Drug interactions in cancer therapy

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Abstract | Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents. Interactions with other medications can cause small changes in the pharmacokinetics or pharmacodynamics of a chemotherapy agent that could significantly alter its efficacy or toxicity. Improvements in *in vitro* methods and early clinical testing have made the prediction of potentially clinically significant drug interactions possible. We outline the types of drug interaction that occur in oncology, the mechanisms that underlie these interactions and describe select examples.

Excipients
Inert substances that are used as diluents or vehicles for drugs.

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A drug interaction is defined as the pharmacological or clinical response to the administration or co-exposure of a drug with another substance that modifies the patient's response to the drug. It is reported that 20–30% of all adverse reactions to drugs are caused by interactions between drugs[1]. This incidence increases among the elderly and patients who take two or more medications. Patients with cancer are particularly at risk of drug interactions as they could be taking many different medications as part of their cancer treatment or for the management of other illnesses. Examples of these types of interaction are shown (TABLE 1) and discussed throughout this article.

Although the term 'drug interaction' usually has a negative connotation, it is important to note that drug interactions can have various outcomes. Interactions between drugs can increase or decrease the therapeutic or adverse response, or result in a unique response that does not occur when either agent is given alone.

The term 'drug interaction' is most often used to describe drug–drug interactions, but there are various substances and/or factors that can alter the pharmacokinetics and/or pharmacodynamics of medications. These include food[2], nutritional supplements[3], formulation excipients and environmental factors (such as cigarette smoking)[4,5].

Drug interactions can occur throughout the process of drug disposition as a result of endogenous and exogenous factors (FIG. 1). Drug interactions can be the result of pharmacokinetic, pharmacodynamic or a combination of mechanisms. Pharmacokinetic interactions involve one drug or substance altering the absorption, distribution, metabolism or elimination of another drug or substance. A common example of a pharmacokinetic interaction occurs when two drugs compete for the same metabolic pathway. When the pathway becomes saturated neither drug can be metabolized fully, which results in higher serum concentrations of the agents and can lead to clinically unfavourable consequences. Pharmacodynamic interactions occur when two drugs or substances have similar molecular targets, but do not affect the pharmacokinetic parameters of each other. When two or more drugs that have similar pharmacodynamic activity are co-administered, the additive effects might result in an excessive response or toxicity. Pharmacodynamic interactions between drugs with opposing effects can reduce the response to one or both drugs.

Knowledge of the mechanism by which a given drug interaction occurs is often clinically useful, as the mechanism could influence both the time course and the methods of circumventing the interaction or, in rare cases, taking advantage of it. Interpatient variability is also an important factor that can influence drug interactions. Important variables are gender, age, genetics and/or comorbid conditions. These can affect patient responses to treatment and the toxicity profile of the agent[6–8].

Pharmacokinetic interactions: absorption

To exert a therapeutic effect a pharmacological agent must reach its target. Most antineoplastic agents are given intravenously and, therefore, factors that influence absorption have little effect on their pharmacokinetics. However, there has been increasing interest in the oral delivery of anticancer agents in chronic therapy, for patient convenience and ease of administration. Imatinib is given orally for the treatment of chronic myeloid leukaemia (CML)[9] and gastrointestinal stromal tumours[10]. Oral delivery necessitates careful consideration of the various factors that influence drug absorption because interactions with other orally administered substances such as food can lead to altered bioavailability.

The net effect of food on the pharmacokinetics of an orally administered medication depends on the chemical properties of the drug and its formulation, gastrointestinal physiology and the type and quantity of food[1].

First-pass effects
The decrease in the bioavailability of an orally administered drug caused by enteric metabolism, hepatic metabolism or elimination before the drug reaches the systemic circulation.

AUC
The area under the curve in a graph of plasma concentration versus time. It is a measure of drug exposure.

At a glance

- Drug–drug interactions are an important concern in the treatment of cancer. They can affect drug dosage, which is important for optimizing the anti-tumour effect of treatments and minimizing their toxicity to normal tissue.
- Interactions can occur between drugs and other drugs, food or herbal supplements, and can also be affected by a patient's genetic composition and physiological status. Most pharmacokinetic drug interactions involve drug metabolism and/or transport as a mechanistic basis. Therefore, it is important to understand the role of human enzymes and transporters in the metabolism and disposition of antineoplastic agents, as well as the mechanisms by which antineoplastics modulate the expression and activity of human enzymes and transporters.
- Pharmacodynamic drug interactions could be the result of overlapping mechanisms of action or combined toxicities to the same target organ. These interactions could be used to increase the therapeutic effect of a combination regimen or to minimize its toxicity.
- It is important that potential drug interactions are identified early in the drug-development process, and this might be made possible by improvements in *in vitro* model systems.

Food delays gastric emptying, raises intestinal pH, increases hepatic blood flow and slows gastrointestinal transit[1], so it can significantly affect the pharmacokinetic profile of some orally administered medications. Food–drug interactions can have four pharmacokinetic effects on the bioavailability of the orally administered anticancer agent: delayed, decreased, increased or unaffected absorption.

Table 1 | **Examples of drug–drug interactions in oncology**

Class of medication that interacts with chemotherapy	Examples of interactions	References
Antacids	Antacids that contain aluminium and magnesium can increase the bioavailability of capecitabine	15
Antibiotics	Penicillins block the elimination of MTX through renal tubular secretion, which results in elevated MTX levels	83,110
Anticoagulants	Altered coagulation has been reported in patients who have taken warfarin concurrently with capecitabine	15
Anticonvulsants	Carbamazepine has been reported to increase systemic clearance of teniposide	111
Anti-emetics	Co-administration of ondansetron with cisplatin and cyclophosphamide can result in a decrease in systemic exposure to both cisplatin and cyclophosphamide	41,42
Antifungal agents	Ketoconazole inhibits the metabolism of irinotecan, which leads to an increase in exposure to SN-38 (the active metabolite of irinotecan)	113
Anti-retroviral agents	Co-administration of delvairdine and saquinavir with paclitaxel has resulted in severe paclitaxel toxicity, which is possibly caused by CYP3A inhibition	57
Corticosteroids	Corticosteroids decrease the anti-tumour efficacy of aldesleukin	91
Herbal supplements	St John's wort decreases the plasma concentration of imatinib and SN-38 (the active metabolite of irinotecan)	52,60
NSAIDs	NSAIDs block the elimination of MTX through renal tubular secretion, which results in elevated MTX levels	84

CYP3A, cytochrome P450 subfamily 3A; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory agents.

