

PHARMACOKINETIC VARIABILITY OF ANTICANCER AGENTS

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Abstract | The translation of advances in cancer biology to drug discovery can be complicated by pharmacokinetic variation between individuals and within individuals, and this can result in unpredictable toxicity and variable antineoplastic effects. Previously unrecognized variables (such as genetic polymorphisms) are now known to have a significant impact on drug disposition. How can the pharmacokinetic variability of anticancer agents be reduced? This will require the understanding of correlations between pharmacokinetics and treatment outcomes, the identification of relevant patient parameters, mathematical modelling of individual and population pharmacokinetics, and the development of algorithms that will tailor doses to the individual patient.

ABSORPTION

The process by which a drug leaves its site of administration and enters systemic circulation. Not relevant to intravenously administered agents.

DISTRIBUTION

The process by which a drug distributes into interstitial and intracellular fluids.

METABOLISM

The process by which a drug undergoes biotransformation to a usually inactive (but sometimes active) metabolite.

EXCRETION

The process by which a drug and/or its metabolites are removed from the body.

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Pharmacokinetics can be defined as the study of the bodily **ABSORPTION**, **DISTRIBUTION**, **METABOLISM** and **EXCRETION** (ADME) profile of drugs (FIG. 1) or, put simply, what the body does to the drug. Most anticancer agents have wide interindividual pharmacokinetic variability and a narrow **THERAPEUTIC INDEX**. Systemic exposure after standard doses of cytotoxic drugs can vary 2–10-fold between patients^{1–3}. Pharmacokinetic parameters of many anticancer drugs are associated with treatment outcome. Therefore, high pharmacokinetic variability can make it difficult to predict how a patient will respond to a drug. Moreover, with decreased predictability comes increased risks of both toxicity and subtherapeutic dosing in the individual patient.

To decrease interindividual pharmacokinetic differences, doses should ideally be tailored to the individual patient (individualized dosing). Traditionally, this has been done by normalizing dose to body surface area (BSA), which is calculated from height and weight. However, studies have shown that this is inadequate⁴. In this review, we discuss the sources of interindividual and intraindividual variation in the pharmacokinetics of anticancer drugs. Several methods for quantifying and accounting for this variability are being explored. We discuss pharmacokinetic and genetic-based methods of dose adjustment and mathematical modelling schemes to guide dosing.

We explore methods of modulating pharmacokinetics using other drugs to reduce variability. Finally, we discuss the impact of pharmacokinetic variability on the design of clinical trials.

The aim of this review is not to catalogue the published pharmacokinetic variability of anticancer agents but instead to focus on concepts and the potential impact of variability on outcome. Most drugs that we refer to in this article are classic cytotoxic agents. The pharmacokinetic data available for these agents are, in general, more extensive than those for the newer, so-called ‘targeted’ agents, by virtue of the long history of use, so we use these here to illustrate the concepts of pharmacokinetic variability. However, the concepts apply to all anticancer agents, past, present and future, regardless of their mechanisms of action.

Quantifying pharmacokinetic variability

The pharmacokinetic profile of a drug is described by several numerical parameters (BOX 1) and whether or not the pharmacokinetics are linear or non-linear (BOX 2). Often, the reported pharmacokinetic data of anticancer agents consist simply of the mean values of these parameters with their standard deviations at each dose level evaluated. However, because it is the interindividual variability in these parameters that is important when understanding differences in patient

Summary

- The field of pharmacokinetics attempts to describe the bodily disposition of drugs in terms of numerical parameters that are calculated from plasma concentrations obtained at time points after drug administration. These parameters can be correlated with treatment outcomes such as toxicity and efficacy.
- Anticancer drugs can have considerable interindividual pharmacokinetic variability, which, given the narrow therapeutic index of these drugs, results in unpredictable clinical effects.
- There are many potential sources of pharmacokinetic variation, including interindividual differences in absorption, distribution, metabolism and excretion of anticancer drugs.
- A considerable amount of research is currently directed towards defining genetic polymorphisms in drug-disposition pathways that explain observed interindividual pharmacokinetic variability.
- Tailoring doses of anticancer drug to the individual patient will decrease interpatient pharmacokinetic variability and reduce the risks of severe toxicity and subtherapeutic treatment.
- Individualized dosing strategies currently being examined in the research setting are promising, although few are used in routine clinical practice.

outcomes, the **COEFFICIENT OF VARIATION (CV)** is the single best descriptor of pharmacokinetic variability. The 'spread' of a parameter is estimated by calculating the variance and standard deviation, and the CV provides a relative measure of data dispersion with reference to the mean. A high CV means the pharmacokinetics in an individual patient are unpredictable.

Once pharmacokinetic variability is recognized, the next step is to identify the many potential sources of the variation. Here, we systematically consider each of the steps of ADME of drugs (BOX 3).

Drug absorption

Most anticancer agents are administered intravenously or orally. Intravenous administration of drug is the most direct route and results in rapid and complete **BIOAVAILABILITY**, so that the prescriber is assured that the patient is receiving the desired dose. By contrast, the bioavailability of oral drugs is subject to absorption barriers and the **FIRST-PASS EFFECT**. As a result, oral agents characteristically have far greater

pharmacokinetic variability than intravenous agents. This is best demonstrated by anticancer agents that can be administered by either route. In a study of etoposide, an epipodophyllotoxin used in testicular and lung cancers, the CV of the **AREA UNDER THE CURVE (AUC)** (see BOX 1) for oral versus intravenous administration was 58% and 28%, respectively⁵. High pharmacokinetic variability can limit the use of oral agents when cure is the goal and subtherapeutic dosing is unacceptable. Etoposide is uniformly administered intravenously when used for testicular cancer, a curable malignancy even when metastatic, to ensure adequate drug exposure.

