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Review

How to dose cytotoxic chemotherapeutic drugs

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ABSTRACT

Because cytotoxic chemotherapeutic agents have narrow therapeutic windows and large interindividual variability in pharmacokinetics/ pharmacodynamics, dosing of these agents requires precise individual adjustment. Although the body-surface area (BSA) has long been used for this purpose, its effectiveness for minimizing interpatient variability in pharmacokinetics has been questioned. In this review, the factors that possibly contribute to inter-individual variability in drug response are reviewed, with a special focus on cytotoxic chemotherapeutic drugs such as platinum-containing agents, taxanes, irinotecan, and antimetabolites. Given that use of BSA fails to minimize inter-patient variability in drug response, causes inconvenience in reconstituting individual doses, and can result in human error, initial flat dosing with subsequent therapeutic drug monitoring might be a reasonable option that also has economic benefits.

KEYWORDS: chemotherapy, pharmacokinetics, pharmacogenomics, pharmacodynamics, cytochrome P450, single nucleotide polymorphism

INTRODUCTION

Classic cytotoxic chemotherapeutic agents are known for their relatively narrow therapeutic windows. This means that “low” doses of these drugs may not be effective and “high” doses may be (very) toxic for the patient. Therefore, the optimal dose should yield maximal therapeutic effects while producing tolerable and manageable toxicities, thereby leading to the best possible treatment. According to the theory that large patients have a larger volume of distribution and a higher metabolic capacity, it is assumed that these patients need to receive a higher dose than smaller patients would to achieve equivalent drug concentrations. For this reason, the administered dose is traditionally adjusted to the body-surface area (BSA) of the individual patient [1]. BSA was originally calculated using a formula based on length and weight that was developed in the 1910s from an investigation that involved only nine individuals [2]. Although validation of the derived formula was not performed initially, the use of BSA was incorporated into animal studies for the purpose of allometric scaling, and later in the 1950s, BSA-based dosing was introduced into pediatric oncology [3, 4]. Without further study, its use was also incorporated into drug dose calculation in adults (to obtain a safe starting dose in phase I trials). Currently it is still the standard method used for many chemotherapeutic agents [5].

With the exception of carboplatin [6, 7], it was a long time before concerns were raised about the appropriateness of the use of BSA in oncology. Many studies have now been performed that clearly show that (most frequently) BSA-based dosing does not yield the desired minimization of interindividual variability in drug exposure in adults. In this review article, potential determinants for pharmacokinetic variables will be discussed, which will call into question the value of BSA-based dosing for adults receiving common

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anti-cancer agents. The dosing for children, however, is not comparable and reaches beyond the scope of this manuscript.

Platinum agents

Cisplatin

Cisplatin is a commonly used anti-cancer drug with a broad spectrum of activity against malignant solid tumors, including lung, head and neck, bladder, germ cell, ovarian, endometrial, and cervical cancers [8]. Because cisplatin binds irreversibly to proteins in plasma, the potentially active form is thought to be that which is unbound in the circulation [9]. Cisplatin is highly protein bound (>90%) and at its peak, unbound cisplatin is about 1/10 of the total cisplatin [10]. Dose-limiting non-hematologic side effects include renal tubular dysfunction, peripheral neuropathy, nausea, vomiting, and hearing loss (ototoxicity) [11]. Although cisplatin-induced toxicity is dose-dependent, individual susceptibility to side effects varies considerably. Previous studies have revealed significant relationships between cisplatin pharmacokinetics (PK) and both the likelihood of tumor response and toxicity [12]. As for most other anticancer agents, the administered dose of cisplatin is normalized by BSA.

Unbound cisplatin clearance (CL) was dependent on BSA and creatinine CL [9].

De Jongh *et al.* reported that interpatient variability in unbound cisplatin CL was 25.6%. When unbound cisplatin CL was corrected for BSA, inter-individual variability remained on the same order (23.6 vs 25.6%). Only a weak correlation was found between unbound cisplatin CL and BSA (r =0.42). In view of the relatively high inter-individual variability in CL and relatively small variability in BSA within the same ethnicity, BSA-based dosing apparently does not increase the accuracy of predicting the exposure to the biologically active unbound fraction of cisplatin compared with a fixed-dose scheme [13]. Loos *et al.* proposed that fixed dosing of cisplatin per BSA cluster (BSA≤1.65 vs 1.66<BSA<2.04 vs BSA≥2.05) could serve as a simple alternative to BSA-based dosing that would be more convenient, would reduce dosing error, and be more cost-effective [14].

Carboplatin

Carboplatin was introduced in 1981 as an analogue of cisplatin, which possessed reduced non-hematologic toxicities when compared with cisplatin. A large number of phase II and some phase III studies have been performed with carboplatin and showed that its antitumor activity and spectrum are broadly similar to those of cisplatin. Early clinical studies established that carboplatin, when administered at the normal phase II dose of 400 mg/m^2, was virtually devoid of nephrotoxicity, ototoxicity, and peripheral neurotoxicity, unlike cisplatin. The dose-limiting toxicity of carboplatin was to the bone marrow, with thrombocytopenia being more marked than leukopenia. Although carboplatin is not significantly toxic to the kidneys, it is clear that pretreatment renal function markedly affects the severity of carboplatin-induced thrombocytopenia. In early studies, it was noted that thrombocytopenia was more prevalent in patients whose pretreatment glomerular filtration rate (GFR) was reduced.