For example, both delayed and decreased absorption is observed when the alkylating agent chlorambucil is given to patients with leukaemia or lymphoma in the fed rather than the fasting state. Delayed absorption of chlorambucil is the result of the slowed rate of gastric emptying. In addition, chlorambucil is unstable and undergoes hydrolysis in gastric fluid. Therefore, a prolonged time in the stomach results in an increased rate of hydrolysis and decreased bioavailability[11].

Some orally administered anticancer agents are prodrugs, which require metabolic activation for cytotoxic activity through first-pass effects in the gastrointestinal tract and/or liver before they reach the systemic circulation. Capecitabine, altretamine, etoposide phosphate and estramustine phosphate sodium[2] are anticancer agents that are used in the treatment of various solid tumours (including breast, colorectal, ovarian, lung, prostate and testicular cancer) and require such activation. Therefore, factors that alter the absorption of these medications can have profound effects on their pharmacokinetics. A decrease in the rate and extent of absorption is noted when estramustine phosphate sodium is given with food or milk, and bioavailability has been reported to decrease by 36% and 63%, respectively[12]. Therefore, it is recommended that estramustine phosphate sodium be taken with water 1 hour before or 2 hours after a meal[13]. By contrast, food has been shown to have only a minor effect on the pharmacokinetics of fluorouracil (5-FU)[14]. The rate of absorption of capecitabine (a 5-FU prodrug) is decreased in a fed state, which results in an increase in hepatic first-pass metabolism, which in turn reduces the extent of systemic absorption of the prodrug[14]. However, a greater effect is seen on the area under the concentration–time curve (AUC) of capecitabine as compared with 5′-deoxy-5′-fluorouridine (5′-DFUR), the precursor to the pharmacologically active compound 5-FU[14]. So, the change in AUC of capecitabine is probably not clinically significant, as capecitabine itself is not the active compound. At present, it is recommended that capecitabine be taken with food, as this was the procedure that was used in the pivotal clinical trials[15].

Therefore, food–drug interactions are optimally managed by scheduling the oral administration of anticancer agents with reference to meal timing — before, during

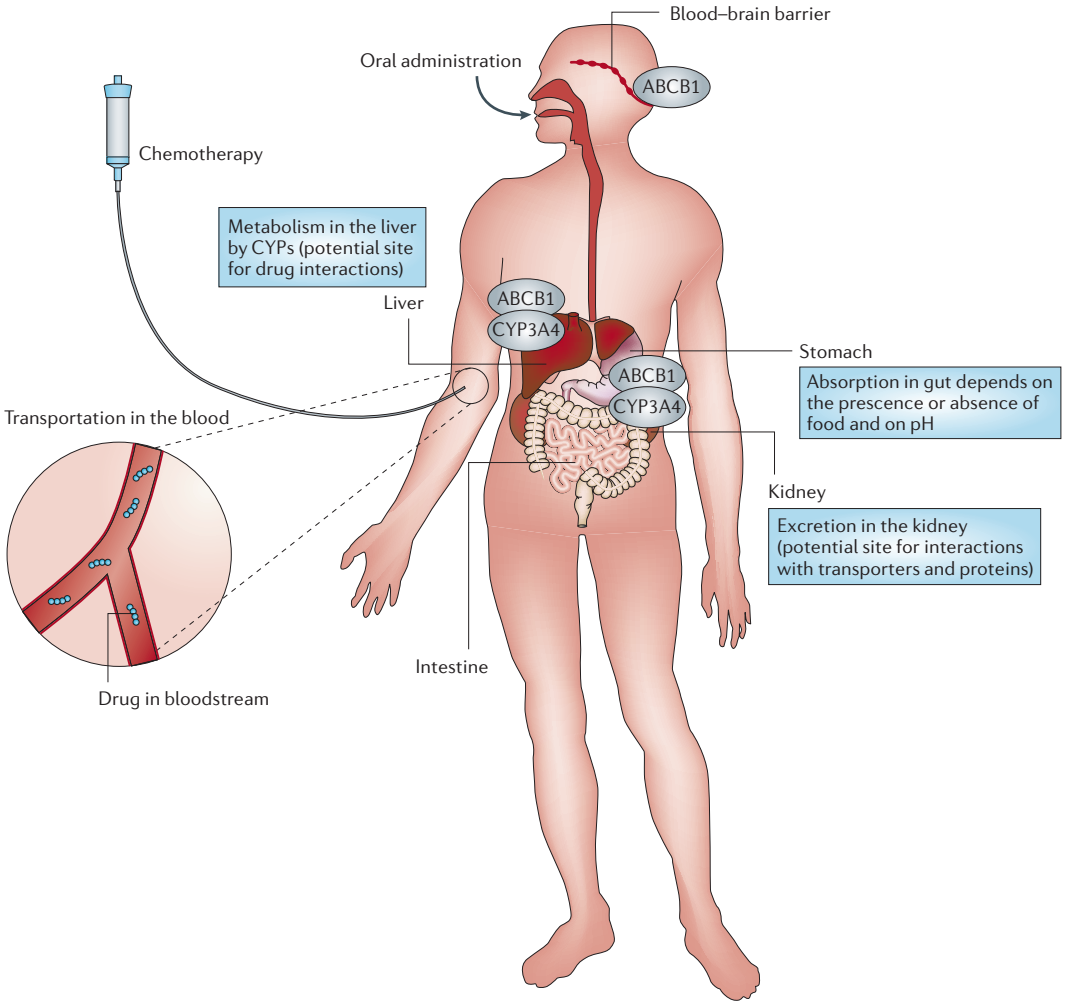

Figure 1 | **Sites of drug disposition.** The process of drug disposition can be divided into four parts — absorption, distribution, metabolism and excretion. Drug interactions can occur throughout the process of disposition as a result of endogenous and exogenous factors. The sites at which interactions can occur, and the sites of action of important mediators of interactions, ATP-binding cassette transporter B1 (ABCB1) and cytochrome P450 3A4 isoform (CYP3A4), are shown. CYP, cytochrome P450 enzymes.

Cytochrome P450 enzymes
A membrane-bound family of haem-containing intracellular oxidizing enzymes that are responsible for the first phase of (oxidative) metabolism of many endogenous steroids, hormones and medications. The CYP3A4 isozyme accounts for approximately 70% of the total CYP activity in the intestine.

Substrates
Substrates are metabolized by enzymes and their plasma concentrations are influenced by substances that inhibit or induce their metabolic pathway.

Inhibitor
Inhibitors inactivate specific CYP enzymes in an irreversible way. Metabolism will return to normal once the inhibitor has been removed and new enzymes have been produced.