Absorption from the gut is governed by absorptive surface area, transit time through the gut, blood flow to the site of absorption, and gastric and intestinal pH^{6,7}. Because these factors can vary between patients and within a patient, they are all potential sources of pharmacokinetic variability. In addition, anticancer drugs are subject to intestinal transport and metabolism.

Intestinal drug transport and P-glycoprotein. P-glycoprotein (P-gp), a drug-efflux pump encoded by *ABCB1*, confers a multidrug-resistance phenotype to cancer cells by actively extruding drugs out of tumour cells^{8–12}. It is also expressed in the intestinal epithelium, where it might impede the oral uptake of anticancer drugs^{13,14}. Studies have shown that the absorption of oral paclitaxel, a taxane used to treat breast and lung cancers, is substantially increased in P-gp-knockout mice compared with wild-type mice, and that P-gp knockouts have a 6-fold higher AUC^{14,15}. Concomitant administration of P-gp inhibitors increases the oral bioavailability of paclitaxel in murine models^{16–20}. As we discuss below, this strategy has also been explored in human trials.

These observations indicate that variation in P-gp activity can lead to variation in drug pharmacokinetics, and recent research has focused on the differential expression of P-gp due to **POLYMORPHISMS** in *ABCB1* (REFS 21–24). In a study of 461 white volunteers, the allelic frequency of the 3435C>T (C to T change at nucleotide 3,435) polymorphism was 0.54, and 29% of the participants were homozygotes²⁵. This

THERAPEUTIC INDEX

Conceptual description of the ratio of the toxic dose to the therapeutic dose of a drug, describing the dose range over which a drug is therapeutic but not unacceptably toxic.

COEFFICIENT OF VARIATION

The ratio of the standard deviation to the mean, multiplied by 100%. A high coefficient of variation means high interindividual variability.

BIOAVAILABILITY

The fraction of an administered dose that reaches systemic circulation.

FIRST-PASS EFFECT

The decrease in bioavailability of an oral drug owing to enteric metabolism, hepatic metabolism and excretion before the drug reaches the systemic circulation.

AREA UNDER THE CURVE (AUC)

The area under the curve in a graph of plasma concentration against time — a measure of drug exposure.

POLYMORPHISM

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

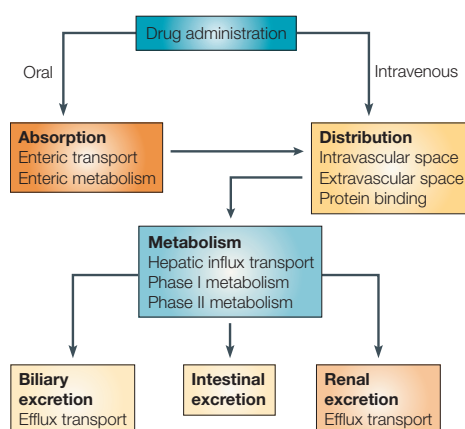


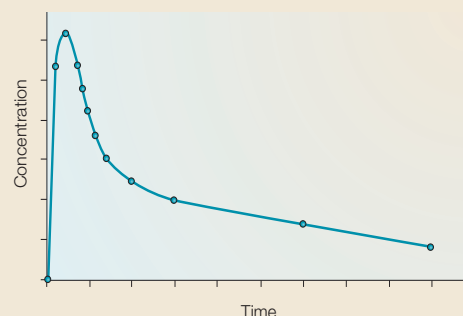
Figure 1 | The process of drug disposition. The process of drug disposition can be divided into four parts — absorption, disposition, metabolism and excretion — and each part has several steps within it. Interindividual and intraindividual differences in these steps are potential sources of pharmacokinetic variability.

Box 1 | The commonly reported pharmacokinetic parameters for anticancer drugs

The minimal data required to characterize a drug's pharmacokinetics are the route of administration, dose administered, dosing interval, plasma drug concentrations, and collection times relative to drug administration. The area under the curve (AUC) in a graph of plasma concentration against time, is a measure of drug exposure (see figure). The measure of the body's ability to remove drug from the blood or plasma, referred to as clearance, is the ratio of dose administered to AUC.

The period of time required for the plasma concentration of a drug to be reduced by one-half is the drug's half-life. For most drugs, half-life is not constant, but initially falls rapidly and then decreases slowly. The initial fall is due to drug distribution to extravascular sites, whereas the slower rate of decrease, representing the terminal half-life, is a function of drug elimination. It is the terminal half-life that determines the dosing interval, with more frequent administration for drugs with short terminal half-lives. As a general rule, the higher the clearance, the shorter the half-life.

The body can be represented as a collection of separate compartments (for example, vascular, interstitial and intracellular) in which a drug distributes at different concentrations. The volume of distribution is the apparent volume required to account for all of the drug in the body if it were present throughout the body in the same concentration as in the plasma. This volume does not have a strict physiological basis but is a proportionality factor between the concentration of drug in the plasma, which is the only compartment accessible to sampling, and the total amount of drug in the body.



polymorphism is correlated with intestinal P-gp protein expression levels and the oral bioavailability of the non-cancer drugs digoxin, used for heart conditions, and phenytoin, an anticonvulsant^{21,23,26}. However, the putative importance of *ABCB1* polymorphisms in anticancer-drug pharmacokinetics remains controversial, with contradictory findings in the published literature and the positive studies consisting of small sample sizes. Nonetheless, this is an emerging area of investigation, as researchers attempt to explain the observed interindividual differences of orally administered drugs. Other intestinal drug-transport proteins that have been described include the products of *ABCC2* and *ABCG2* (REFS 27,28).