Pharmacokinetic studies provided a rationale for this observation [15]. The carboplatin molecule is stable in plasma, and protein-bound platinum predominates. Platinum bound to plasma proteins is not cytotoxic. Approximately 70% of an administered dose of carboplatin is excreted in the urine as the intact drug [15]. Carboplatin clearance seems to be poorly correlated to BSA, but the renal clearance of carboplatin is closely correlated with the GFR, suggesting that the renal excretion of carboplatin is accomplished exclusively by glomerular filtration [15]. These relatively simple kinetics suggest that the area under the concentration versus time curve (AUC) for carboplatin (and consequently the toxicity and therapeutic efficacy of the drug) will be dictated primarily by the pretreatment GFR. Various dosing equations have been proposed to calculate an appropriate dose for a target exposure of carboplatin in a patient with a known GFR. The most simple and widely used formula to calculate the carboplatin dose was proposed by Calvert *et al.* [15], relating the ultra filterable AUC to the GFR by Dose = AUC×(GFR + 25), with dose in mg, target AUC in mg/mL min (usually 5-7), and GFR in mL/min. The 25 mL/min is a constant included

to account for non-renal clearance. In many instances, the GFR is substituted by the estimated creatinine clearance (Ccr) as calculated with the Cockcroft-Gault formula [16] or the Jelliffe formula [17]. As shown by Jodrell *et al.* in ovarian cancer patients, carboplatin dosing according to AUC leads to more predicable toxicity, and increasing the AUC above 5 to 7 mg/mL × minutes does not improve the clinical efficacy [18].

Taxanes

Paclitaxel

The primary route of elimination of paclitaxel is hepatic metabolism and biliary excretion. Three metabolites of paclitaxel-6α-hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6α,3'-p-dihydroxypaclitaxel have been detected in humans. All 3 metabolites have been reported to be less potent than paclitaxel in inhibiting cell growth *in vitro*. The metabolism of paclitaxel is catalyzed by cytochrome P450 (CYP) enzymes. The formation of 6α-hydroxypaclitaxel is catalyzed by CYP2C8, whereas the formation of 3'-p-hydroxypaclitaxel is catalyzed by CYP3A4. 6α,3'-p-dihydroxypaclitaxel is formed by stepwise hydroxylation by CYP2C8 and CYP3A4. Because the ratio of α-hydroxypaclitaxel to 3'-p-hydroxypaclitaxel has been reported to be 6:1 in human bile, CYP2C8 is the principal enzyme involved in the elimination and detoxification of paclitaxel most of the time [19].

Among single nucleotide polymorphisms of *CYP2C8*, the activity of *CYP2C8*3* in hydroxylation of paclitaxel was significantly lower (P<0.01) than that of *CYP2C8*1* protein (15% of wild type). The allelic frequency of **3* is 18% in African-Americans, and it is very rare in Caucasians and Japanese. The intrinsic clearance of paclitaxel by *CYP2C8*2* is decreased by half. The allelic frequency of **2* in Caucasians is 13%, and it is very rare in African-Americans and Japanese [20, 21]. P-glycoprotein, an ATP-dependent efflux pump, which is encoded by the *MDR1* (*ABCB1*) gene, is also involved in the biliary excretion of paclitaxel [19]. As for the *MDR1* gene, the PK parameters of paclitaxel were not significantly different among groups with different genotypes of the gene [19].

Grochow *et al.* conducted a study to determine the relationship between the morphometric measures (height, weight, and BSA) of 287 patients receiving nine different anti-neoplastic agents and PK parameters, including CL and volume of distribution [22]. They found that only the clearance of paclitaxel, a parameter thought to be closely related to the effects of cytotoxic agents, was correlated with one of these measures, namely, body size. They concluded that with the exception of paclitaxel, normalization of dose to BSA for the drugs studied did not modify the variability in PK parameters [22, 23]. The data for paclitaxel were later independently confirmed in another study, where it was shown that the coefficient of variation (CV) in unbound paclitaxel clearance was statistically significantly reduced after correction for BSA, providing a pharmacokinetic rationale for BSA-based dosing of this drug. However, the effect of BSA on total and unbound clearance is modest at most, as seen in Fig. 1 [24].

Docetaxel

Docetaxel was shown to be more than 98% plasma protein-bound independent of concentration at 37°C and pH 7.4 [25]. Docetaxel binds to plasma proteins including lipoproteins, alpha1 acid glycoprotein (AAG), and albumin, with AAG and lipoproteins binding the major part of docetaxel in plasma. The plasma concentration of AAG is expected to fluctuate dramatically, with concentrations from 4 to 62μM in patients with cancer; and it is the most variable of these proteins among individuals, especially cancer patients. Therefore, it is the main determinant of variability in docetaxel's binding to plasma proteins [25].

Bruno *et al.* reported that baseline AAG level and first-course exposure were the most significant predictors of severe neutropenia (P<.0001) [26]. The higher the AAG level at baseline, the lower the odds of experiencing grade 4 neutropenia during the first course of treatment. According to the logistic regression model, a 1 g/L increase in baseline AAG (e.g. from the median to approximately the 95th percentile in this population) results in an 83% decrease in the odds of experiencing grade 4 neutropenia. The effect of changes in drug exposure is the opposite, with a 430% (4.3-fold) and a 300% (3.0-fold) increase of

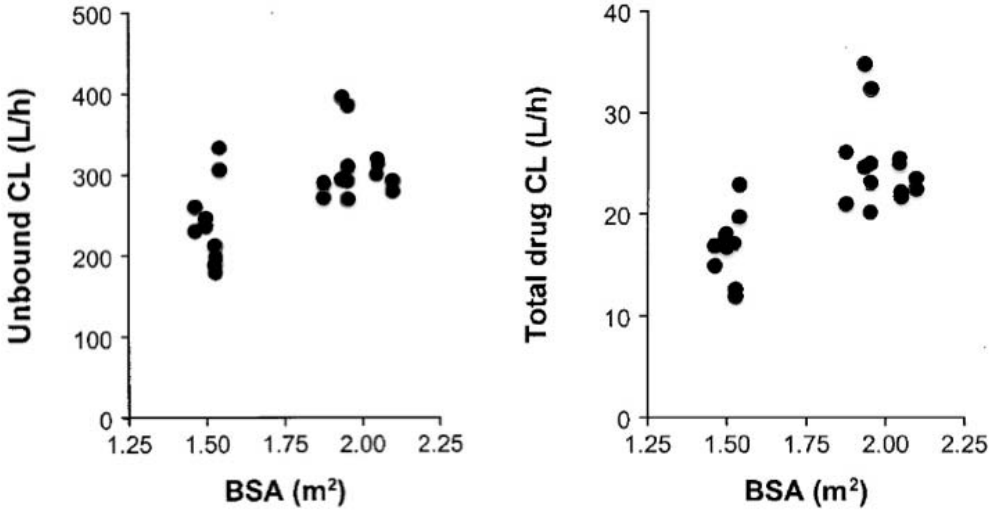

Fig. 1. Relationships between clearance (CL) of total or unbound paclitaxel and body-surface area (BSA), modified from reference [22].

