Clinical pharmacology

Drug-drug interactions in oncology: implications for general practice

What is the relevance of anticancer drug interactions to general practitioners?

Although anticancer drugs are generally prescribed by specialists, patients with cancer often rely on their general practitioners to prescribe supportive therapy (e.g. anti-emetics, analgesics, anti-infectives, and growth factors) and treatment for co-morbid conditions. Drug-drug interactions may result in plasma concentrations that are reduced, with loss of therapeutic effect, or increased, with enhanced toxicity. Drug-drug interactions may also occur with shared toxicity or efficacy (for example, anticancer drugs are often used in combination to enhance efficacy). Drug-drug interactions may occur between anticancer medications or between anticancer medication and drugs commonly prescribed to treat co-morbid diseases or as supportive therapy for the anticancer treatment (e.g. anti-emetics, analgesics, anti-infectives, and growth factors).

The incidence of drug-drug interactions has been shown to correlate with the number of concomitant medications. Karas reported that the actual risk of interaction increases from 16% with 3 medications to 72% with 6 medications and 100% with 7 or more medications. This is important to remember because anticancer medications are often administered in combination, and elderly cancer patients frequently have co-morbid conditions. Therefore cancer patients, particularly those over 65 years of age, are at high risk of drug-drug interactions.

Why do drug-drug interactions occur?

Pharmacokinetic drug interactions occur when one drug influences the exposure to and/or disposition of another drug (Table I). Changes in metabolism and absorption are more often implicated than altered distribution or excretion. Many drugs are metabolised primarily by the hepatic cytochrome P450 (CYP) mixed oxidase enzyme system, consisting of more than 50 enzymes. The CYP enzymes most often implicated in drug-drug interactions are CYP3A4, CYP2D6, and CYP1A2. Many cytotoxic and non-cytotoxic drugs are cleared by the CYP system and drug-drug interactions may occur when CYP enzymes are inhibited (which may cause significant toxicity) or induced (which may cause sub-therapeutic drug concentrations). Induction or inhibition of membrane transporter proteins (e.g. p-glycoprotein (p-gp)) in the intestinal epithelium may affect drug absorption.

Pharmacodynamic interactions may occur when drugs have similar methods of action (including shared toxicity) and influence the same physiological process.

Table I. Mechanisms of pharmacokinetic drug-drug interactions

Absorption	Alteration in gastrointestinal motility influences bioavailability
	Alteration in drug-metabolising enzymes in intestinal epithelium (cytochrome P450)
	Alteration in membrane transporter proteins in intestinal epithelium (p-glycoprotein)
	Alteration in gastric pH affects dissolution of dosing formulation
Distribution	Competition for plasma or tissue protein binding may result in an increase in unbound (active) drug – but this is usually temporary
Metabolism	Induction of hepatic CYP450 reduces efficacy
	Inhibition of hepatic CYP450 increases toxicity
Elimination	Altered hepatic function
	Altered renal function
	Changes in glomerular filtration rate (altered cardiac output)
	Altered renal tubular resorption (altered urinary pH)
	Changes in renal tubular secretion (competition for active secretion)
	Altered activity of membrane transporter proteins (p-glycoprotein)

How can anticancer drug-drug interactions be recognised and prevented?

Although not all drug-drug interactions can be predicted, avoided, or distinguished from direct anticancer drug toxicity, a high level of awareness should be maintained. In all patients on anticancer drugs, drug interactions should be considered before prescribing concomitant medication by consulting the package inserts or references (the Medicines Information Centre offers a free telephonic service: (021) 406-6829 or (0860) 110-0531).

A detailed medication history should be taken and updated at each visit. Patients should be questioned regarding complementary and alternative medicines (CAMs) and over-the-counter (OTC) drug use. Studies have shown a high prevalence of CAM use in South Africa. There is little scientific evidence available on interactions between CAM and anticancer drugs. Several interactions with CAMs (e.g. St John's wort, garlic, ginseng, and parsley) have been reported. There is *in vitro* evidence of potential CAM-drug interactions with two commonly used CAMs in South Africa: *Sutherlandia frutescens* (Cancer bush) and *Hypoxis hemerocallidea* (African potato).