Intestinal drug metabolism and CYP3A. As part of the first-pass effect, orally administered drugs are subject to intestinal metabolism. CYP3A is a major subclass of the CYTOCHROME P450 ENZYMES and is located in both the liver and gut. Members of the CYP3A family account for more than 70% of intestinal cytochrome p450 expression^{29,30}. CYP3A4 is localized to the apex of mature enterocytes, adjacent to the microvillus border, and is the predominant P450 enzyme in the intestines^{29–35}. Kolars and colleagues performed an elegant experiment in which they administered cyclosporine, a CYP3A4 substrate, directly into the small bowel of two patients during the anhepatic phase of liver transplantation surgery³⁶. By measuring drug metabolite levels in the portal venous blood, they found that as much as 50% of cyclosporine was metabolized by enterocyte CYP3A4, demonstrating that intestinal metabolism can comprise a significant portion of the overall metabolism of a drug.

The potential for interindividual variability in CYP3A4 activity was shown by a study of 20 patients who underwent small-intestine biopsies³⁷. Investigators found an 11-fold variation in CYP3A4 protein content and an 8-fold variation in mRNA levels. Hepatic CYP3A4 is involved in the metabolism of many different anticancer drugs (for example, the taxanes, etoposide, irinotecan, ifosfamide, imatinib and the *Vinca* alkaloids). Therefore, CYP3A4 polymorphisms might have important consequences for the pharmacokinetics of oral agents. However, for anticancer agents, a statistically significant correlation between genetic variation in *CYP3A4* and drug pharmacokinetics has not yet been described.

Although CYP3A4 and CYP3A5 have overlapping substrate specificity, the relative importance of CYP3A5 in intestinal metabolism of anticancer drugs is less clear. Although an early study of small-intestinal CYP3A expression reported its presence in most of the 20 patients examined³⁷, a more recent study of 10 human small intestines failed to detect any CYP3A5 protein³⁸. At the very least, this indicates that CYP3A5 expression in the small bowel is variable. As a result, oral agents that are significantly metabolized by this enzyme in the gut might display interpatient variation in bioavailability.

Drug distribution

Following absorption or intravenous administration, a drug distributes from the intravascular space to its target in the extravascular space. Most drugs bind to plasma proteins, such as albumin and α_1 -acid glycoprotein. The amount of drug that moves to the extravascular space depends, in part, on how much drug is bound — protein-bound drug is not free to

CYTOCHROME P450 ENZYMES
A family of haeme-containing intracellular oxidizing enzymes that are responsible for the first phase of metabolism of many drugs.

Box 2 | Linear versus non-linear pharmacokinetics

Drugs have either linear or non-linear pharmacokinetics. Linear pharmacokinetics means that the area under the curve (AUC) is directly proportional to dose. Therefore, a doubling of the dose results in a doubling of the AUC. Other characteristics of linear pharmacokinetics are a half-life that is independent of concentration and a clearance that is independent of dose and dosing interval. Therefore, AUC is not affected by changes in the administration interval. For example, the AUC after a 75 mg/m² dose equals the total AUC for three daily doses of 25 mg/m². The AUC would be the same if the 75 mg/m² were given continuously over 72 hours.

Non-linear pharmacokinetics commonly implies that some aspect of the pharmacokinetic behaviour of the drug is saturable^{132,133}. This can be due to saturation of drug transport or metabolic systems and is recognized by a decrease in drug clearance at higher doses. The implication of non-linear pharmacokinetics is that AUC will vary with dose and dosing interval. For example, at higher doses of 5-fluorouracil, used in colorectal cancer, there is saturation of the enzyme that converts it to the inactive dihydrofluorouracil by dihydropyrimidine dehydrogenase^{134–136}, so that a doubling of the dose from 7.5 mg/kg to 15 mg/kg results in a 135% increase in AUC⁷. Therefore, the behaviour of drugs with non-linear pharmacokinetics is not as predictable as that of drugs with linear pharmacokinetics.

distribute and only 'free' drug is pharmacologically active. Because protein binding is usually a saturable process, differences in plasma protein levels between patients will result in variable drug distribution^{39–41}. In cancer patients, malnutrition and hepatic dysfunction due to liver metastases commonly lead to hypoalbuminaemia. For a highly bound drug, the same dose results in higher levels of unbound drug in the hypoalbuminaemic patient than in a patient with normal synthetic function. Alternatively, an inflammatory condition can lead to increased protein binding due to increased levels of α_1 -acid glycoprotein and other acute-phase reactants⁴². Therefore, differences in medical condition among patients and within patients over time can lead to variability in the volume of distribution. However, in spite of the potential impact of protein binding on volume of distribution, there is a general consensus that changes in plasma protein binding does not result in clinically important pharmacokinetic changes for most drugs.

Drug metabolism

Metabolism is the most crucial and complex step of drug disposition and can be a major source of pharmacokinetic variability. Hepatic uptake of drugs is mediated by transporter proteins. Once in the liver, anticancer drugs undergo phase I and phase II reactions. Phase I reactions are oxidative or reductive reactions and result in the loss of pharmacological activity or the activation of inactive *PRODRUGS*. Phase II reactions conjugate phase I products to form usually inactive polar derivatives for renal and biliary elimination. Many of the genes that encode drug transporters and phase I and II enzymes are polymorphic, and as such are candidate sources of interindividual pharmacokinetic variability. Few identified polymorphisms to date have been shown to alter the pharmacokinetics of anticancer drugs, but we describe some examples below.