Inducer
Inducers increase the production of enzymes and therefore accelerate metabolism. Consequently, the plasma levels of substrates are lowered.

P-glycoprotein
A transmembrane protein that is formed by two homologous halves, and which works as an ATP-dependent efflux pump. It is the product of the ATP-binding cassette gene *ABCB1*, which is also referred to as the multidrug resistance gene *MDR1*.

or after a meal — to improve chemotherapy outcomes. The effects of food on the pharmacokinetics of other orally administered anticancer agents are summarized in TABLE 2, and more detailed information is available in a comprehensive review by Singh and Malhotra[2].

The absorption of orally administered anticancer agents that are not prodrugs can also be altered by metabolism within the gastrointestinal tract. Evidence indicates that the activity of cytochrome P450 enzymes (CYP enzymes) in the gut wall is a significant factor that alters the bioavailability of orally administered anticancer agents that are CYP3A substrates[16] (TABLE 3). Drug–food, drug–herb or drug–drug interactions can occur when an orally administered CYP3A substrate is given concomitantly with an inhibitor or inducer of intestinal CYP activity.

One of the best described examples of a food that alters intestinal CYP3A activity is grapefruit juice. Grapefruit juice is known to be a potent inhibitor of intestinal CYP3A4, and therefore increases the bioavailability of various drugs, such as the anti-inflammatory and immunosuppressive agent cyclosporine and the calcium-channel blocker nifedipine[17]. Bergamottin and 6′,7′-dihydroxybergamottin are thought to be the clinically-important inhibitors of CYP3A4 in this juice[18,19].

Dose-dependent CYP inhibition has been observed[20] following administration with grapefruit juice, but changes in pharmacokinetics, which could result in toxic drug exposure, are difficult to predict as the mechanism seems to be multifactoral. Therefore, clinical trials that evaluate orally administered anticancer agents typically prohibit the use of grapefruit juice. As a result, there is limited data that pertains to the interactions between grapefruit juice and anticancer agents.

ABCB1, which is an ATP-binding cassette transporter (Abc) family protein (also referred to as P-glycoprotein (P-gp)), has been implicated in modulating the absorption of drugs. It is located on the apical membrane of intestinal epithelial cells, and is orientated so that substrates are secreted from the epithelial cell back into the intestinal lumen, thereby limiting intestinal

Polymorphism
The presence of two or more alleles with a frequency of at least 1% in the general population at the same gene locus.

Induction
Induction means that a substance stimulates the synthesis of an enzyme and metabolic capacity is increased.

Table 2 | **Effect of food on the pharmacokinetics of orally administered anticancer agents**

Anticancer agents	Effect of food	Pharmacokinetic parameters affected
Busulfan[114],fluorouracil[115], methotrexate[116]and topotecan[117]	Delayed absorption (effect on rate)	Change in C_{max} and T_{max}
Altretamine[118], capecitabine[14], chlorambucil[11], estramustine[12], gefitinib[119], melphalan[120] and thioguanine[121]	Decreased absorption (effect on extent)	Change in AUC and C_{max}
Erlotinib[44] and tretinoin[122]	Increased absorption (effect on extent and/or rate)	Increase in AUC and usually C_{max} and/or T_{max}
Etoposide[123], imatinib[124], mercaptopurine[125] and temozolomide[126]	Unaffected absorption (no effect on rate or extent)	No significant change in AUC and C_{max}*

AUC, area under the concentration–time curve; C_{max}, change in maximum plasma drug concentration; T_{max}, time to reach C_{max}. *Concluded when 90% confidence interval for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, fall within the equivalence limits of 80–125% for AUC and C_{max}.

absorption and decreasing the bioavailability of orally administered agents[21]. In addition to being substrates for this transporter, some medications — as well as food (for example, grapefruit juice) and herbal products — can inhibit its activity, which leads to interactions with other drugs[22,23]. Select ABCB1 substrates and inhibitors are listed in BOX 1. Some excipients that are used in pharmaceutical formulations can also interfere with ABCB1 activity. For example, Cremophor[24,25] and Tween 80 (REF. 26) are used to formulate poorly soluble compounds (for example, Taxol and Taxotere) and might modulate the activity of ABCB1 (REF. 27). Genetic polymorphisms of human ABCB1 have been described that might also alter protein function, affect the pharmacokinetics of ABCB1 substrates[21,28] and influence the potential for drug interactions.

Within the intestinal epithelium, ABCB1 is found in close proximity to CYP3A4, and shares many substrates and inhibitors[29]. A substrate for both ABCB1 and CYP3A4, such as docetaxel, vinblastine or irinotecan (TABLE 3), can be absorbed directly into the systemic circulation, metabolized by CYP3A4 in the enterocyte or secreted back into the intestinal lumen by ABCB1. Drug that is pumped back into the lumen can be reabsorbed at a distal site and exposed again to any of these three fates, which creates a cycling effect. If one such medication is given concurrently with a second substance that inhibits both proteins, such as ketoconazole, increased amounts of the medication will be absorbed in the unmetabolized form, thereby increasing drug exposure.

Pharmacokinetic interactions: distribution

Drug distribution to the target site after absorption is determined largely by blood flow to the area and the binding properties of the drug to plasma proteins. Anticancer drugs can bind to several blood components, such as albumin, α1-acid glycoprotein, lipoproteins and immunoglobulins. The unbound drug is regarded as the biologically active fraction because it is able to exert its effect on the pharmacological target within tissues. Therefore, binding to blood components limits the activity of the drug.

In theory, drug displacement from blood components or tissue-binding sites increases the apparent distribution volume. However, the effect of displacement is difficult to predict because an increase of the free fraction not only makes the drug more available for its target, but also increases the amount of drug available for metabolic and renal elimination. Cytotoxic drugs, which are often highly protein-bound, such as paclitaxel and etoposide, could theoretically interact with other highly protein-bound drugs such as warfarin, which is routinely used for the prevention and treatment of thromboses in patients with cancer. However, the therapeutic implications of the displacement of anticancer drugs from their protein-bound state have not yet been shown to be significant[30]. This is probably because although changes in protein binding can influence individual pharmacokinetic parameters, they rarely alter a patient's overall exposure to a drug[30].

Pharmacokinetic interactions: metabolism

Although some medications are metabolized at the site of absorption, the primary site of metabolism is the liver. Drugs, food and herbal supplements that compete for metabolism by the same CYP enzyme, or that inhibit or induce CYP enzymes, can interact, and these interactions can be predicted from the known CYP-mediated effects of a compound (TABLE 3). Drug interactions that involve a metabolizing enzyme can be either induction or inhibition reactions[31]. However, the co-administration of an enzyme-inducing substance with a substrate for the same enzyme system leads to increased metabolism, and therefore reduced serum concentrations of the substrate. Substances that inhibit CYP metabolism can increase serum concentrations of substrates for the inhibited enzyme[32]. Furthermore, two drugs can competitively inhibit each other reversibly if both are substrates of the same enzyme.