Interactions with supportive therapy

Anti-emetics

Many 5-HT_3-receptor antagonists (except granisetron) may cause minor alterations in the concentrations of some anticancer drugs (e.g. cisplatin and cyclophosphamide). Glucocorticoids are inducers of CYP3A4 and could result in lower concentrations of anticancer drugs metabolised by this enzyme (Table II). NK-1 receptor antagonists (e.g. aprepitant) are involved in many interactions – refer to the package insert.

Analgesics

Analgesics are an essential part of postoperative and palliative care. Some opioid analgesics are metabolised by the CYP enzyme system, including fentanyl (CYP3A4), methadone (CYP3A4), codeine (CYP2D6), and oxycodone (CYP2D6), and may not have effective analgesic effect when used concurrently with enzyme-inducing anticancer drugs (e.g. glucocorticoids). Morphine is not metabolised by CYP.

Table II. Medications commonly used in supportive therapy, with potential interactions with anticancer agents

Anti-emetics	5-HT_3-receptor antagonists (not granisetron)
	Glucocorticoids
	NK_1-receptor antagonists
Growth factors	Erythropoietins
	Colony-stimulating factors
Anti-infectives	Macrolides
	Aminoglycosides
	Broad-spectrum antimicrobials
	Azole antifungals

Anti-infectives

Macrolides and azole antifungals inhibit CYP3A enzymes and should be used with caution with anticancer drugs metabolised by CYP3A enzymes (Table III). Combination of nephrotoxic and ototoxic antibiotics and anticancer agents (e.g. aminoglycosides and platinum preparations) should be avoided. Macrolides may prolong the QT interval and/or cause torsades de pointes and should be avoided in patients receiving cardiotoxic chemotherapy (e.g. the anthracyclines doxorubicin and daunorubicin). Diarrhoea is a very common adverse effect of combination anticancer therapy, and this can be exacerbated by antibiotic-associated diarrhoea (with or without *Clostridium difficile* infection, which should be excluded in all cases).

Interactions with therapy for co-morbid conditions

Antihypertensive treatment

All the calcium-channel blockers (CCBs) are metabolised by CYP3A4. Verapamil and diltiazem are inhibitors of CYP 3A4 and p-gp, and the concentrations of anticancer drugs that are substrates of CYP3A (Table III) or p-gp (e.g. doxorubicin) (Table IV) may be increased, with enhanced toxicity. Verapamil absorption is reduced by toxic damage to the upper part of the small intestines caused by COPP (cyclophosphamide, vincristine, procarbazine, prednisone) and VAC (vindesine, adriamycin, cisplatin) regimens. Angiotensin-converting enzyme (ACE) inhibitors have been shown to inhibit erythropoietin synthesis and may exacerbate the anaemia associated with some anticancer agents.

Anticoagulants

Cancer patients are at increased risk of venous thromboembolism. Numerous drug-drug interactions are known with warfarin and cytotoxic drugs. An increase in the anticoagulant effect of warfarin was observed in patients on carboplatin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, procarbazine, tamoxifen, and vincristine. Interactions may occur, mainly due to inhibition or induction of CYP enzymes metabolising warfarin. The interaction with tamoxifen is particularly important and a warfarin dosage reduction of about 50% is advised with close monitoring of INR to avoid bleeding complications.

Lipid-lowering treatment

Most HMG-CoA reductase inhibitors (statins) are CYP substrates (except pravastatin and rosuvastatin), and drugs that induce CYP3A4 may reduce statin concentrations. Concomitant use of CYP3A4 inhibitors (Table III) with statins will increase the risk of developing myopathy and rhabdomyolysis. Imatinib can increase the serum levels of simvastatin 2- to 3.5-fold and the simvastatin dose should be reduced appropriately (about halved).