the odds of grade 4 neutropenia and febrile neutropenia, respectively, associated with a 50% decrease in CL.

Docetaxel is extensively metabolized by CYP3A. The major metabolites and less than 10% of the parent drug are excreted into the feces, and total urinary excretion is less than 10% [27]. The metabolites demonstrate substantially reduced cytotoxic activity as compared with the parent drug, making biotransformation by CYP3A a major route of inactivation. Furthermore, total CYP3A activity has been identified as a strong predictor of docetaxel clearance and most likely accounts to a large extent for the observed inter-individual variability in drug clearance and AUC. Because of its lower level of expression, the role of CYP3A5 in hepatic drug clearance is generally regarded to be significantly less than that of CYP3A4 [28]. Although the fact that docetaxel is predominantly metabolized by CYP3A makes the agent subject to a host of enzyme-mediated drug interactions, data on potential interactions are lacking in humans [29].

CYP3A4 is generally the most abundant CYP present in the human liver and seems to be the most important in drug metabolism. The CYP3A enzyme is localized in the liver and small intestine and thus contributes to first-pass and systemic metabolism. Expression of CYP3A varies as much as 40-fold, and this interindividual difference in enzyme expression may be owing to several factors including up- or down-regulation by environmental stimuli (e.g. smoking, drug intake, or diet) and genetic mutations [30].

More than 30 single nucleotide polymorphisms (SNPs) have been identified in the *CYP3A4* gene. Unlike other human P450s (CYP2D6, CYP2C19), there is no evidence of a 'null' allele for *CYP3A4*. Generally, variants in the coding regions of *CYP3A4* occur at allele frequencies of 5% and appear as heterozygous with the wild-type allele. These coding variants may contribute to, but are not likely to be, the major cause of inter-individual differences in CYP3A-dependent clearance because of the low allele frequencies and limited alterations in enzyme expression or catalytic function [30].

CYP activity can be significantly affected by non-genetic factors such as nutritional status, the presence of inflammatory conditions, concomitant medications that can induce or inhibit activity, and concomitant liver disease or hepatic metastasis [31]. There is marked inter-individual variation in CYP3A4 activity that cannot be explained by identified genetic polymorphisms. Furthermore, CYP3A4 activity is particularly prone to either inhibition or induction by concomitantly administered medications [31].

CYP3A4 would, therefore, seem to be an ideal candidate for a phenotype test that would predict the potential for toxicity and allow individualized

dose adjustments to be made. Several probe-based tests for CYP3A4 activity have been described, such as the Erythromycin Breath Test (ERMBT) and other measures of CYP3A4 activity that use three other probes (midazolam, dexamethasone, and urinary cortisol) [31]. These studies confirm that variation in CYP3A4 activity as assessed by probes is an important determinant of the disposition of docetaxel [31].

It is still debatable whether the inter-patient variability of docetaxel clearance has a clinically meaningful relationship with BSA. Although docetaxel clearance may be weakly related to BSA, this measure does not contribute substantially to explaining the inter-individual variability (less than 10%). This is immediately evident from the wide overlap in the AUC values seen in patients receiving different doses of docetaxel (i.e. 75 and 100 mg/m^2), in spite of the drug being administered on the basis of BSA (Fig. 2) [23]. Population PK studies of docetaxel have demonstrated that clearance is significantly decreased not only with decreased BSA, but also with age, increased concentrations of AAG, albumin, bilirubin, and/or transaminases. Patients with elevated plasma levels of bilirubin and/or transaminases have between a 12 and 27% decrease in docetaxel clearance and should receive reduced doses [27].

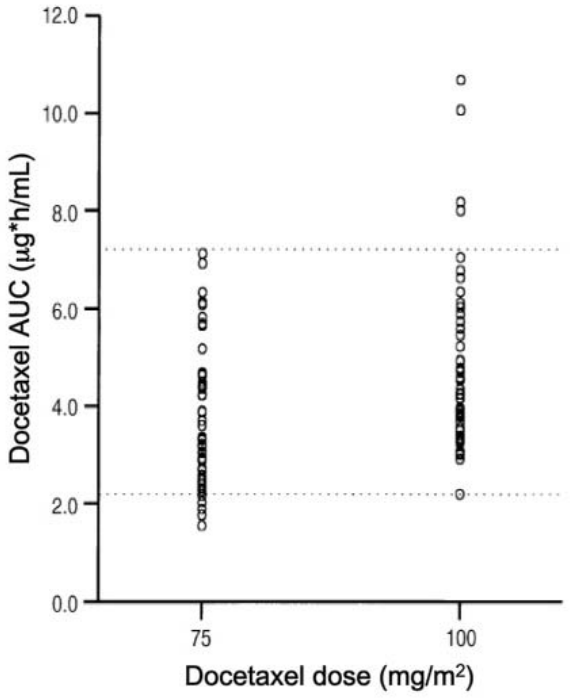

Fig. 2. Area under the blood concentration-time curve (AUC) of docetaxel as a function of drug dose, modified from reference [23].