Box 1 | **Substrates and inhibitors of ABCB1 used in anticancer therapy**

Substrates
Actinomycin D[97]; daunorubicin[99]; docetaxel[101]; doxorubicin[103]; etoposide[105]; imatinib mesylate[106]; irinotecan[107]; mitoxantrone[108]; paclitaxel[109]; topotecan[110]; vinblastine[103]; vincristine[111].

Inhibitors
Gefitinib[98]; tariquidar[100]; teniposide[102]; valspodar (PSC 833)[104].

Drugs can also alter nuclear-receptor expression and/or serve as ligands for the receptors, and can therefore alter the expression of drug-metabolizing enzymes and transporters. The co-administration of drugs that are nuclear-receptor agonists or antagonists can lead to severe toxicity, a loss of therapeutic efficacy or an imbalance in physiological substrates. It is suggested that many drug–drug interactions that involve CYP3A are the result of drug-mediated activation of the pregnane X receptor (PXR, also known as NR1I2)[33–35]. Ligand-bound PXR transfers to the nucleus and transcribes genes that encode drug-metabolizing enzymes and drug transporters, which in turn accelerates systemic clearance on continued drug exposure[36]. Similarly, constitutive andostane receptor (CAR, also known as NR1I3), the transcriptional targets of which include CYP2B isoforms[37], is activated on treatment with the prototypical inducer phenobarbital.

Adverse effects that occur when two anticancer agents are given as part of the same therapeutic regimen have been attributed to metabolic drug–drug interactions, although this has not been proven. Such interactions can also occur between an antineoplastic agent and a medication that is taken to prevent side effects of the treatment (such as the interaction between chemotherapy agents and the anti-emetic agent ondansetron), with a medication taken for the management of a chronic condition (such as St John's wort (SJW) or paroxetine) or with a medication that is prescribed for the treatment of an acute illness (such as rifampin or ketoconazole)[38].

Potential drug interactions between chemotherapy agents and anti-emetics have been extensively evaluated. Perhaps the most commonly used class of anti-emetics are serotonin antagonists. There are many of these compounds on the market, all of which have similar pharmacodynamic effects but have different pharmacokinetic properties. Only some of these agents inhibit the metabolism of a CYP enzyme. For example, granisetron does not inhibit CYP activity[39], whereas ondansetron has been shown to inhibit CYP1A1, CYP1A2, CYP2D6, CYP3A4 and CYP3A5 *in vitro*[40]. Potential CYP-mediated pharmacokinetic interactions that reduce systemic exposure to the antineoplastic agent have been reported between ondansetron and both cisplatin[41] and cyclophosphamide[42]. However, the clinical significance of these interactions is unclear. Concomitant administration of a serotonin antagonist with a highly anti-emetic chemotherapy agent such as cisplatin and cyclophosphamide is the standard care[43], and so far no untoward effects have been reported.

Metabolic drug interactions can also be observed when an isoenzyme substrate is given with an inhibitor or inducer that is specific to the same isoenzyme. For example, erlotinib is metabolized predominantly by CYP3A4, so inhibitors of this enzyme would be expected to increase systemic availability and inducers would be expected to decrease it. Co-treatment with the CYP3A4 and ABCB1 inhibitor ketoconazole increased the AUC of erlotinib by 66% (REF. 44). This could result in increased erlotinib toxicity, such as skin rash or diarrhoea. Prior co-treatment with the CYP3A4 inducer rifampicin increased erlotinib clearance by threefold and reduced AUC by 66% (REF. 44), which could result in the loss of clinical activity. Similarly, concurrent therapy with oral ketoconazole resulted in a 44% increase in AUC in patients who received etoposide orally[45].

Gefitinib is also a CYP3A4 substrate, so the influence of a hepatic enzyme inducer (rifampin) and an enzyme inhibitor (itraconazole) on its metabolism was examined in a two-part study[46]. First, 18 healthy male volunteers received one dose of gefitinib alone (500 mg) and then again on day 10 of a 16-day regimen of 600 mg of rifampin a day. During rifampin administration, the mean maximum plasma gefitinib concentration (C_{max}) was 65% lower and the mean AUC was 83% lower than after gefitinib alone. Second, 48 individuals received 200 mg of itraconazole a day for 12 days. Twenty-four individuals each received one dose of gefitinib (250 or 500 mg) alone and on day 4 of a 12-day regimen of itraconazole. There was a 3-week washout period between each treatment for both trials. During itraconazole administration, the gefitinib C_{max} after administration of the 250 and 500 mg doses was increased by 32% and 51% and the AUC was increased by 58% and 80%, respectively. Because gefitinib was well tolerated during itraconazole administration, it was concluded that the increased gefitinib exposure induced by enzyme inhibitors would probably not result in clinically significant adverse effects; however, the investigators warned that the clinical effect of reduced gefitinib exposure following rifampin administration needs further evaluation.

Herbal supplements. Although rifampin is the prototypical enzyme inducer that is used in the evaluation of drug–drug interactions, some herbal supplements such as echinacea, kava, grape seed and SJW (*Hypericum perforatum*) are also thought to be enzyme inducers[3]. Consideration must be given to their potential effect on drug metabolism when taken in combination with anticancer agents because of the increased use of herbal products and nutritional supplements by patients with cancer in recent years[47].

Several metabolic interactions have been identified between anticancer drugs and SJW[3,48]. SJW is a ligand for PXR and therefore induces the transcription of genes under its regulation, such as *CYP3A* and UDP glucuronosyltransferases (UGTs)[33,49,50]. The administration of SJW induces intestinal and hepatic expression of CYP3A4 in addition to intestinal expression of ABCB1 (REF. 51).

Five patients with cancer were treated with SJW to determine its effect on the metabolism of irinotecan[52]. Irinotecan is a camptothecin derivative that results in DNA damage on interaction with topoisomerase I, and is used in the treatment of metastatic carcinoma of the colon or rectum. It is a prodrug that undergoes hydrolysis by human carboxylesterases 1 and 2 (CES1 and CES2) to form the pharmacologically active compound 7-ethyl-10-hydroxy-camptothecin (SN-38). SN-38 can then be inactivated through glucuronidation by UGTs[53,54] (FIG. 2).

C_{max}
The highest concentration that a drug reaches in the serum/plasma.