Psychotropic drugs

Appropriate treatment of depression and anxiety is important in cancer patients. Selective serotonin reuptake inhibitors (SSRIs) are CYP substrates. Fluoxetine and its major metabolite have long half-lives. Combining SSRIs with 5-HT_3-receptor antagonists or opioids, tramadol and pentazocine, may result in increased serotonin levels and increase the risk of serotonin syndrome. Co-administration of fluoxetine and ondansetron also reduces the anti-emetic effect of the latter. When prescribing benzodiazepines together with agents that inhibit CYP3A4 (Table III), benzodiazepines that are not metabolised by CYP (e.g. estazolam, lorazepam or oxazepam) should be prescribed.

Treatment of gout

Hyperuricaemia is a well-known complication of leukaemia and lymphoma and their treatment. Allopurinol inhibits gastrointestinal and hepatic xanthine oxidase, and increases the bioavailability of 6-mercaptopurine. An increase in systemic 6-mercaptopurine exposure has been associated with death in a number of patients. Allopurinol may also increase the incidence of serious bone marrow depression caused by cyclophosphamide. Probenecid reduces the renal elimination of methotrexate and may enhance haematological toxicity.

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Antiretroviral therapy

HIV-infected patients are at increased risk of malignancy. Malignancy remains an important cause of death despite the reduction of HIV-related morbidity and mortality associated with highly active antiretroviral therapy (HAART). HAART is known to be fraught with clinically relevant pharmacokinetic and pharmacodynamic interactions and the addition of anticancer therapies to HAART increases the risk even further.

Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates as well as inhibitors and/or inducers of CYP450. In addition, PIs inhibit the important drug transporter p-gp. Anticancer drugs that are p-gp substrates are listed in Table IV. The concomitant administration of PIs or NNRTIs with anticancer drugs should be

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Table III. Anticancer medications subject to potential CYP-mediated interactions (from Antoniou and Tseng)

Drug-drug class	Metabolism	Metabolite(s)	Theoretical interaction
Taxanes			
Paclitaxel	CYP2C8 > CYP3A4		Inhibition: ↑ risk myelosuppression /peripheral neuropathy Induction: ↓ efficacy
Docetaxel	CYP3A4		Induction: ↓ efficacy
Vinca alkaloids			
Vincristine, vinblastine, vinorelbine	CYP3A4		Inhibitors:↑ risk myelosuppression /autonomic and peripheral neuropathy Induction: ↓ efficacy
Epipodophyllotoxins			
Etoposide, teniposide	CYP3A4 (main), CYP2E1, CYP1A2 (minor)		Inhibitors: ↑ risk mucositis, myelosuppression and tranaminitis Induction: ↓ efficacy
Camptothecins			
Irinotecan	hCE-2, CYP3A4 and UCT1A1	SN-38 (active) Inactive	Inhibitors: ↑ risk myelosuppression Induction: ↓ efficacy
Topotecan	Non-enzymatic hydrolysis (major), CYP and glucuronidation (both minor)		Inhibitors: ↑ risk myelosuppression Induction: ↓ efficacy
Alkylating agents			
Cyclophosphamide	CYP2B6 > CYP2C19	Active	CYP2B6 inhibitors (i.e. ritonavir, efavirenz): ↓ efficacy
	CYP3A4	Inactive (possibly toxic)	CYP3A4 inhibitors: ↑ toxicity (myelosuppression, nausea and vomiting)
Ifosfamide	CYP3A4 CYP3A4 and CYP2B6 detoxification	Active (toxic)	Induction:↑toxicity (myelosuppression, arrhythmia, haemorrhagic cystitis)
Dacarbazine	CYP1A2 > CYP2E1	Active	Inhibition: ↑ toxicity (nausea, vomiting and myelosuppression)
Imatinib	CYP3A4 Inhibitor of CYP3A4, CYP2D6 and CYP2C9		Inhibition by imatinib may affect many concomitant drugs
Endocrine therapies			
Tamoxifen	CYP3A4 > CYP1A2 (main) May induce CYP3A4 May inhibit CYP2C9	N-desmethyltamoxifen	CYP3A4 induction: ↓ concentrations of parent and metabolite CYP3A4 inhibition: ↑ risk of adverse effects Tamoxifen may induce CYP3A4 and may ↓ efficacy of substrates May potentiate anticoagulant effect of warfarin
Exemestane	CYP3A4 and aldoketoreductase		Inducers: ↓ efficacy Inhibition: ↑ risk of adverse effects (e.g. musculoskeletal pain, peripheral oedema, hot flushes)
Anastrozole	Glucuronidation, hydroxylation, N-dealkylation (CYP3A4 possible)	Inactive	Inducers of CYP3A4 or glucuronidation (e.g. ritonavir): ↓efficacy Inhibition: ↑ risk of adverse effects (hot flushes, peripheral oedema, etc.)
Toremifene	CYP3A4	Active	Induction: ↑ efficacy Inhibition: ↑ risk of adverse effects
Glucocorticoids	CYP3A4 CYP3A4 inducer		Inhibitors: ↑ risk corticosteroid-related toxicity Inducers: ↓ efficacy Reduces efficacy of CYP3A4 substrates

