducing therapeutic efficacy [91].

Excretion-related DDIs are less common because most anticancer drugs undergo hepatic metabolism rather than renal excretion. However, nephrotoxic co-medications (e.g., aminoglycosides) may impair renal function, affecting the clearance of renally excreted agents like methotrexate and cisplatin [92].

PARP Inhibitors (e.g., olaparib, rucaparib); These agents are metabolized by CYP3A4 and are susceptible to interactions with CYP3A4 inhibitors (e.g., fluconazole) or inducers (e.g., rifampicin). For example, fluconazole can increase olaparib exposure, raising the risk of toxicity [93].

CDK4/6 Inhibitors (e.g., palbociclib, ribociclib); These drugs are also metabolized by CYP3A4. Co-administration with CYP3A4 inhibitors (e.g., clarithromycin) can significantly increase their plasma concentrations, leading to severe neutropenia or QT prolongation [94]

Immune Checkpoint Inhibitors (e.g., pembrolizumab, nivolumab); These agents are less prone to pharmacokinetic DDIs but can interact pharmacodynamically with other drugs. For example, combining immune checkpoint inhibitors with corticosteroids may reduce their efficacy due to immunosuppression [95].

CAR-T Cell Therapy; While CAR-T cells are not metabolized by traditional pathways, concomitant use of tocilizumab (an IL-6 inhibitor) for managing cytokine release syndrome (CRS) can alter the immune response and potentially affect CAR-T cell efficacy [96].

The significant occurrence of DDIs in cancer underscores the urgent necessity for proactive management techniques to guarantee patient safety and therapeutic effectiveness. A highly effective method is regular DDI screening, employing drug interaction software like Lexicomp and Micromedex to detect and address potential interactions during treatment planning. Furthermore, patient education is essential in mitigating hazards, since several patients are oblivious to the fact that over-the-counter drugs, herbal supplements, and specific diets might considerably affect the efficacy of chemotherapy.

A further critical method is therapeutic drug monitoring (TDM), especially for medicines with narrow therapeutic indices like methotrexate, where little variations in plasma drug concentrations may result in significant toxicity or diminished efficacy. Moreover, interdisciplinary collaboration among pharmacists, oncologists, and other healthcare professionals [97] is essential for addressing intricate drug-drug interactions, particularly in patients undergoing novel targeted treatments or immunotherapies, where interactions may be inadequately documented.

Research continuously demonstrates a high prevalence of DDIs in oncology, with studies from India and Pakistan finding interaction rates of 88.9% and 92%, respectively—substantially higher than those found in other patient populations [2]. Research in Korea revealed a DDI rate of 63.2% among patients undergoing targeted treatments, in contrast to 21.2% in those administered standard chemotherapeutic drugs. Principal risk factors for DDIs encompass polypharmacy, advanced cancer stage, and the existence of comorbidities. Due to the intricacy of cancer treatment protocols, comprehensive screening, patient education, and collaborative management strategies are crucial for minimizing DDI-related problems and enhancing therapeutic outcomes [98].

Examples of the most common antineoplastic drug-drug interactions and the possible consequences are summarized in Table 1.

5. Conclusion

The management of DDIs and DFIs is a critical component of cancer care, given the complexity of modern treatment regimens and the narrow therapeutic index of many anticancer agents. Conventional chemotherapeutic agents, targeted therapies, and immunotherapies each present unique challenges in terms of pharmacokinetics, pharmacodynamics, and interaction potential. The high prevalence of DDIs and DFIs in oncology—ranging from moderate to severe—underscores the need for vigilant monitoring and proactive management to optimize therapeutic outcomes and minimize adverse effects.

Cancer patients, particularly the elderly, often require multiple medications for comorbid conditions, increasing the risk of DDIs. To mitigate this risk, healthcare providers should prioritize medication reconciliation, regularly reviewing and streamlining

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the patient's medication list to eliminate unnecessary drugs. Additionally, the use of drug interaction software, such as Lexicomp and Micromedex, can help identify potential DDIs and provide evidence-based recommendations. For absorption-related interactions, acid-reducing agents like proton pump inhibitors can reduce the bioavailability of orally administered TKIs. Strategies to address this include advising patients to take TKIs on an empty stomach or separating their doses from acid-suppressive medications by several hours. When possible, non-acid-suppressive options should be considered for managing gastrointestinal symptoms [99].