Hepatic drug uptake. The members of the organic anion-transporting polypeptide (OATP) transporter families transport drugs and their metabolites from the blood into the hepatocytes. A recent review has

compiled the currently known OATP genetic polymorphisms⁴³. Although none of these have yet been found to have clinical or pharmacokinetic consequences in humans with regard to anticancer agents, there is a pertinent example from outside oncology: an *in vivo* study of 120 healthy Japanese individuals given pravastatin, a lipid-lowering agent, demonstrated that individuals with the variant allele *SLCO1B1*15* of the transporter gene *SLCO1B1* had lower clearance values than those who were homozygous for *SLCO1B1*1b* (REF. 44). We are currently analysing the results of a *PHARMACOGENETICS* trial in which 65 patients receiving irinotecan underwent genotyping of relevant OATPs to determine if observed interindividual differences in irinotecan clearance can, at least in part, be explained by OATP polymorphisms.

Phase I metabolism. Phase I metabolism is dominated by the cytochrome P450 system, and more than 55 cytochrome P450 isoenzymes have been identified in humans. The important isoforms for anticancer drugs are CYP1A, CYP2B, CYP2C and CYP3A (REF. 45). CYP3A proteins are involved in the metabolism of 45–60% of all used drugs^{46,47}, and CYP3A4 accounts for most CYP3A in the liver^{48,49}. As is the case in the small intestine, CYP3A5 is not uniformly present in human livers and might be expressed in only 25–30% of people^{37,48,50}. The pharmacokinetic and clinical consequences of this observation are unknown, though one can expect that if a particular drug is extensively metabolized by this enzyme, then the clearance will manifest a high CV.

Cancer patients can have reduced cytochrome P450 activity compared with healthy individuals. CYP2C19, which is involved in the metabolism of the chemotherapeutic agent cyclophosphamide used in lymphoma and breast cancer, has reduced activity in patients with advanced cancer compared with a healthy reference population⁵¹. This difference cannot be explained by genetic differences between the two groups. In study of CYP3A activity in patients with advanced cancer, researchers noted a 14-fold variation in enzyme activity within this population, again not

PRODRUGS

Pharmacologically inactive derivatives of active drugs that must undergo metabolic conversion to the active agent.

PHARMACOGENETICS

The study of genetically determined variations in drug response.

Box 3 | Sources of ADME pharmacokinetic variability in cancer

Below are common sources of pharmacokinetic variability arranged according to the steps of absorption, distribution, metabolism and excretion (ADME) that they most affect. Prescribers should consider these variables when evaluating the potential for unexpected or unwanted outcomes when treating with anticancer agents.

Absorption

- Previous surgery, radiation or chemotherapy
- Nausea and/or vomiting
- Patient compliance
- Diet
- Genetic differences in intestinal drug-metabolizing and drug-transport systems
- Concomitant medications

Distribution

- Amount of body fat
- Presence of extravascular fluid collections (for example, PLEURAL EFFUSION)
- Hypoalbuminaemia
- Concomitant medications

Metabolism

- Hepatic dysfunction
- Altered hepatic blood flow (age-related changes)
- Genetic differences in hepatic drug-metabolizing and drug-transport systems
- Concomitant medications

Excretion

- Hepatic dysfunction
- Renal insufficiency
- Urinary pH
- Genetic differences in drug-elimination pathways
- Concomitant medications

explained by genetic polymorphisms⁵². The reason for these differences are not obvious, but hypotheses include increased levels of cytokines, impaired liver function and increased inflammatory response^{42,53–55}. These cancer-related effects can contribute to the interpatient pharmacokinetic variation of agents that are substrates of these enzymes.

Other phase I enzymes include ketoreductase, aldehyde dehydrogenase, carboxylesterases, dihydropyrimidine dehydrogenase (DPD) and cytosine deaminase. Many of these are polymorphic with described consequences for non-cancer agents, but in anticancer therapy the best-known example of a phase I functional variant is DPD deficiency. This enzyme is rate-limiting in the catabolism of 5-fluorouracil (5-FU), a standard colorectal chemotherapy, and is responsible for the degradation of 80–90% of the drug to an inactive metabolite⁵⁶. Out of 19 DPD variant alleles associated with decreased enzyme activity, a G to A point mutation in the splice donor site flanking exon 14 appears to be the most common, with an estimated frequency of 0.0091 in Caucasians^{57,58}. This mutation results in a truncated protein product and reduced activity, severely so in homozygotes⁵⁹. The pharmacokinetic consequences of DPD deficiency are decreased clearance and

increased half-life of 5-FU. Clinically, low levels of DPD have been associated with severe 5-FU-induced toxicity, including diarrhoea, neutropaenia and death^{59–62}. The low frequency of this mutation, however, makes pre-treatment screening impractical in clinical practice.

Phase II metabolism. For anticancer agents, one well-studied phase II conjugation reaction is glucuronidation, which is catalysed by uridine diphosphate glucuronosyltransferases (UGTs)⁶³. Many of these enzymes are polymorphic and these variants can have pharmacokinetic consequences. For example, gene transcriptional efficiency is inversely correlated with the number of TA repeats in the TATA box of *UGT1A1* (REF. 64), and we have reported on the pharmacokinetic impact of this *UGT1A1* polymorphism in a phase I study of irinotecan⁶⁵. In that study, we found that the AUC for SN-38, the active metabolite of irinotecan, is directly correlated with the number of TA₇ (7 TA repeats) alleles ($P=0.03$) so that TA₇ homozygotes had the highest AUC values and a mean AUC that was 1.6 times greater than that of TA₆ homozygotes. Clinically, these patients also had a significantly higher risk of severe neutropaenia. As the TA₇ allele exists at a frequency of 0.29, genetic screening in this instance might indeed be practical.