Table IV. Anticancer drugs that are p-glycoprotein substrates

Chlorambucil	Etoposide
Cisplatin	Methylprednisolone
Dactinomycin	Mitoxantrone
Daunorubicin	Paclitaxel
Dexamethasone	Tamoxifen
Docetaxel	Vinblastine
Doxorubicin	Vincristine

used with caution. Due to limited human *in vivo* studies, often with conflicting results, careful monitoring of the efficacy and toxicity of both the antineoplastics and antiretrovirals is recommended. Patients receiving PI and NNRTI-based HAART should undergo antiretroviral therapeutic drug monitoring.

Pharmacodynamic interactions have been described with several antiretroviral drugs and anticancer therapy. Zidovudine increases the risk of haematological toxicity associated with anticancer drugs. The concomitant use of stavudine or didanosine with vinca alkaloids, taxanes and ifosfamide may increase the risk of peripheral neuropathy. Shared gastrointestinal tract adverse effects are also common, notably diarrhoea due to the PIS.

Further reading

Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. Review. *Clin Pharmacokinet* 2005; 44(2): 111-145.

Beijnen JH, Schellens JH. Drug interactions in oncology. Review. Lancet Oncol 2004; 5(8): 489-496.

Bernard SA. The interaction of medications used in palliative care. *Hematol Oncol Clin North Am* 2002; 16(3): 641-655.

Blower P, de Wit R, Goodin S, Aapro M. Drug-drug interactions in oncology: why are they important and can they be minimized? Review. *Crit Rev Oncol Hematol* 2005; 55(2): 117-142.

Karas Jr S. The potential for drug interactions. *Ann Emerg Med* 1981; 10:627-630.

Lee AH, Ingraham SE, Kopp M, Foraida MI, Jazieh AR. The incidence of potential interactions between dietary supplements and prescription medications in cancer patients at a Veterans Administration Hospital. *Am J Clin Oncol* 2006; 29(2): 178-182.

McLeod HL. Clinically relevant drug-drug interactions in oncology. Review. *Br J Clin Pharmacol* 1998; 45(6): 539-544.

In a nutshell

In all patients on anticancer drugs, drug interactions should be considered before prescribing concomitant medication by consulting the package inserts or other medicine information sources.

Patients on anticancer drugs are at high risk of drug-drug interactions as they are prescribed multiple drugs and are often elderly.

It is important to take a detailed medication history, including complementary/alternative and over-the-counter medicines.

Enhance monitoring for signs and symptoms of interactions when potentially interacting drugs need to be co-administered.

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