Other chemotherapeutic agents

Irinotecan (CPT-11)

CPT-11 has an extremely complex pharmacologic profile, which is dependent on a host of enzymes involved in metabolic transformation and on active transport proteins regulating intestinal absorption and hepatobiliary secretion mechanisms (Fig. 3) [32].

The liver is the main organ involved in the disposition of irinotecan and its metabolites, and their directional movement across the hepatocytes requires the coordinated activities of both influx and efflux transporters [33]. The influx transporters are expressed on the basolateral domains of the hepatocytes and facilitate the intracellular uptake of drugs before their elimination into the bile, which is mediated by the efflux transporters. Among the influx transporter family, members of the organic anion transporting polypeptides (OATPs) are abundantly expressed at the basolateral membranes of hepatocytes and mediate the uptake of a large number of structurally divergent compounds [33]. OATP1B1 (encoded by the *SLCO1B1* gene) mediates the uptake of a wide array of chemically divergent compounds and drugs. Recently, Nozawa *et al.* have demonstrated that OATP1B1 transports 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan, but not irinotecan itself or glucuronidated SN-38 (SN-38G) [34]. This finding suggests that the liver may take up SN-38 from the circulation preferentially via OATP1B1 expressed in the basolateral membrane of the hepatocytes [35]. Polymorphic variants in the *SLCO1B1* gene were recently shown to influence the PK of several drug substrates with significant pharmacologic consequences in different ethnic groups [33]. Several SNPs with altered transporter activity have been found in *SLCO1B1*. A common *SLCO1B1* SNP, 521T>C (Val174Ala), has been associated with the reduced transporter activity of OATP1B1. This SNP exists in various haplotypes

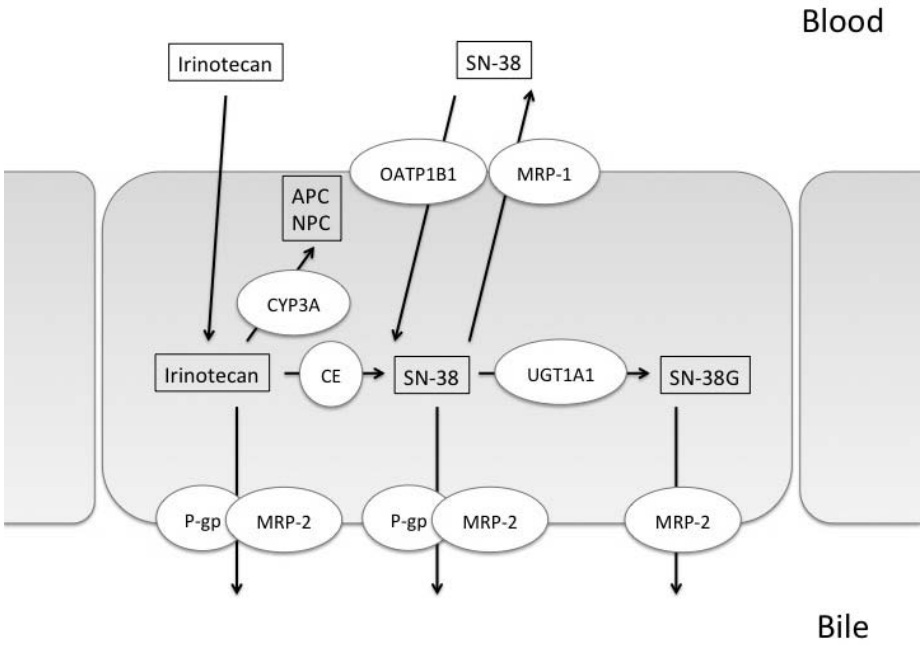

Fig. 3. Pharmacokinetic pathway of irinotecan. CE: carboxyesterase, UGT: uridine diphosphate-glucuronosyltransferase, P-gp: p-glycoprotein, MRP: multidrug resistance-associated protein, OATP: organic aniontransporting polypeptide, APC: 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycampothecin, NPC: 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycampothecin.

with other *SLCO1B1* SNPs, and a major haplotype that has been associated with reduced transporter activity for SN-38 is designated **15* (*388A>G and 521T>C*). Patients with the **15* haplotype showed a significantly higher AUC_{SN-38} than those with **1a* or **1b* haplotypes (*P*=0.006) [35]. The clearance of irinotecan is 3-fold lower in patients carrying the **15* haplotype than in cancer patients with the reference genotype **1a/*1a* (9.57 ± 3.15 vs. 28.86 ± 10.97 L/h/m^2; *P*=0.001). The AUC from zero to infinity and normalized by dose and body surface area (AUC0-nf/dose/BSA) was significantly higher among patients harboring the **15* haplotype than among patients with the reference genotype for irinotecan (39.27 ± 15.17 vs. 17.32 ± 6.30 h/m^2; *P*=0.003) [33]. The frequency of the **15* allele in Asian populations (range 2-11%) was comparable to that observed in Japanese (10-15%) individuals, and recent studies have shown a similarly high frequency of the **15* allele in Caucasian populations (14%) [33].

Transporters such as ABCB1 and ABCC2 play a role on the elimination of CPT-11 and its metabolites into the bile [36]. Irinotecan and SN-38 are transported from the hepatocytes to the bile by P-glycoprotein (Pgp; encoded by *ABCB1*) [37]. Mathijssen *et al.* reported that the *ABCB1 1236C>T* polymorphism was associated with significantly increased exposure to irinotecan (*P*=0.038) and its active metabolite SN-38 (*P*=0.031) [38]. This finding was not replicated by the study by Innocenti *et al.*, but they showed that patients with the *ABCB1 IVS9-44A>G* genotype have decreased exposure to SN-38, although there is no evidence of function for this intronic variant [36]. The multidrug resistance-associated protein-1 (MRP-1, encoded by *ABCC1*) is responsible for the efflux of SN-38 from the hepatocytes into the interstitial space. *ABCC1 1684T>C* was associated with an increased SN-38 AUC and a reduced ratio of SN-38G/SN-38 [36]. The multidrug resistance-associated protein-2 (MRP-2, encoded by *ABCC2*) appears to be the principal transporter involved in hepatobiliary secretion of irinotecan, SN-38, and SN38G, and multiple functional polymorphic variants of *ABCC2* have been described [39]. *ABCC2 3972C>T* is associated with increased exposure to 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycampothecin (APC; a metabolite of CPT-11) and SN-38G [36].