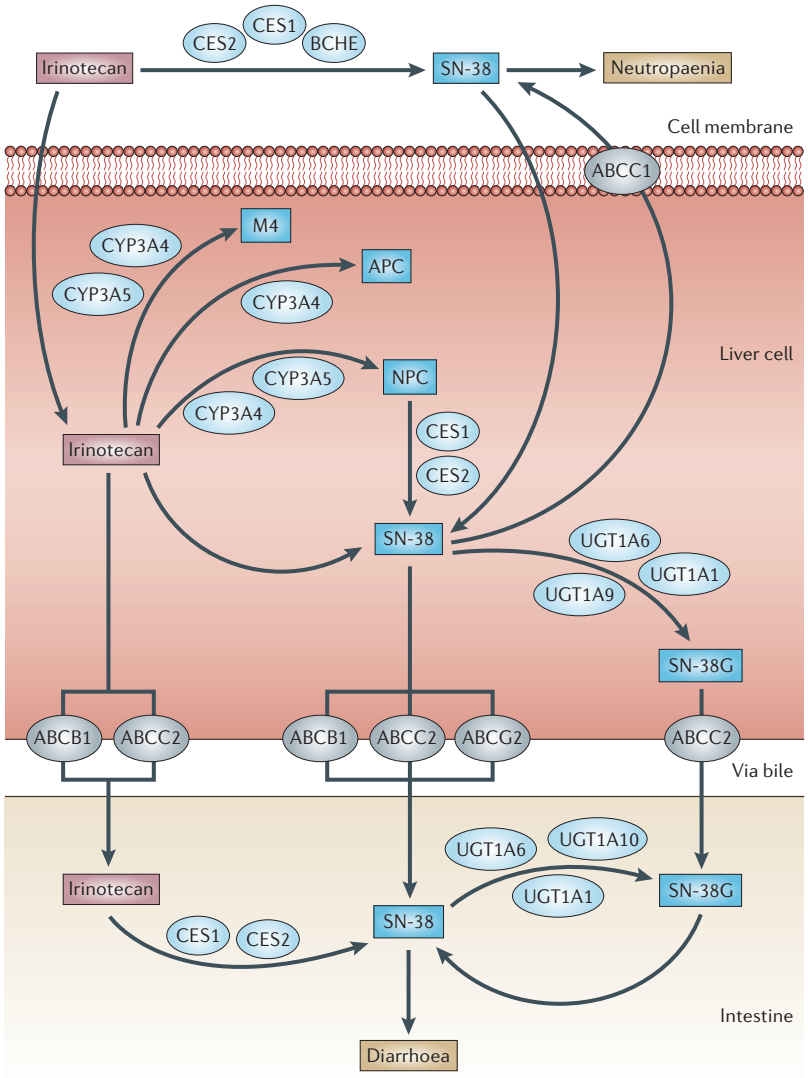

Figure 2 | **Metabolism and transport of irinotecan.** Irinotecan is metabolized in the liver by cytochrome P450 (CYP) isoforms, and is transported across cell membranes by members of the ABC-binding cassette transporter family. These enzymes and transporters are involved in the processing of other drugs, and are therefore potential mediators of drug–drug interactions. The four human metabolites of irinotecan, SN-38, SN-38G, APC and NPC are shown. UGT1A1, human UDP glucuronosyltransferase isoform 1A1; CES, carboxylesterase. Reproduced with permission from REF. 112 © (2005) PharmGKB.

The patients were treated with irinotecan (350 mg m^{-2}, intravenously) in the presence and absence of SJW (900 mg a day, orally for 18 days) in an unblinded, randomized crossover design. Compared with irinotecan alone, the AUC of SN-38 decreased by 42% (95% CI = 14–70%) during concomitant administration of irinotecan and SJW[52]. Although myelosuppression was worse in patients who were not exposed to SJW, patients who received treatment with irinotecan should refrain from taking SJW because the plasma concentration of irinotecan can be decreased, which could result in a loss of anti-tumour activity. The full effects of enzyme modulation on irinotecan pharmacokinetics have been assessed in a series of clinical evaluations and are summarized in TABLE 4.

Based on the profound inductive effects of SJW on CYP3A4, it is advised that all patients who receive chemotherapy should refrain from concomitant ingestion of SJW because of the increased risk of treatment failure.

HAART. Drug–drug interactions between chemotherapy and highly active anti-retroviral therapy (HAART) are also probable, as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) — which are HAART components — are also substrates, inhibitors and inducers of the CYP system. Although pharmacokinetic evaluations of these potential drug–drug interactions are limited[55] they can be predicted from the known metabolism of these agents. PIs and NNRTIs can also give rise to interactions through their induction or inhibition of the expression of ABCB1 (REF. 56). Two patients who were treated with the anti-retroviral agents delavirdine, saquinavir and didanosine at the same time as taking paclitaxel were noted to have severe paclitaxel toxicity[57]. It is possible that this was caused by the inhibition of CYP3A by delavirdine and/or saquinavir.

Imatinib. Although most anticancer agents are substrates for the CYP system, some anticancer agents such as imatinib mesylate are also potent inhibitors. Imatinib is therefore involved in two types of drug interaction. On the one hand, it is primarily metabolized by CYP3A[58,59] so inhibitors of this enzyme system (such as erythromycin and ketoconazole) or inducers (such as dexamethasone, carbamazepine and SJW) are likely to affect the concentration of imatinib. The administration of SJW has been shown to increase imatinib clearance by 43% ($P < 0.001$) in patients who were taking imatinib for the treatment of Philadelphia-chromosome-positive CML and gastrointestinal stromal tumours[60]. On the other hand, imatinib has also been shown to inhibit CYP3A4, CYP2C9 and CYP2D6, and could cause drug interactions (owing to increased plasma concentrations[60,61]) when it is given with medications that are metabolized by these enzymes. The clinical significance of the interactions caused by the inhibitory nature of imatinib has not been fully evaluated, but they are unlikely to be significant. Other anticancer agents that inhibit the activity of CYP enzymes are listed in TABLE 3.

Interpatient variability. Genetic polymorphisms in drug-metabolizing enzymes and/or transporters must also be considered when assessing the potential for drug interactions. Polymorphisms that are associated with a reduced level of enzyme expression could lead to an increased concentration of concomitantly administered drug that had not been observed previously in a population with a wild-type genotype (which encodes for normal enzyme function). Conversely, patients with polymorphisms that are associated with an increase in enzyme activity could demonstrate a reduced response if they are treated with an agent that is a substrate for this enzyme[62].

