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# Drug interactions in cancer treatment: a potential role for oncology pharmacists

Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents.

## Introduction

This short article cannot give a detailed understanding of special topics. It aims to give a wide overview of this area of interest and to invite pharmacists to include this into their work.

Patients with cancer are at particularly high risk of drug interactions as they are commonly given several drugs, including antineoplastics, hormonal and supportive drugs. The majority of cancer patients are elderly and require many different drugs for coexisting conditions such as cardiovascular, gastrointestinal and psychiatric disorders, so the adverse interaction rate increases among the elderly and those who take two or more drugs for the management of underlying illnesses [1]. The age-related decline in hepatic and renal function also reduces their ability to metabolise and eliminate drugs and increases the potential for toxicity. Improvements in laboratory analysis and early clinical testing have made the prediction of potentially clinically significant drug interactions possible but not all drug–drug interactions can be foreseen, and those that are predictable are not always inevitable. Nonetheless, awareness of the potential for these interactions means the risk can be minimised by selecting appropriate drugs and by monitoring for signs of interaction.

Drug interactions can be classified as pharmaceutical, pharmacokinetic, pharmacodynamic or a combination of mechanisms [2]. Although a drug–drug interaction is most commonly observed, various factors such as food, nutritional supplements, complementary alternative medicines and environmental factors can interact.

## Pharmaceutical interactions

Pharmaceutical interactions occur when two or more chemically or physically incompatible drugs are prepared in the same container prior to parenteral administration, resulting in the degradation of one or more drugs. For example, a covalent mesna-platinum adduct is formed by adding mesna, a thiol compound, to a cisplatin solution [3]. Other observations include the precipitation of etoposide and paclitaxel after dilution in infusion fluids at low pH, as well as the rapid inactivation of mitomycin to inactive mitosenes if the drug is reconstituted in pH 4–5 fluids such as 5% dextrose [4]. Check the compatibility of anticancer drugs before administering them.

## Pharmacokinetic interactions

Pharmacokinetic interactions arise when one drug affects the absorption, distribution, metabolism or elimination of another drug. For instance, drugs that inhibit the activity of drug-



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metabolising enzymes may effect the blood levels of other drugs. The classic illustration is a xanthine oxidase inhibitor, allopurinol, which can inhibit the oxidative catabolic conversion of 6-mercaptopurine and consequently increase its oral bioavailability dramatically [5]. In addition, drugs that increase or decrease gastrointestinal motility may have a major impact on the oral bioavailability of other drugs. Food–drug interactions can also occur and may affect the bioavailability of orally administered anticancer agents,

delaying, decreasing or increasing their absorption.

Following absorption, drug distribution to the target site is directed primarily by the blood supply and the binding properties of the drug to plasma proteins. Competition for plasma protein binding can modify drug distribution. If two concomitantly administered drugs rely on binding to a similar plasma protein, plasma levels of unbound (active) drug may increase. Anticancer agents such as paclitaxel and etoposide, which are recognised to be highly protein-bound, could hypothetically interact with other highly protein-bound drugs such as warfarin, which may be used to prevent or treat deep vein thrombosis in cancer patients [6].

Pharmacokinetic interactions most frequently occur via induction or inhibition of metabolising enzymes, mainly the cytochrome P450 (CYP) enzymes in the liver. Co-administration of an enzyme-inducing drug with a substrate for the identical enzyme system can result in increased metabolism, and consequently reduced serum concentrations of the substrate. Drugs that inhibit CYP metabolism can also increase serum concentrations of substrates for the inhibited enzyme. Anticancer drugs that are totally or partially metabolised by CYP enzymes include cyclophosphamide, taxanes, etoposide, irinotecan, aromatase inhibitors, tamoxifen, vinca alkaloids, bicalutamide, imatinib, gefitinib and erlotinib [7, 8].