Drug excretion

The main routes of drug excretion are through the biliary tract and kidneys. Excretion of anticancer agents through the lungs, skin, sweat and tears is quantitatively negligible.

Biliary excretion. A range of transport systems are involved in the biliary excretion of drugs, including the ATP-binding cassette (ABC) transporters ABCB1, ABCC2 and ABCG2. ABCB1 is involved in the transport of AMPHIPATHIC and lipid-soluble drugs, whereas ABCC2 is mainly involved in the secretion of conjugated metabolites. The role of ABCG2 has not been fully characterized. Catalogues of ABC-transporter polymorphisms have been published^{66–70}, and these are all potential sources of pharmacokinetic variability. ABCB1, ABCC2 and ABCG2 seem to be involved in the transport of SN-38 from the liver into the biliary tree^{71,72}, and we are actively involved in the discovery of polymorphisms that affect irinotecan pharmacokinetics.

Concomitant medications and disease processes affecting the liver can negatively affect these transport mechanisms and reduce biliary excretion of anticancer drugs. For example, mechanical obstruction of the biliary tree by hepatic metastasis can interfere with biliary excretion, and the fall in serum albumin associated with malnutrition has been associated with decreased biliary excretion of anticancer drugs^{73–76}. Cancer patients occupy the entire spectrum of hepatic function, from unaffected to frank liver failure, and this invariably results in pharmacokinetic variability.

PLEURAL EFFUSION
An abnormal collection of fluid between the thin layers of tissue (pleura) lining the lung and wall of the chest cavity.

AMPHIPHATHIC
Containing both hydrophilic and hydrophobic domains.

Renal excretion. Some anticancer drugs, such as platinum compounds, are eliminated primarily through the kidneys. Diseases that cause renal insufficiency, as gauged by the GLOMERULAR FILTRATION RATE (GFR), reduce the clearance of these drugs. The GFR decreases with age and can also be altered by nephrotoxic drugs. For example, the coadministration of non-steroidal anti-inflammatory pain medications, such as aspirin and ibuprofen, with cisplatin, a platinum agent used in bladder and testicular cancer, has had lethal effects⁷⁷, presumably by reducing cisplatin clearance. Urinary pH can also influence drug excretion. For example, the administration of sodium bicarbonate makes urine more alkaline and this increases the excretion of methotrexate⁷⁸, an antifolate analogue used in leukaemia, lymphoma and breast cancer. Concomitant medications, vitamins or foods that alter urinary pH can also affect renal drug excretion.

Other sources of pharmacokinetic variability

Age. Age-related changes in drug disposition (TABLE 1) can make age a significant pharmacokinetic variable. This is important because there is an 11-fold greater incidence of cancer in persons 65 years of age or older, and more than 60% of all cancers diagnosed are in individuals in this age bracket⁷⁹. These changes can be subtle and are not reflected in routine blood tests. For example, the metabolic changes described in TABLE 1 will not alter standard liver-function tests (such as serum aspartate aminotransferase and alanine aminotransferase) so that age-related hepatic dysfunction might go unrecognized, putting the patient at risk of overdose. There are currently no guidelines as to when anticancer dosing should be adjusted for age, and clinical trials directed at the elderly are required.

Prescription drug interactions. As we have already alluded to, drug–drug interactions can affect every step of drug disposition. An oncologist must not only consider the impact of the patient's prescription medication list as they decide on anticancer-drug dosing, but must also consider the possible pharmacokinetic and therapeutic consequences every time he/she prescribes a new drug. A recently described example of a drug–drug interaction with potential therapeutic implications is that of tamoxifen, a selective oestrogen-receptor modulator used in breast cancer therapy, and selective serotonin reuptake inhibitor (SSRI) antidepressants (examples include paroxetine and fluoxetine). Tamoxifen and SSRI antidepressants are both metabolized by CYP2D6.

Tamoxifen is used in breast cancer therapy in both the metastatic setting and adjuvant setting (when cure is the goal) and for the prevention of breast cancer in high-risk women. A frequent side effect of therapy is hot flashes, for which SSRI antidepressants are commonly prescribed. Investigators reported the results of a prospective clinical trial of 80 breast cancer patients beginning tamoxifen therapy⁸⁰. After 4 months of treatment, 29% of patients were taking SSRI antidepressants. Mean plasma concentrations

of endoxifen, an active metabolite, decreased by 56% with paroxetine coadministration ($P=0.02$). Moreover, reductions in endoxifen concentrations were statistically more pronounced in patients with variant as compared with wild-type CYP2D6 genotype. Although it is not known at present whether lower endoxifen concentrations have a clinical consequence, these data raise the question of whether concomitant administration of SSRI antidepressants to reduce the side effects of tamoxifen might actually jeopardize a patient's therapy.

Herbal and vitamin supplements. There is increasing concern over the risks associated with herbal medicines and nutritional supplements when used in combination with chemotherapy. Because they are not regulated by the United States Food and Drug Administration, little is known about their pharmacology. The increased use of these products by cancer patients over recent years⁸¹ and the perceived absence of risk can have unexpected pharmacokinetic and toxic effects. For example, St John's wort (*Hypericum perforatum*) is a known ligand for the pregnane X receptor (PXR) and can therefore induce the transcription of genes regulated by PXR, including CYP3A and UGTs^{82–85}. The use of St John's wort decreases plasma concentrations of the active metabolite SN-38 in irinotecan-treated patients, prompting concerns that the efficacy of irinotecan might be reduced⁸⁶. Patients who take herbal remedies that might cause unwanted interactions are now routinely excluded from cancer clinical trials. The unknown affects of these products on anticancer therapy should prompt government regulation to, at the very least, standardize the impact of herbal remedies on patients undergoing cancer treatment.