Table 3 | **Anticancer therapy modulating or metabolized by cytochrome P450 (CYP) enzymes**

Anticancer therapy	Cytochrome P450 enzyme isoforms inhibited	Primary isoforms that mediate biotransformation	References
Anastrazole*	1A2, 2C8, 2C9 and 3A4	3A4	127
Busulfan		3A4	128
Corticosteroids‡ (dexamethasone, methylprednisone and prednisone)	3A4	3A4	129
Cyclophosphamide		2B6, 2D6 and 3A4	69,70,130
Cytarabine	3A4	3A4	131
Docetaxel		3A4	132,133
Doxorubicin		3A4	134
Erlotinib		1A2 and 3A4	44
Etoposide		3A4	45,135
Exemestane*		3A4	136
Gefitinib	2C19 and 2D6	3A4	137
Idarubicin	2D6	2C9 and 2D6	131
Ifosphamide		3A4	138
Imatinib mesylate*	2C9, 2D6 and 3A4	3A4	59–61
Irinotecan		3A4	54
Ketoconazole*	3A4 and 2C9		139
Letrozole*	2A6 and 2C19	2A6 and 3A4	140
Paclitaxel		2C8 and 3A4	141,142
Tamoxifen*	3A4	1A2, 2A6, 2B6, 2D6, 2E1 and 3A4	63,65,143,144
Teniposide		3A4	134
Tretinoin*		2C8 and 3A4	145
Vinblastine	2D6	3A4	146
Vincristine	2D6	3A4	146
Vinorelbine	2D6	3A4	146

* Available as an oral formulation only. ‡ CYP3A4 inducer. This table is based on material in REFS 6,147.

For example, tamoxifen requires metabolic conversion by the CYP system (by CYP3A, CYP2D6, CYP2C9, CYP2C19, CYP2B6 and CYP1A2 (REF. 63)) into anti-oestrogenic metabolites, which are more potent than the parent compound[64]. The most important metabolites of tamoxifen are *N*-desmethyltamoxifen, which is formed by CYP3A4, and 4-hydroxytamoxifen and endoxifen[65], which are formed by CYP2D6. Therefore, interindividual variability in the relative activities of these CYP isoforms could affect the nature of drug interactions with tamoxifen.

Endoxifen concentrations have been assessed in patients with breast cancer who took tamoxifen at the same time as paroxetine, which is a selective serotonin reuptake inhibitor (SSRI) metabolized by CYP2D6 that is commonly prescribed for the management of depression and the non-hormonal treatment of hot flushes that result from treatment with tamoxifen. Plasma endoxifen concentrations were lower in patients who were also taking paroxetine than in patients who were not taking paroxetine[66]. However, the endoxifen concentrations decreased by 64% (95% CI = 39–89%) in women with a wild-type *CYP2D6* genotype, but only by 24% (95% CI = 23–71%) in women with a non-functional *CYP2D6* genotype ($P = 0.03$).

A prospective study enrolled 80 hormone-receptor-positive women who were taking tamoxifen as adjuvant treatment for newly diagnosed breast cancer, 24 of whom were taking SSRI antidepressants (inhibitors of CYP2D6)[67]. Consistent with previous observations, plasma endoxifen concentrations were significantly lower in women with a CYP2D6-homozygous non-functional genotype or a heterozygous genotype compared with those who were homozygous for the wild-type genotype. In women with a homozygous wild-type genotype, the mean plasma endoxifen concentration among women who were taking CYP2D6 inhibitors was 58% lower than those who were not, and the potency of CYP2D6 inhibition influenced the extent of reduction in endoxifen concentration[67]. Plasma endoxifen concentrations were significantly lower in woman with a CYP2D6 homozygous non-functional genotype or a heterozygous genotype after 4 months[67]. These data indicate that plasma concentrations of tamoxifen metabolites might be directly affected

Table 4 | **Examples of drug interactions with irinotecan**

Concomitant medication	Possible mechanisms of interaction	Pharmacokinetic changes	References
Carbamazepine	Induction of CYP3A4	Decreased exposure to irinotecan and its active metabolite SN-38 in both adult and paediatric patients	97
Cyclosporine	Inhibition of ABCB1-mediated biliary excretion of SN-38	The AUC of SN-38 increased by 23% to 63%; irinotecan clearance decreased by 39% to 64% when compared with historical controls	148
Gefitinib	Probably caused by the inhibition of ABCG2-mediated efflux of irinotecan	Irinotecan clearance decreased by 8%; the median AUC of SN-38 increased by 26%	75
Ketoconazole	Inhibition of CYP3A4; inhibition of UGT1A1	Relative APC formation was reduced by 87%; relative exposure to SN-38 (calculated on the basis of dose) was significantly increased by 109%	113, 149
Phenobarbital	Induction of CYP3A4	Irinotecan clearance increased by 27%; AUC of SN-38 decreased by 75%	148
Phenytoin	Induction of CYP3A4	The AUCs of irinotecan, SN-38 and SN-38G were approximately 40%, 25% and 25%, respectively, of those previously determined in patients who did not receive phenytoin	150
St John's wort	Induction of CYP3A4	AUC of SN-38 decreased by 42%	52

AUC, area under the concentration–time curve; ABCB1, ATP-binding cassette transporter B1; CYP3A4, cytochrome P450 enzyme 3A4; UGT1A1, UDP glucuronosyltransferase 1A1.

by polymorphisms in CYP2D6 as well as by SSRIs, which illustrates the importance of pharmacogenetics in the evaluation of potential drug–drug interactions. However, the clinical relevance of this pharmacokinetic interaction is unknown. In the absence of clinical data that includes outcomes such as toxicity, breast cancer recurrence and mortality, definitive recommendations about which SSRI to prescribe with tamoxifen and whether genotype predicts response cannot be made.

Prediction of clinically significant metabolic drug interactions. As metabolic drug interactions can result in clinically significant alterations in the pharmacokinetics and/or pharmacodynamics of anticancer agents, it is desirable to be able to predict these interactions before observations of untoward drug effects in patients. Improvements in laboratory-based assessments of drug interactions have made this possible. Prediction begins with the identification of the important metabolic pathways that are involved in the biotransformation of the test agent, the specific enzymes responsible for these biotransformation reactions and the metabolites that are generated by the biotransformation process.

Once *in vitro* and *in vivo* testing is complete, an informed assessment can be made about the potential for drug interactions. For example, the activity of a prodrug that is converted to an active metabolite will be decreased by inhibitors and increased by inducers, whereas the reverse is true for drugs that are inactivated by metabolism. However, when a drug interaction changes the relative concentrations of a parent drug and its metabolite(s), which are approximately equipotent in terms of efficacy and safety considerations, inhibition and induction could be of little therapeutic consequence.