Levels of drug-metabolising enzymes may vary between patients. Genetic polymorphisms have been documented for a number of CYP isoforms, including CYP2A6, CYP2D6, CYP2C9 and CYP2C19, so these must be borne in mind when assessing the risk of drug–drug interactions. For example, tamoxifen requires metabolic conversion by the CYP system into anti-oestrogenic metabolites, which are more potent than the parent compound. These include N-desmethyltamoxifen, formed by CYP3A4, and 4-hydroxytamoxifen and endoxifen, formed by CYP2D6. The inter-patient variability in the relative levels of these CYP isoforms

affects the efficacy of tamoxifen and has a tremendous effect on treatment outcomes in terms of toxicity, breast cancer recurrence and mortality [9].

Having undergone metabolism, most anticancer drugs are eliminated by the kidneys. Substances that change kidney or hepatic functions can interfere with the elimination of other agents and their metabolites. Some drugs either compete for active secretion, or modify the activity of membrane transporter proteins such as ABCB1 in the renal tubules. Concomitant administration of verapamil, an inhibitor of ABCB1 and vinblastine, an ABCB1 substrate in mice, results in increased concentrations of vinblastine and its metabolites within the liver and kidneys [10]. Gefitinib, a recognised ABC transporter inhibitor, could also interfere with the renal and/or biliary excretion of irinotecan and SN-38, which would result in increased plasma concentrations and toxicity [11]. Inhibitory effects on the organic anion transporter-mediated renal excretion by non-steroidal anti-inflammatory drugs and probenecid are likely to cause drug interactions with methotrexate that can result in a severe and even life-threatening bone marrow suppression and acute kidney injury [12].

### Pharmacodynamic drug interactions

Pharmacodynamic interactions generally result from co-administration of two or more drugs with similar mechanisms of action. Pharmacodynamic interactions can be broadly categorised as synergistic, antagonistic or additive [13]. Synergistic interactions occur when the effect of two drugs is greater than the sum of their individual effects. Synergistic effects can increase antitumour activity and may improve clinical outcome. Examples are CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for Non-Hodgkin's lymphoma and CAF (cyclophosphamide, doxorubicin, 5FU) for breast cancer. Combination regimens are frequently preferred to overcome resistance, minimise non-overlapping toxicity and maximise antitumour activity. Antagonistic interactions mean the effect of two drugs is less than the sum of their individual effects, as when corticosteroids are given with interleukin-2 [14]. Additive means the effect of two drugs is the sum



of the effects of each agent. Additive effects that increase renal toxicity have been observed when cisplatin is given with other nephrotoxic agents such as aminoglycosides and amphotericin B.

### An example: the right combination of treatments while minimising risks

A 42-year-old premenopausal female with stage II invasive ductal carcinoma of the left breast (ER/PR positive, HER2 gene amplified, nuclear grade 3) underwent modified radical mastectomy and axillary lymph node dissection. Subsequently, she received AC (doxorubicin + cyclophosphamide) x 4 followed by weekly paclitaxel and trastuzumab x 12. She then received trastuzumab every three weeks as a maintenance dose. In this case, there is a synergistic pharmacodynamic interaction between the monoclonal antibody trastuzumab and chemotherapy which has been confirmed by several adjuvant breast cancer trials in reducing disease recurrence in patients whose tumours overexpressed the HER2 protein. Prognosis for women with HER2-positive disease has improved substantially. However, trastuzumab and the anthracycline-based regimen might bear a risk of cardiotoxicity. Therefore, the ejection fraction should be measured at baseline, after the AC phase of the regimen and before the trastuzumab is added, and then after the taxane/trastuzumab and before starting the maintenance phase.

### Conclusion

Healthcare professionals should always keep updating their knowledge to develop a better understanding of drug interactions and help improve the quality of care among cancer patients. If they are aware of possible drug interactions, oncology pharmacists can minimise these risks by recommending the most suitable drugs and by monitoring for signs of an interaction.

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References continued on page 11