Food. Foodstuffs can also interfere with drug pharmacokinetics. The best-described example of this is grapefruit juice, which decreases the intestinal activity of CYP3A4 (REFS 87,88). As a result, the oral bioavailability of drugs that are subject to enteric metabolism by this enzyme might be augmented by concomitant (or even previous) use of grapefruit juice. This interaction can be viewed as positive for oral anticancer drugs that otherwise have low bioavailability. However, the use of grapefruit juice can also cause unexpected and toxic drug exposure. Pharmacokinetic trials of oral anticancer agents routinely prohibit the use of grapefruit juice.

Ethnicity. Differences in drug pharmacokinetics across ethnic groups have been observed for non-anticancer agents; one well-described example is the increased oral clearance of drugs that are CYP3A and/or P-gp substrates in African Americans compared with Caucasians^{89–92}. However, similar ethnic differences have not yet been demonstrated for anticancer drugs. A clinical trial of docetaxel, which is a substrate for CYP3A4, CYP3A5 and P-gp, in Caucasian and African-American patients failed to show any difference in docetaxel pharmacokinetics

GLOMERULAR FILTRATION RATE
A measure of renal function that equals the quantity of glomerular filtrate formed per unit of time in all nephrons of both kidneys.

Table 1 | Age-related changes that affect absorption, distribution, metabolism and excretion

Change	Impact on drug pharmacokinetics	References
Absorption		
Reduced gastric-acid secretion; reduced splanchnic blood flow; reduced gastrointestinal motility; concurrent use of many drugs (polypharmacy)	All can potentially reduce drug bioavailability. The multiple concomitant drugs taken by elderly patients can compete for binding sites on transporter proteins or change pH. Effects of age-related changes on absorption are unclear.	137–140
Distribution		
Increased proportion of body fat; reduced intracellular water; reduced plasma albumin; anaemia; polypharmacy	Between ages of 25 and 75 years, fat content increases from 15% to 30% of body weight and intracellular water is reduced from 42% to 33%, causing a reduction in Vd of water-soluble drugs and an increase in Vd of lipid-soluble drugs. Anaemia is a risk factor for increased toxicity of red-cell-bound drugs. A decrease of up to 15–20% in plasma albumin can increase the free fraction of drug.	141–145
Metabolism		
Reduced liver mass; reduced cytochrome P450 activity; polypharmacy	Autopsy studies indicate that the mass of the liver is reduced by 20–50% by 80 years of age, thereby decreasing the amount of metabolic enzymes. Phase I metabolism is reduced, with 30% less activity of several members of the P450 system in healthy older people compared with healthy younger people. Phase II metabolism is preserved.	145–147
Excretion		
Reduced hepatic blood flow; reduced renal blood flow; reduced GFR/CrCl; polypharmacy	Hepatic excretion of drugs can be negatively impacted by a reduction in blood flow to the liver. Loss of nephron mass with age is predictable, with a reduction in GFR by 1 ml/min for every year over the age of 40 years. A reduction in GFR is not reflected by an increase in serum creatinine, and calculated estimates of CrCl in the elderly might not be accurate.	148–150

CrCl, creatinine clearance; GFR, glomerular filtration rate; Vd, volume of distribution.

or drug-induced myelosuppression between the two groups⁹³. Nonetheless, the observation of ethnic differences in outcomes after anticancer drug therapy could prompt the discovery of functional polymorphisms when there are ethnic differences in the allelic frequencies of important drug-disposition genes.

Strategies for dose individualization

Dose individualization is the best method of reducing interindividual variability. The traditional practice of normalizing dose to BSA takes into account only two of a multitude of variables — height and weight. Although BSA has been found to correlate statistically with the pharmacokinetics of a few anticancer agents (such as docetaxel⁹⁴ and paclitaxel⁹⁵), for most agents it has not. Dose normalization to BSA only makes sense when there is a statistically significant relationship between pharmacokinetics and BSA and when that relationship explains a substantial portion of the interpatient pharmacokinetic variability.

Pharmacokinetic-based dosing. Dosing schemes that are driven by the pharmacokinetic properties of a drug can be useful for individualizing dose. The classic example is carboplatin, an analogue of cisplatin that is used in lung and ovarian cancer. When it was first introduced, its dosing was based on BSA. However, clinicians quickly realized that some

patients were being underdosed, whereas others experienced unexpected toxicity⁹⁶. A strong correlation was found between carboplatin clearance and GFR (correlation coefficient, $r=0.85$), which led to the formula that is currently used: $\text{dose} = \text{AUC} \times (\text{GFR} + 25)$, where AUC is chosen (based on clinically established disease-specific AUC targets) and the patient's GFR is calculated^{97,98}. Dosing of carboplatin based on this formula is now routine.