Other studies showed that certain haplotypes of *ABCC2* were associated with the incidence of severe diarrhea and altered irinotecan clearance [39]. *ABCG2* polymorphisms appear to play a limited role in the disposition of irinotecan [40].

Irinotecan is metabolized by an extremely complex pathway after transport into the hepatocytes. Irinotecan is, in fact, a prodrug that is converted to its active but toxic metabolite SN-38, which is 100-fold to 1000-fold more active than irinotecan, by carboxyesterase (CE) *in vivo* (Fig. 3) [32]. Irinotecan also undergoes oxidative metabolism by CYP3A4/5 to the inactive metabolites APC and 7-ethyl-10-(4-amino-1-piperidino] carbonyloxycampothecin (NPC). The latter may be functionally important as it can be hydrolyzed by CE to SN-38. The recognition that CPT-11 is a substrate of CYP3A is an important finding because it makes this agent subject to a host of enzyme-mediated drug interactions, even with commonly prescribed co-medications. For example, the prototypic CYP3A inhibitor, ketoconazole, inhibits the conversion of CPT-11 into APC and NPC almost completely. In addition, loperamide inhibits formation of APC and NPC by 50%, whereas ondansetron inhibits their formation by 25 and 75%, respectively [32].

Over time, SN-38 is metabolized to an inactive form, SN-38G, by uridine diphosphate-glucuronosyltransferase (UGT) 1A1 glucuronidation. The AUC for SN-38G is ~7fold larger than that for SN-38, suggesting extensive conversion of SN-38 into SN-38G *in vivo*, but high levels of inter-patient variability have also been found [32]. Recently, a series of studies have provided evidence that *UGT1A1*28* genetic polymorphism may have an important influence on irinotecan toxicity [41]. It has been shown that there is a significant reduction in SN-38 glucuronidation in individuals with the **28* variant and that this haplotype is significantly associated with a reduced SN-38G/SN-38 AUC ratio [42]. In 2005, the US Food and Drug Administration required that a warning to this effect be added to the irinotecan package insert, which stated: "Patients homozygous/heterozygous for the *UGT1A1*28* allele: Patients homozygous for the *UGT1A1*28* allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. Heterozygous carriers of the *UGT1A1*28* allele may also be at increased risk; however, most patients have tolerated normal starting doses." In a prospective phase II trial, we have shown that patients who are heterozygous carriers of the *UGT1A1*28* allele have a significant increase in Cmax and AUC_{0-t} for SN-38 compared to those who are homozygous for the wild type allele (unpublished data).

There is a significant racial difference in *UGT1A1* polymorphisms among Asians, Caucasians, and Africans. Although the association of *UGT1A1*28* with the toxicities of irinotecan was first described in Japanese patients, the frequency of *UGT1A1*28* in Japanese individuals is one-third of that in Caucasians. Another low-activity allele **6 [211G>A (G71R)]*, which is not detected in Caucasians or Africans, is as frequent as the **28* allele in the Japanese. Moreover, the AUC ratio of SN-38G to SN-38 was decreased in patients having **6* haplotypes [42]. When the dose effect of the genetic marker **6* or **28* on PK parameters was further analyzed, patients with one haplotype harboring either **6* or **28 (*6/*1, *6/*60, *28/*1*, and **28/*60)* had lower SN-38G/SN-38 AUC ratios (median, 3.62; interquartile range, 2.74-5.18) than patients without **6* or **28 (*1/*1, *60/*1, and *60/*60)* (5.55, 4.13-7.26), and patients with two haplotypes harboring **6* or **28 (*6/*6, *28/*28*, and **28/*6)* had the lowest AUC ratio (2.07, 1.45-3.62) (P<0.0001). Similarly, the number of **6*- or **28*-containing haplotypes affected the AUC ratios of SN-38 to irinotecan. In multivariate analysis, the homozygous and double heterozygous haplotypes of **6* and **28 (*6/*6, *28/*28*, and **6/*28)* were significantly associated with severe neutropenia [43]. Recently, a warning was added to the Japanese irinotecan package insert for the **6* allele. In the genotype-directed dose-finding study of irinotecan based on *UGT1A1 *28* and **6* genotypes in Japanese patients with gastrointestinal cancer, patients with haplotypes harboring none or one of the *28 or *6 allele could tolerate 150mg/m^2 of irinotecan; and dose limiting toxicities (DLT) occurred in only 2% suggesting the maximum tolerated dose is even higher. On the other hand, 40% of patients with the homozygous haplotype showed DLT, but the

optimal dose was not determined because very few patients were treated at the lower dose level [44].

Recently, Mathijssen *et al.* retrospectively examined 82 patients undergoing chemotherapy with CPT-11 for malignant solid tumors and reported an interpatient variation for the absolute clearance of CPT-11 of 32.1% (expressed in L/h) and a BSA-corrected clearance of 34.0% (expressed in L/h/m^2) [45]. The metabolic clearance of SN-38, the pharmacologically active metabolite of CPT-11, also remains similar after normalization to BSA (63% when calculated in L/h and approximately 65% when calculated in L/h/m^2). They concluded that BSA, as well as several other body-size measures tested, are unrelated to CPT-11 clearance and metabolism and recommended that development of alternative dosing strategies to reduce the marked inter-individual variability should be pursued. Interestingly, the variability in CPT-11 clearance is higher when expressed relative to BSA (expressed in L/h/m^2 rather than in L/h), suggesting that use of BSA further increases the variability of the effects induced by this agent and thus may even be harmful. This last evaluation seems to provide a further reason to change current practice and administer flat doses rather than BSA-based doses [23].