Variations in enzyme activity can also lead to alterations in the ability to metabolize drugs, which could reveal previously unobserved drug interactions. This is often observed when the concentration of xenobiotic(s) exceeds the capacity of the metabolizing enzymes, which results in saturation and drug concentrations that are higher than predicted. The absence of enzymes or reduced enzymatic activity leads to increased plasma drug concentrations, and clearance is often delayed, which can potentially result in increased toxicity; on the other hand, increased enzymatic activity can result in subtherapeutic drug concentrations. Enzyme activity is influenced by a patient's physiological status (which includes age, sex, and concomitant illness) and the co-administered medications, which affect the extent of biotransformation[6]. The rate and extent of metabolism is also dependent on the expression of the enzyme, which can be influenced by genetic polymorphisms. Therefore, some patients will experience an interaction between two particular drugs whereas others will not. It is estimated that genetics can account for 20–95% of the variability in therapeutic response and toxicity[8]. Of the drugs that are known to be involved in adverse drug reactions, 86% are metabolized by polymorphic CYP enzymes[68].

When evaluating drug–drug interactions, it is important to note the relative inhibitory potential of a drug for a particular enzyme. It is also necessary to consider whether the substrate is metabolized by a single enzyme or by multiple enzymes. For example, cyclophosphamide requires hepatic CYP-catalysed metabolism to exhibit its cytotoxic activity. The active metabolite, 4-hydroxycyclophosphamide, is produced mainly by CYP2B6 and CYP3A4 (REF. 69). However, as many as 6 enzymes (CYP2A6, CYP2B6, CYP3A4, CYP2C8, CYP2C9 and CYP2C19) have been implicated in the metabolism of

Pharmacogenetics
The study of genetically determined variations in drug response.

Box 2 | **Conditions under which drug interactions are likely to be clinically significant**

- Drug elimination occurs primarily through a single metabolic pathway.
- A drug is a potent inhibitor or inducer of a drug-metabolizing enzyme.
- One or both of the interacting drugs has a steep dose-response curve.
- One or both of the interacting drugs has a narrow therapeutic range.
- Inhibition of the primary metabolic enzyme or the induction of a secondary metabolic enzyme results in diversion of the drug into an alternative pathway, which generates a metabolite that has toxic or modified pharmacodynamic activity.
- A drug has nonlinear pharmacokinetics, or the interaction results in a conversion from linear to nonlinear pharmacokinetics.
- The drug is metabolized through, or inhibits, a polymorphic drug-metabolizing enzyme.

Based on material in REFS 1,31.

this compound[69,70]. Therefore, the pharmacokinetics of cyclophosphamide are less likely to be influenced by drug–drug interactions caused by the inhibition of an individual CYP because multiple enzymes are involved in its metabolism.

A summary of the various factors that influence the clinical significance of drug interactions is provided in BOX 2.

Pharmacokinetic interactions: elimination

ABCB1 has a role in the renal elimination of substances by active secretion into the urine. It is localized at the brush-border membrane of the proximal renal tubule (luminal side), where it pumps drug molecules into the tubular filtrate. ABCB1 inhibition results in an increase in the systemic exposure and tissue distribution of drugs that are ABCB1 substrates, whereas the induction of ABCB1 leads to a decrease in systemic exposure. ABCB1 that is expressed in the liver also has a role in the elimination of unchanged drugs and metabolites. Localized in the canalicular membrane of hepatocytes, the efflux protein pumps drug molecules into the bile, where they can be reabsorbed from the intestine or eliminated in the faeces. Concomitant administration of an inhibitor of ABCB1 (such as the cardiovascular agents amiodarone (anti-arrhythmic) and verapamil (anti-hypertensive)) and the ABCB1 substrate vinblastine to mice results in increased concentrations of vinblastine and its metabolites within the liver and kidneys[71]. This increase in drug concentrations does not seem to be caused by the inhibition of drug metabolism.

Irinotecan and its metabolites are transported across the cell membrane by several members of the Abc family[72]. Substrates and/or inhibitors of these transporters could interfere with the renal and/or biliary excretion of irinotecan and SN-38, which would result in increased plasma concentrations and toxicity[73] (TABLE 4). A phase II clinical evaluation of the combination of gefitinib with irinotecan, leucovorin and infusional 5-FU in patients with colorectal cancer showed excessive gastrointestinal and haematological toxicity in over 50% of the patients[74]. The doses that could be tolerated when there was an interaction were approximately one-third of those that are commonly used. The observed side-effect profile (which is both gastrointestinal and haematological) is consistent with an interaction between irinotecan and gefitinib, and is similar to observations in other clinical studies of these two agents in combination[75]. One possible mechanism for this interaction is that gefitinib inhibits the Abc transporter, which results in a decrease in ABCG2-dependent active drug extrusion of irinotecan and therefore an increase in toxicity[76,77]. *ABCG2* (formerly breast cancer resistance protein (*BCRP*)) is another gene in the Abc family that has been shown to be involved in drug transport.

The directional movement of drugs across organs such as the gastrointestinal tract, liver and kidneys requires drug uptake transporters as well as efflux transporters. For example, organic anion transporters (OATs) and organic anion-transporting polypeptides (OATPs) are expressed in organs of importance to drug disposition and response, such as the CNS, liver and intestine[78,79], and can mediate the cellular uptake of several structurally diverse compounds. Typically, larger and more lipophilic organic anions are transported in the liver by OATPs, whereas small hydrophilic organic anions are extracted by OATs, which are highly expressed on the basolateral side of renal proximal tubules. OATPs transport antineoplastic agents such as methotrexate[80] and paclitaxel[81]. OAT substrates include various antineoplastic agents such as methotrexate[79].

In vitro experiments conducted in mouse proximal tubule cells that stably express basolateral human OATs have shown dose-dependent competitive inhibition of OAT-mediated methotrexate uptake by non-steroidal anti-inflammatory drugs (NSAIDs) that are used for the treatment of mild pain (such as salicylate, ibuprofen, ketoprofen, phenylbutazone, piroxicam and indomethacin), the rarely used probenecid, and penicillin G, which is mainly used in this population for infection prophylaxis[82]. In addition to alterations in protein binding, and decreased glomerular filtration that is due to the inhibition of prostaglandin synthesis, inhibitory effects on the OAT-mediated renal excretion of methotrexate are likely to underlie these drug interactions. Severe and even life-threatening drug interactions have been observed with these combinations of medications, including bone-marrow suppression and acute renal failure[83–85].

Uptake transporters
Membrane-bound proteins that are predominately involved in the movement of substances and/or drugs into the cell.