Metabolism-related interactions, particularly those involving the CYP450 enzyme system, are among the most common in cancer therapy. To manage these interactions, healthcare providers should avoid co-administering strong CYP inhibitors (e.g., ketoconazole) or inducers (e.g., rifampicin) with anticancer agents metabolized by CYP enzymes. Therapeutic drug monitoring can also play a crucial role in ensuring optimal dosing for agents with narrow therapeutic indices, such as imatinib and methotrexate. For excretion-related interactions, nephrotoxic co-medications can impair the clearance of renally excreted agents like cisplatin and methotrexate. Regular monitoring of renal function, adequate hydration, and supportive care measures are essential to prevent toxicity in these cases.

Dietary and herbal supplement interactions pose additional challenges due to the variability in supplement quality and their potential to alter drug metabolism. Patients should be educated about the risks of consuming certain foods (e.g., grapefruit juice) and supplements (e.g., garlic, ginseng) during chemotherapy. When supplement use is unavoidable, standardized, high-quality products should be recommended to minimize variability and potential interactions. Newer therapies, such as targeted therapies and immunotherapies, introduce new interaction risks. For example, immune checkpoint inhibitors should not be combined with immunosuppressive agents like corticosteroids unless absolutely necessary, as this may reduce their efficacy. Similarly,

Table 1. Most common DDIs and their possible results [2,100].

Potential DDIs	Potential outcomes
Cyclophosphamide + doxorubicin	Increased risk of cardiomyopathy
Cisplatin + furosemide	Increased risk of ototoxicity and nephrotoxicity of cisplatin.
Dexamethasone + doxorubicin	It reduced doxorubicin plasma concentrations.
Ondansetron + oxaliplatin	Prolong the QT interval.
Dexamethasone + vincristine	It decreased vincristine plasma concentration.
Doxorubicin + Dexamethasone	It reduced doxorubicin exposure.
Cyclophosphamide + Ondansetron	Decreased cyclophosphamide systemic exposure.
Allopurinol + Cyclophosphamide	Cyclophosphamide toxicity (bone marrow suppression, nausea, vomiting).
Ciprofloxacin + Doxorubicin	It increased doxorubicin exposure.
Fluorouracil + Leucovorin	Increased concentrations of 5-fluorouracil and fluorouracil toxicity (granulocytopenia, anemia, thrombocytopenia, stomatitis, vomiting).
Asparaginase + Vincristine	Increased vincristine exposure causes neurotoxicity.
Cisplatin + Docetaxel	Increased risk of neuropathy.
Methotrexate + Omeprazole	Increased concentration of methotrexate and its metabolite and an increased risk of methotrexate toxicity.
Cisplatin + Doxorubicin	Increased risk of Secondary malignancy, i.e., secondary leukemia.

PARP inhibitors and CDK4/6 inhibitors require careful monitoring for CYP3A4-mediated interactions, with dose adjustments as needed.

Effective management of DDIs and DFIs requires a multidisciplinary approach involving oncologists, pharmacists, nurses, and other healthcare providers. Routine DDI screening should be incorporated into the standard care process for all cancer patients, and patients should be actively engaged in discussions about their medications, dietary habits, and supplement use to identify potential interactions. Ongoing education for healthcare providers is also essential to keep them informed about emerging therapies and their interaction profiles.

As cancer treatment continues to evolve, with the development of novel targeted therapies and immunotherapies, the landscape of DDIs and DFIs will also change. Future research should focus on expanding and updating interaction databases to include newer agents, leveraging pharmacogenomics to predict individual patient risks, and collecting real-world evidence to better understand the clinical impact of interactions. By addressing DDIs and DFIs through evidence-based strategies, healthcare providers can enhance the safety and efficacy of cancer treatments, ultimately improving patient outcomes and quality of life. The integration of clinical pharmacy services, patient education, and multidisciplinary collaboration is essential to achieving this goal.

Conflict of Interest Statement:

The authors have no conflicts of interest, financial or otherwise, to declare.

Contribution of Researchers

S.S.; Literature review, Writing - T.B.; Conceptualization, Supervision, critical review.

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