Furthermore, environmental factors such as the use of other drugs, herbs, and cigarette smoking also influence the PK of irinotecan. In smokers, the dose-normalized AUC of irinotecan was significantly lower than that of non-smokers (P<.001). In addition, smokers showed an almost 40% lower exposure to SN-38 (P<.001) and a higher relative extent of glucuronidation of SN-38 into SN-38G (P<.006). The incidence of grade 3 to 4 neutropenia was 6% in smokers versus 38% in non-smokers (odds ratio [OR], 0.10; 95% confidence interval [CI], 0.02-0.43; P<.001), although there was no significant difference in incidence of delayed-onset diarrhea (6 vs 15%; OR, 0.34; 95% CI, 0.07-1.57; P<.149). This study indicates that smoking significantly lowers both the exposure to irinotecan and treatment-induced neutropenia, suggesting a potential risk of treatment failure [46]. St. John's wort (SJW), a widely used herbal product, has been known to induce the CYP3A4 enzyme. In an unblinded, randomized crossover study, the plasma level of the active metabolite SN-38 decreased by 42% (95% CI 14-70%) after co-treatment with SJW [47]. Similarly, anti-epileptic drugs such as phenytoin and carbamazepine substantially accelerate irinotecan and SN-38 metabolism, resulting in decreased levels of SN-38 and a requirement for higher dose of irinotecan in patients receiving those drugs [48].

On the other hand, inhibition of CYP3A4 leads to significantly increased formation of SN-38. With co-administration of the strong CYP3A4 inhibitor ketoconazole, the relative exposure to the CYP3A4-mediated metabolite APC was reduced by 87% (P=0.002) whereas the relative exposure to the pharmacologically active metabolite SN-38 increased by 109% (P=0.004). Ketoconazole showed no effect on the beta-glucuronidation pathway [49].

Interaction with S-1 is also reported in a single patient, in whom co-administration of S-1 resulted in a 77% reduction in the plasma concentration of SN-38 compared with administration of irinotecan alone [50]. We could not confirm this finding (unpublished data).

Because of the complex pharmacogenomics as well as the influence of co-administered drugs and smoking, it is unlikely that dose adjustment of irinotecan based on only one or a few parameters is possible. We suggest that dose adjustment be based on comprehensive modeling including a combination of the above parameters or simply on dose-related toxicity such as bone marrow toxicity.

Vinorelbine

Vinorelbine is a vinka alkaloid that has been used in the treatment of a wide range of cancer types. Mechanisms of vinorelbine clearance in human are not clear, but animal studies suggest biliary excretion is a major elimination route, and studies indicated that vinorelbine is a substrate of ABCB1. In addition, the CYP3A isoenzyme is the principle metabolic enzyme acting on vinorelbine [51]. Studies relating to vinorelbine pharmacogenetics are limited; and in one study involving 41 Caucasian cancer patients, no association was found between vinorelbine clearance and the tested SNPs of CYP3A5 or ABCB1 [51]. In this study, the creatinine clearance

estimated before treatment correlated with vinorelbine clearance, confirming the contribution of renal elimination to vinorelbine clearance [52]. BSA did not correlate with vinorelbine clearance, partially because the variation in clearance was greater than 4-fold across the cohort [51]. Furthermore, many co-administered CYP3A inhibitors, such as azole antifungals and macrolide antibiotics, affect the PK of vinorelbine [53, 54].

Anti-metabolites

Gemcitabine

Gemcitabine, a cytotoxic anti-metabolite, is a cytidine analogue with activity against a wide variety of solid tumors. Once administered intravenously, gemcitabine enters the cell via members of the nucleoside transporter family. Among them, SLC29A1 and SLC28A1 are the most efficient transporters [55], with SLC29A1 being the most abundant and widely distributed. In tumor samples, over-expression of SLC29A1 mRNA and protein correlates with prolonged survival among patients with pancreatic cancer treated with gemcitabine. However, no functionally significant *SLC29A1* gene polymorphisms have been identified so far [55]. In contrast, *SLC28A1* has a high degree of genetic and functional variation. The *SLC28A1 1153* deletion, which resulted in a frameshift mutation followed by a stop codon, occurs at a frequency of 3% in the African-American population and not in Caucasians and Asians. *SLC28A1 565G>A* (Val189Ile) results in reduced affinity for gemcitabine. This variant allele is common, with an overall population frequency of 28%, 19%, and 35% in Caucasians, Africans, and Asians, respectively [56]. SNP *SLC28A1* (Asp521Asn) variants are more common in Asian populations compared to Caucasians (allele frequency of 46 vs 11%). Although this SNP results in no functional change *in vitro*, increased rates of myelotoxicity have been observed in NSCLC patients treated with gemcitabine [57].

Intracellular gemcitabine is phosphorylated to gemcitabine monophosphate (dFdCMP) by deoxycytidine kinase (DCK). Studies have shown a correlation between higher levels of DCK activity and increased sensitivity to gemcitabine [58]. Interestingly, low DCK expression also correlated significantly with increasing age. Age-related methylation of the *DCK* gene has been postulated, in part, to account for the different outcomes [59]. Ethnic differences have been observed in DCK, with Asians showing a higher frequency of promoter variants -C360G/-C201T, which may predispose them to greater gemcitabine toxicity, than Caucasians [60]. dFdCMP is phosphorylated to gemcitabine diphosphate (dFdCDP) by CMPK1, then converted to gemcitabine triphosphate (dFdCTP) by nucleotide kinases. dFdCMP and dFdCTP are incorporated into DNA by DNA polymerase then inhibit DNA synthesis. CMPK1 360C>T and 240G>T was associated with shorter survival and time to progression (TTP) [61].