Alternatively, initial treatment doses can be used to establish the individual's pharmacokinetics for that drug, on which subsequent doses are based. Such a scheme has been used for oral busulfan, an alkylating agent that is used in leukaemia therapies, which has linear kinetics (BOX 2) but high interindividual variability. Pharmacokinetic-based dosing of this sort is appropriate for busulfan, for which there is not only a correlation between AUC and hepatic VENO-OCCLUSIVE DISEASE (VOD), but also between AUC and recurrence rates after allogeneic bone-marrow transplant^{99–103}. However, this strategy still suffers from the risk of subtherapeutic and supratherapeutic dosing during the initial doses. A paediatric study of busulfan circumvented this problem by administering a test dose before definitive dosing¹⁰⁴. Twenty-nine patients who were to undergo busulfan-based chemotherapy first received a small test dose of 0.5 mg per kg of body weight. Test dose AUCs were

VENO-OCCLUSIVE DISEASE
A complication of bone-marrow transplantation in which there is obstruction of the terminal venules and/or sinusoids in the liver. Clinical features include hyperbilirubinaemia, painful hepatomegaly and fluid retention.

determined, and definitive doses were calculated by multiplying 0.5 mg/kg by the ratio of the target AUC to the test-dose AUC. The investigators demonstrated that the actual AUC of the definitive dose was within 80–120% of target AUC in 83% of patients and within 90–110% in 52%. The incidence of VOD was 3.4% in the test group versus 24.1% in a control group (that had been treated with standard doses). This strategy has been accepted as standard of care in some academic institutions.

Genotype-directed dosing. The goal of pharmacogenetics is to identify patients who are at risk for poor outcome to drug treatment. Pharmacogenetics can also identify those patients who will have favourable pharmacokinetics that allow them to tolerate higher-than-standard doses with possible increased antitumour effect. For example, variation in the *UGT1A1* gene correlates with irinotecan toxicity (see section on phase II metabolism)⁶⁵. Homozygosity for the TA_7 allele has been identified as a high-risk genotype for high SN-38 AUC and toxicity, whereas TA_6 homozygotes are low-risk. It is reasonable to expect that this second group will tolerate higher, and perhaps more efficacious, doses. We are currently planning a clinical trial in colorectal cancer patients to determine whether this is the case. As more drug-disposition polymorphisms are discovered, pathway-based models can be created, as it is more likely that a combination of polymorphisms in several disposition proteins is more important than a single variant. A patient could then undergo relevant genotyping before treatment and be dosed according to the results.

Phenotype-based dosing. As we have discussed, a clear relationship between genetic polymorphisms and enzyme activity has not yet been established in most cases. For this reason, researchers are exploring phenotype-based dosing as a surrogate. For example, investigators have developed a novel method of estimating the interpatient variability of CYP3A4 by measuring the urinary metabolite of exogenous cortisol¹⁰⁵. Urinary 6- β -hydroxycortisol (6- β -OHF) is significantly correlated with the clearance of docetaxel, which is metabolized by CYP3A4. In a clinical trial of docetaxel in 59 patients with non-small-cell lung cancer, patients were randomized to either a conventional BSA-based dosing group or an individualized dosing group¹⁰⁶. In the second group, estimated clearance was calculated based on the individual's measured 24-hour urinary 6- β -OHF after an administered dose of cortisol, and docetaxel dose was calculated as the product of the estimated clearance and a previously determined target AUC. The standard deviation of the AUC was significantly smaller in the individualized group compared with the BSA-based group ($P < 0.01$). Although this particular method of dosing is cumbersome, it does demonstrate the potential of this approach for reducing interpatient pharmacokinetic variability.

Population pharmacokinetic modelling. Population pharmacokinetics is the study of the variability in plasma drug concentrations between individuals who receive standard dosage regimens and who represent the target patient population. Population pharmacokinetic models aim to account for observed interindividual variation in terms of patient variables called covariates. These covariates can include any sources of variability. Population modelling allows the quantification of the relative importance of the covariates; Bayesian estimation, which evaluates the individual's data relative to the population pharmacokinetic model, can then be used to estimate patient-specific pharmacokinetic parameters to calculate an optimal dose for the individual. A detailed description of modelling methods is beyond the scope of this review, but several comprehensive discussions are available in the literature^{107–110}.

Epirubicin, an anthracycline used in breast cancer therapy, exemplifies how population modelling can lead to dose individualization. Because epirubicin is predominantly cleared by the liver, its pharmacokinetics are altered (specifically, clearance is reduced) in patients who have hepatic dysfunction, and this can result in severe toxicity with standard doses. The current product label recommends dose reduction based on serum BILIRUBIN levels (as a surrogate measure of hepatic function)¹¹¹. These recommendations are not based on data, as patients with hepatic dysfunction were excluded from the original dosing studies. For this reason, Ralph and colleagues used a population modelling approach to develop new dosage guidelines that are better tailored to the patient¹¹². Based on a data set of 109 breast cancer patients treated with epirubicin, of whom 72 were known to have liver metastases, the authors developed a population pharmacokinetic model, with clearance as the predicted parameter and serum aspartate aminotransferase (AST; a standard blood test for liver function) as the most relevant covariate: clearance (in litres (l) per hour (h)) = $72.9 - (72.9 \times 0.135 \times \ln(\text{AST}))$. Other covariates, including bilirubin, did not improve the model. With this formula and a measured AST, a patient's epirubicin clearance can be predicted. Then, using the relationship $\text{AUC} = \text{dose/clearance}$ and a target AUC of 4000 nanograms·h/ml, based on published toxicity data¹¹³, the oncologist can calculate a safe but effective dose that is individual to the patient. Despite impressive data indicating that models such as this one can improve dosing, these models have, in general, not been adapted in clinical practice, and prospective studies will be required to demonstrate the efficacy of such a strategy.