Efflux transporters
Membrane-bound proteins that are predominately involved in the movement of sustances and/or drugs out of the cell.

Competitive inhibition
Competitive inhibition occurs when two or more drugs compete for the active (binding) site of a single CYP enzyme. This competitive inhibition can decrease the metabolism of one of the drugs, therefore altering its pharmacokinetic behaviour.

Clinically significant drug interactions
Interactions that lead to a change in the therapeutic activity or toxicity of a drug to the extent that dosage adjustment or increased monitoring is necessary.

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 can be categorized broadly as: synergistic (when the effect of two drugs is greater than the sum of their individual effects); antagonistic (when the effect of two drugs is less than the sum of their individual effects); additive (when the effect of two drugs is merely the sum of the effects of each); and sequence-dependent (when the order in which two drugs are given governs their effects). Although pharmacodynamic interactions are relatively common in clinical practice, adverse effects can usually be minimized if the interactions are anticipated and appropriate counter-measures taken.

Synergistic interactions. Pharmacodynamic interactions have been used for years for therapeutic benefit in oncology (combination chemotherapy). Synergistic effects can result in increased cytotoxic activity and translate into an improved clinical response. For example, it is well known that leucovorin increases the activity of 5-FU in the treatment of colorectal cancer[86] by stabilizing the complex of 5-FU and thymidylate synthase (TS)[87]. However, it is important to keep in mind that synergistic interactions can also increase adverse effects. Although leucovorin is commonly used as a modulator to increase the anti-tumour effectiveness of 5-FU, its use can also increase 5-FU toxicity[88].

Antagonistic interactions. Administration of corticosteroids with interleukin 2 (IL2) results in an antagonistic interaction[89]. Clinical studies that evaluated the use of the corticosteroid dexamethasone in patients who received immunotherapy with IL2 showed that they were able to tolerate an increased dose of IL2, but experienced significantly less toxicity[90]. Patients with advanced cancer who were treated with dexamethasone and IL2 did not show an objective tumour response (0/6) compared with a control population who did not receive dexamethasone (9/27) (REF. 91). In addition, animal experiments have shown that giving steroids to tumour-bearing mice abrogated the *in vivo* anti-tumour effect of IL2 (REF. 92). The mechanism of this interaction might be caused by corticosteroid-mediated inhibition of IL1 production, which blocks the release of IL2 and tumour-necrosis factor. Regardless of the precise mechanism, concomitant administration of corticosteroids with IL2 results in reduced toxicity and a loss of therapeutic efficacy.

Additive interactions. Various additive pharmacodynamic interactions have been described. Clinical studies have reported that concurrent administration of trastuzumab and doxorubicin increases the risk of cardiac toxicities in patients with metastatic breast cancer when compared with trastuzumab used alone[93]. Increased renal toxicity has been observed when cisplatin is given with other nephrotoxic agents such as aminoglycosides[94,95], amphoteracin B[96] and rituximab[97]. Vinorelbine has been associated with new or worsening neuropathy in patients with previous or current exposure to paclitaxel[98–100], although the underlying, additive effect that induces neuropathy is not well understood. These observations indicate that cumulative neurotoxicity with vinorelbine and paclitaxel is a possibility. Paclitaxel treatment might cause latent neuronal damage, which only becomes clinically apparent following vinorelbine administration.

Sequence- or schedule-dependent interactions. An advantageous sequence-dependent pharmacodynamic interaction has been observed when paclitaxel is infused before carboplatin, which results in decreased thrombocytopaenia compared with carboplatin alone[101–105]. The pharmacokinetics of neither compound is altered when given in combination. However, the carboplatin AUC increased from 34 μg per ml per hour when carboplatin was given alone, in comparison to 57 μg per ml per hour when given after paclitaxel[103,105]. A proposed explanation involves a direct effect of paclitaxel on platelets. Paclitaxel binds directly to tubulin and is concentrated in tubulin-rich platelets. Platelet longevity can be prolonged by the inhibition of tubulin-mediated platelet activation by paclitaxel[102] or impaired clearance through the reticuloendothelial system. It is possible that paclitaxel reduces the toxicity of carboplatin to megakaryocytes or megakaryocyte precursors in the bone marrow. *In vitro* studies indicate that paclitaxel might spare megakaryocyte colony-forming units[106].

Clinical evidence indicates that a sequence-dependent and schedule-dependent combined pharmacokinetic and pharmacodynamic interaction is seen when paclitaxel is given before an anthracycline, and this might influence the cardiotoxicity of the combination[107,108]. Also, several studies have evaluated the pharmacokinetics and pharmacodynamics of paclitaxel when it is given in combination with doxorubicin[109]. However, these studies consistently report an increase in doxorubicin peak concentration with no effect on paclitaxel pharmacokinetics, independent of the administration sequence or duration of infusion[102]. Taken together, they form the basis of the current clinical recommendations for administering doxorubicin[102].

Evaluation of drug interactions

Many drugs show clinically significant drug interactions, which represent a therapeutic challenge for the researcher, clinician and patient. Clinicians should include an assessment of the use of herbal therapies when taking medication histories given the high prevalence of use and potential hazards that can result from concomitant administration with anticancer agents. This is especially important because many patients do not consider it necessary to tell their doctor about their use of herbal supplements and over-the-counter products.

Patients with cancer could be receiving different cytotoxic agents as part of their cancer treatment, medication to prevent side effects and medication for

co-morbid conditions (such as cardiovascular disease, gastrointestinal disorders, diabetes, respiratory illnesses). As cytotoxic drugs generally have a narrow therapeutic index, even a slight increase or decrease in cytotoxic activity caused by a drug interaction could result in excessive toxicity or reduced efficacy. Through increased awareness of the potential for drug interactions, physicians can minimize these risks by prescribing appropriate medications and by monitoring for signs of an interaction.

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Competing interests statement
The authors declare no competing financial interests.

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CORRIGENDUM

Drug interactions in cancer therapy

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The references cited in Box 1 of this article were incorrect. The corrected box and references are reproduced below. The authors apologize for the error.

Box 1 | **Substrates and inhibitors of ABCB1 used in anticancer therapy**

Substrates

Actinomycin D[151]; daunorubicin[152]; docetaxel[153]; doxorubicin[154]; etoposide[155]; imatinib mesylate[156]; irinotecan[157]; mitoxantrone[158]; paclitaxel[159]; topotecan[160]; vinblastine[154]; vincristine[161].

Inhibitors

Gefitinib[162]; tariquidar[163]; teniposide[164]; valspodar (PSC 833)[165].

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