Gemcitabine is inactivated by cytidine deaminase (CDA). Upregulation of CDA may play a role in gemcitabine resistance, while impaired activity may result in increased toxicity [62, 63]. In a recent report of a Japanese patient with pancreatic cancer treated with gemcitabine and cisplatin who developed severe hematologic and non-hematologic toxicity, germline genotyping revealed that patients homozygous for CDA 208G>A ($Ala^{70}Thr$) showed a 5-fold higher exposure to gemcitabine than homozygotes with wild-type alleles [64]. A subsequent prospective study (*n*=256) in Japan reported that patients with this variant have decreased CDA enzyme activity and gemcitabine clearance and greater hematologic toxicity [65]. This variant is more common in Africans than in Japanese individuals or Europeans (13 vs 4.3 vs 0%, respectively) [66, 67]. A synonymous variant CDA 435C>T ($Thr^{145}Thr$) was associated with a lower response rate and shorter TTP in Asian lung cancer patients receiving carboplatin/gemcitabine, although no functional change in CDA was seen *in vitro* [57].

S-1

S-1, a fourth-generation oral fluoropyrimidine, is an oral formulation of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1.2 and is currently one of the most widely prescribed agents for the standard treatment of gastric cancer in Japan. S-1 combined with cisplatin produced a high response rate in non-small cell lung cancer in a phase II trial [68] and is currently approved for this indication in Japan.

FT is a prodrug of 5-fluorouracil (5-FU) synthesized more than 30 years ago. 5-FU exerts its cytotoxic effect via the inhibition of thymidylate synthase and/or its incorporation into RNA molecules. The formation of 5-FU from FT is known to be mainly catalyzed by human CYP2A6 [69]. The expression of this enzyme exhibits enormous interindividual variability. The CYP2A6 content of human liver microsomes has been estimated to range from < 0.1 to 60 pmol/mg protein, and the level of CYP2A6 mRNA also varies widely among liver samples [70]. *CYP2A6* polymorphisms may affect the PK of FT. Patients with lower CYP2A6 activity may benefit less from FT treatment because of insufficient exposure to 5-FU. Genotypes *CYP2A6 *2, *4, *5,* and **20* show no enzyme activity; while genotypes *CYP2A6 *6, *7, *9, *10, *11, *12, *17, *18,* and **19* show reduced activity [71]. Because the variants are more frequent in Asians than in Caucasians [72], racial differences in S-1 tolerance may be caused by differences in the activity of CYP2A6.

In non-small cell lung carcinoma (NSCLC) patients treated with the standard dose of S-1, the $AUC_{0–10h}$ for tegafur was 1.5-fold higher in patients with the *CYP2A6*4* allele, a deletion of the entire gene leading to a failure to express functional CYP2A6 protein, than in patients without the *CYP2A6*4* allele ($P < .05$). Furthermore, patients with the *CYP2A6*4* allele had a significantly lower maximum plasma concentration (102.6 ± 32.9 ng/mL) for 5-FU than patients without the *CYP2A6*4* allele (157.0 ± 65.5 ng/mL, $P<.05$) [73]. In 49 patients with metastatic adenocarcinoma of the biliary tract, *CYP2A6* polymorphisms (**1, 4, 7, 9, or 10*) were genotyped. Although the polymorphisms were not significantly associated with response rate or toxicities such as diarrhea and neutropenia, the AUC_{0-24h} of FT in the CYP2A6 *1/*1 genotype was 39% higher compared to that in the other genotypes and the AUC_{0-24h} of 5FU was 26% lower [74]. The allele frequency of *CYP2A6*4* in Caucasians is 0.5% compared to 15% to 25% in Asians [72]. A PK comparison of 18 Asian and 19 Caucasian patients with advanced solid tumors showed that Asians had significantly higher FT and CDHP exposure compared to Caucasians. Although 5-FU exposure was similar in both populations, diarrhea was more common in Caucasian patients [75]. In fact, the recommended dose for S-1 is different in Asia ($40mg/m^2$ twice daily) than in the United States ($25\text{-}30mg/m^2$ twice daily). Comparison of Japanese and American PK data at equivalent dose levels, showed the AUCs for 5-FU in American patients are similar to those in Japanese patients. On the other hand, American patients had lower AUCs for FT, suggesting a higher rate of conversion from the latter compound to 5-FU [76].

The marked interpatient variability in dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme of 5-FU catabolism, is an additional factor influencing 5-FU pharmacodynamics [77]. Approximately 90% of the active compound, 5-FU, is then further metabolized by DPD in the liver to form inactive metabolites; and CDHP prevents its degradation [78]. The rest of 5-FU is converted to F-RNA, which inhibits RNA synthesis causing cytotoxicity, and FdUMP, which inhibits thymidylate synthase activity and DNA synthesis, producing cytotoxicity [78]. About 40 different mutations and polymorphisms have been identified in DPD. Only *DPYD**2A* and *DPYD**13* have been consistently associated with DPD deficiency [79]. A SNP with a G to A transition (*DPD*2A*) is more common in severe DPD deficiency. A homozygous *DPYD*2A* genotype results in complete deficiency, while a heterozygous genotype results in partial deficiency of the DPD protein [79]. The allele frequency is less than 1% in Caucasians and slightly higher in Asians [80]. Because CDHP has been reported to be predominantly excreted in the urine, renal function is a key factor determining the PK of CDHP, and impaired renal function causes high plasma concentrations of CDHP [81]. Variability in the plasma concentration of CDHP is then assumed to affect the PK of 5-FU [81]. In patients with advanced solid tumors who received S-1 $30mg/m^2$ bid, the dose-adjusted AUC_{0-48h} of CDHP was higher in Asians compared to Caucasians [75]. As discussed above, Asians have a higher dose-adjusted AUC_{0-48hr} for FT as well as CDHP and similar 5-FU exposure [75]. The dose-limiting toxicity (DLT) is mainly hematologic, and the recommended dose is 80 mg/m^2/day in Asian patients; while the DLT is mostly diarrhea, and 60 mg/m^2/day is recommended in western patients. The exact mechanisms that account for the different toxicity profiles are unknown [76].