Pharmacokinetic modulation

Pharmacological inhibitors of key metabolic and transporter enzymes can be used to enhance the activity of drugs and reduce interindividual variability. This strategy has been most thoroughly studied with paclitaxel. Oral administration of paclitaxel allows for chronic continuous dosing, and both non-clinical and clinical studies have indicated that prolonged drug

BILIRUBIN

A breakdown product of haeme that circulates in the plasma, is taken up by the liver and conjugated so that it is water soluble, and is then excreted in the bile. It is routinely measured as a blood test to assess liver function.

exposure improves drug activity^{114–116}. However, as we discussed earlier, low bioavailability owing to the efficient transport by P-gp^{14–20,117,118} limits paclitaxel's clinical usefulness. In a Phase I study, coadministration of the P-gp inhibitor cyclosporine increased the apparent bioavailability of oral paclitaxel 8-fold, from 4% to 47%¹¹⁷. The investigators speculated that in addition to P-gp inhibition, drug exposure was further improved by the concomitant inhibition of hepatic and intestinal CYP3A4 by cyclosporine. Phase II studies of the combination of oral paclitaxel and cyclosporine in non-small-cell lung cancer¹¹⁹ and gastric cancer¹²⁰ showed acceptable antitumour efficacy with overall response rates comparable to other single-agent studies in these diseases^{121–126}.

Cyclosporine also inhibits the biliary excretion of irinotecan metabolites¹²⁷, and as part of a dose-escalation study, 41 colorectal cancer patients were treated with irinotecan every 2 weeks both with and without oral cyclosporine¹²⁸. Twenty patients underwent pharmacokinetic sampling during both treatments, and investigators demonstrated significant increases in irinotecan, SN-38 (active metabolite) and SN-38G (inactive metabolite) AUCs and marked reduction in irinotecan clearance (5.8 l/h/m² versus 13.4 l/h/m²). Indeed, the effect of adding cyclosporine to 100 mg/m² irinotecan was to bring the AUC in line with previously published values of AUC for 250 mg/m² standard-dose irinotecan alone, demonstrating that similar drug exposure can be obtained with a 60% lower dose. At current average wholesale prices in the United States, the approximate cost for the recommended doses of cyclosporine and irinotecan for a 1.8 m² patient per 2-week cycle is US\$1,134 versus \$1,553 for irinotecan 250 mg/m². In light of the high cost of chemotherapy, this example demonstrates a practical method of cost savings without compromising treatment.

Clinical trial design

Traditionally, Phase I pharmacokinetic studies of new anticancer agents aim to establish the Phase II recommended dose using the smallest sample size possible (usually 1–6 patients per dose level). If the true interindividual pharmacokinetic variability of a drug is high, the chances of observing that variation are low with such small patient samples. However, as the number of patients treated with the drug increases through Phase II and III studies, patients with extreme pharmacokinetics are eventually captured, but without correlative pharmacokinetic data to explain their unexpected clinical outcome (such as severe toxicity due to low drug clearance). This can be avoided by enrolling extra patients in the Phase I pharmacokinetic study at the dose that will be carried forward into Phase II and III trials to better understand the relationship of pharmacokinetic variability to toxicity and potential biomarkers. Although some investigators have adopted this practice, in general pharmaceutical companies are reluctant to invest the additional money and clinical-trial time, as doing so is not a regulatory requirement.

The recognition of significant interindividual variability should also prompt the consideration of expanding pharmacokinetic analysis into later-phase studies. Because the typical Phase I population consists of patients with advanced cancer whose disease is refractory to standard therapy, toxicity, and not efficacy, is the only expected clinical outcome in Phase I trials. Pharmacokinetic variability can best be correlated with efficacy by performing pharmacokinetic analyses in Phase II and III trials, in which efficacy is a defined end point.

The randomized concentration-controlled trial (RCCT) recognizes the relationship between variability in pharmacokinetics and variability in drug effect¹²⁹. In contrast to traditional randomized dose-controlled trials, in which drug effects to different drug dosages are measured, RCCTs assign individuals to concentration ranges. The relationship of concentration to effect is then analysed. Instead of retrospectively observing concentrations at pre-specified doses, the investigator controls concentration by adjusting dose. A recent trial of topiramate, an antiepileptic agent, demonstrates its potential value for defining the relationship between plasma concentration and response¹³⁰. The general concept of the RCCT could be incorporated into early dose-finding trials of anticancer drugs in which patients are not assigned to dose levels but to concentration levels.

Future directions

Recent advances in our understanding of cancer biology have led to the development of many new drugs. However, we must recognize the difficulties in translating an exciting compound into an efficacious drug that can be administered to a diverse population of patients. There are many steps between ingestion (or injection) and action on the target, with many sources of pharmacokinetic variability that can obscure the activity and efficacy of an agent. These sources of variability require careful consideration of the dose-response curve, both in populations of patients and in individual patients.

There needs to be greater attention to the development of pharmacokinetic information in the context of larger cancer clinical trials by collecting DNA samples (from peripheral mononuclear cells) for the genotyping of candidate polymorphisms (or even whole-genome typing) and plasma for population pharmacokinetics. Although there have been extensive studies of the relationship of pharmacokinetic data to clinical outcomes, the greater challenge will be relating genotypic data (particularly if whole-genome typing is used) to variability in both pharmacokinetics and clinical effects. Hopefully this will lead to advances comparable to those achieved with whole-genome microarray profiling to predict response and/or survival in breast cancer, leukaemia and lymphoma. Eventually, we will be able to tailor dosing based on whole-genome typing and, because this typing will be conducted before any foreseeable need for anticancer therapy, the benefits will apply to any type of pharmaceutical intervention¹³¹.

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Competing interests statement
The authors declare no competing financial interests.

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