Capecitabine

Capecitabine is an oral prodrug of 5-FU that undergoes a three-step enzymatic activation process by CE, CDA, and thymidine phosphorylase before becoming the active drug. These enzymes are expressed in hepatic and tumor tissues, and the final enzymatic reaction is highly active in tumor tissue, which provides the rationale for the tumor specificity of capecitabine. After conversion to 5-FU, 60-90% of capecitabine is catabolized to fluoro-beta-alanine (FBAL) by DPD [82]. FBAL is excreted into the urine, and an increase in FBAL is thought to reflect an elevated amount of 5-FU in the tissue as well as a decrease in the renal clearance. The rate of clearance of capecitabine in women is less than that in men, and the AUC for FBAL is approximately 10% higher in women than in men [82]. Also, an age-related increase in the concentration of FBAL (20% increase in age leads to 15% increase in AUC) and sensitivity to its toxicity has been described [82]. Capecitabine can induce hemolysis to cause an isolated rise in bilirubin levels in 20~70% of patients. Grade 3 and/or 4 bilirubinemia correlates with the AUC for5-FU, and this might indicate that higher exposure of red blood cells to 5-FU increases hemolysis. A small study has shown that acetaminophen and morphine increased 5-FU clearance by 26 and 41%, respectively, and loperamide decreased 5FU clearance by 31% [82]. DPD deficiency is a cause of life-threatening toxicity also for patients treated with capecitabine. It has been suggested that SNPs in the promoter region of TS, which can result in altered translational activity, are associated with response to capecitabine treatment. It has been also reported that patients with higher baseline levels of serum folate experienced a significantly increased incidence of toxic events [83].

DISCUSSION

Baker *et al.* retrospectively studied the PK of 33 anticancer agents tested in phase I trials during the period 1991-2001 among 1,650 adult patients [84]. Twelve of the drugs were administered orally, 19 were administered intravenously, and two were administered by both routes. For only five agents (including paclitaxel) did BSA-based dosing reduce the interindividual pharmacokinetic variability. In contrast, for the other 28, the variability was not statistically significantly reduced by BSA; the rationale for using BSA to adjust the dosing of these (and other) compounds could therefore be questioned. Indeed, these results did not support the use of BSA in dose calculations and suggested that alternate dosing strategies should be evaluated. The researchers concluded that BSA should not be used to determine starting doses of investigational agents in future phase I studies [84]. Other studies have been conducted to determine whether BSA was the correct parameter on which to base the dose adjustment for anticancer drugs, and for many of these agents such as anthracyclines (epirubicin and doxorubicin), etoposide, ifosfamide, methotrexate, and others, no convincing relationship between this measure and PK parameters has been found [84].

Given how inappropriate it is to use BSA to normalize the effects of most anticancer agents, more adequate measures are urgently required. For agents such as CPT-11, cisplatin, and oral topotecan (for which it has already been shown that the inter-individual variability is not modified by employing BSA), flat-fixed doses can probably be implemented without compromising safety and activity profiles, in the absence of a better alternative. The dose can be adjusted for subsequent cycles on the basis of the toxicity induced in each patient. Similarly, in early clinical trials, it can be safely advised to perform all studies with flat-fixed doses and to plan them in combination with a rigorous PK evaluation, with the aim of finding a correlation between patient variables (including BSA) and PK parameters (including clearance) of the drugs tested [84]. This procedure, besides reducing the variables influencing PK values, has significant economic implications. In fact, the ability to manufacture a unit dose of an agent has evident benefits for the pharmaceutical company involved, as reconstituting individualized doses is more expensive and less accurate than preparing fixed doses without modifications for different patients. Accuracy can be compromised not only during the drug reconstruction, but also by the clinicians calculating the BSA, and the use of flat-fixed doses can eliminate a source of error that contributes to increased inter-individual variability of PK parameters and outcomes of treatment [84].

ABBREVIATIONS

AAG	:	alpha1 acid glycoprotein
APC	:	7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycampothecin
AUC	:	area under the concentration versus time curve
BSA	:	body-surface area
Ccr	:	creatinine clearance
CI	:	confidence interval
CDA	:	cytidine deaminase
CDHP	:	5-chloro-2,4-dihydroxypyridine
CE	:	carboxyesterase
CL	:	clearance
CV	:	coefficient of variation
CYP	:	cytochrome P450
dFdCMP	:	gemcitabine monophosphate
dFdCDP	:	gemcitabine diphosphate
dFdCTP	:	gemcitabine triphosphate
DCK	:	deoxycytidine kinase
DLT	:	dose-limiting toxicities
DPD	:	dihydropyrimidine dehydrogenase
FBAL	:	fluoro-beta-alanine
FT	:	tegafur
FU	:	fluorouracil
GFR	:	glomerular filtration rate
MRP	:	multidrug resistance-associated protein
NPC	:	7-ethyl-10-(4-amino-1-piperidino] carbonyloxycampothecin
NSCLC	:	non-small cell lung carcinoma
OATP	:	organic anion transporting polypeptide
OR	:	odds ratio
Oxo	:	potassium oxonate
Pgp	:	P-glycoprotein
PK	:	pharmacokinetics
SJW	:	St. John's wort
SN-38	:	7-ethyl-10-hydroxycamptothecin
SN-38G	:	glucuronidated SN-38
SNP	:	single nucleotide polymorphism
TTP	:	time to progression
UGT	:	uridine diphosphate-glucuronosyltransferase

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