Pharmacogenetics of irinotecan and oxaliplatin in advanced colorectal cancer

Kweekel, D.M.

4

CLINICAL AND PHARMACOGENETIC FACTORS ASSOCIATED WITH IRINOTECAN TOXICITY

Dina M Kweekel, Henk-Jan Guchelaar, Hans Gelderblom

Cancer Treatment Reviews 2008 Nov;34(7):656-69

SUMMARY

Irinotecan is a topo-isomerase-I inhibitor with broad antitumor activity in solid tumors. Its use may lead to severe toxicities, predominantly neutropenia and diarrhea which can be life-threatening. This review discusses clinical determinants and pharmacogenetic factors associated with irinotecan toxicity. Age, performance status, co-medication and elevated transaminases have been associated with increased risk of diarrhea or neutropenia. Also, elevated bilirubin levels, due to liver impairment, conjugation disorders or UGT1A1*28 genotype, have been associated with increased incidence of grades ≥3 intestinal toxicity and neutropenia.

UGT1A1*28 homozygosity is strongly associated with irinotecan-induced neutropenia and polymorphisms in the transporting peptides ABCB1 and OATP1B1 have also been associated with gastrointestinal toxicity and irinotecan pharmacokinetics, respectively. In the irinotecan product label, it is advised to reduce the irinotecan starting dose for UGT1A1*28 homozygotes. However, due to the lack of prospective data, it is yet unknown whether dose reduction leads to reduced toxicity or altered antitumor effect. Combined toxicity analysis reveals that most patients experiencing grade 3–4 diarrhea and/or neutropenia are not homozygous for UGT1A1*28. Future studies should combine pharmacogenetics with clinical determinants such as performance status and co-medication as to predict irinotecan toxicity and to develop predefined dosing algorithms.

INTRODUCTION

Irinotecan is a topo-isomerase-I inhibitor with broad antitumor activity in solid tumors. Irinotecan may cause serious side effects that require close monitoring and immediate treatment. The toxicity profile of irinotecan is dependent on drug dose and schedule, but in all regimens severe diarrhea and neutropenia are the principal dose-limiting toxicities (Table 1).[1] The incidence of grade 3 or 4 hematological toxicity varies between 5% and 33% depending on irinotecan dosage and regimen.[2] Common reasons for irinotecan-related hospitalization (second-line single agent, weekly dosage schedule) are diarrhea with or without nausea or vomiting (18% of patients treated with irinotecan) and neutropenia/leukopenia with or without diarrhea (8%).[3] Two types of diarrhea can be distinguished; acute and late diarrhea. The acute form is of cholinergic origin and can be prevented in almost all cases by subcutaneous atropine administration. Late diarrhea, occurring more than 24 h after administration of irinotecan (usually at day 5), is prolonged and can be life-threatening, because it may lead to dehydration and electrolyte imbalances especially when it occurs in combination with vomiting. Patients with the combination of diarrhea and neutropenia are especially at risk, as destruction of the gastro-intestinal barrier may give rise to systemic infections with gut flora. Febrile neutropenia is often observed in combination with grade 3 or 4 diarrhea.[4] Severe delayed-onset diarrhea therefore needs to be treated with intensive courses of oral loperamide. The use of high-dose loperamide treatment at the first sign of loose stools significantly decreases the incidence of grade 3 or 4 late diarrhea during irinotecan treatment ($p= 0.04$).[5]

In this article, we give an overview of the literature describing clinical and pharmacogenetic variables associated with irinotecan toxicity. Although prospective irinotecan dosing studies, based on these variables are rare, we conclude this review with general recommendations for dosing strategies based on the currently available literature, which may help the clinician to personalize treatment in the individual patient.

Grade 3-4 adverse events (%)	Single agent 350 mg/m^2	Combination therapy 180 mg/m^2 with 5FU/LV
Gastrointestinal		
Severe late-onset diarrhea	20	13
Acute cholinergic syndrome	9	1
Nausea and vomiting*	10	2-3
Asthenia	10	6
Constipation**	10	3
Hematological		
Neutropenia	79	83
Severe neutropenia***	23	10
Febrile neutropenia	6	3
Anaemia	59	97
Thrombocytopenia	7	33
Fever without infection or neutropenia	12	6

Table 1

Adverse events resulting from irinotecan use; numbers indicate the percentage of patients experiencing the adverse effect. 5FU, fluorouracil; LV, leucovorin. * Despite antiemetics use. ** Due to irinotecan and/or loperamide use. *** Neutrophil count <500/mm3 (grade 4 neutropenia).

CLINICAL DETERMINANTS ASSOCIATED WITH IRINOTECAN TOXICITY

The occurrence of irinotecan toxicity is thought to be multifactorial. In the following section we review the literature on clinical determinants related to irinotecan toxicity. Clearly, these association studies were not initiated and designed to investigate toxicity risk factors as a primary endpoint. Moreover, most of the risk factors are probably interrelated. Since a correlation between toxicity and systemic irinotecan exposure (e.g. Area Under the serum Concentration–time curve, AUC) has been demonstrated [6,7] we also included pharmacokinetic studies.

AGE

With increasing age, changes in organ function and body composition may cause a different pharmacokinetic behavior of drugs. Although these separate changes may not be apparent, as a whole they can have a serious impact on, for example, volume of distribution or duration of exposure to a drug such as irinotecan.[8] Therefore, in some studies older patients have a higher risk of toxicity when using standard dosed chemotherapeutic drugs.

Delayed-onset diarrhea was found to be slightly more frequent ($p= 0.059$) and more severe ($p< 0.008$) in patients >65 years of age.[4,9] Combined analysis of 3 early studies of weekly irinotecan regimens showed that grade 3 or 4 diarrhea occurred twice as frequent in patients aged >65 years ($p= 0.002$).[3] In a study of oral irinotecan, only patients aged >65 years developed grade 4 diarrhea.[10] Also, grade 3 and 4 neutropenia were seen somewhat more frequently in patients aged >65 years.[4] However, studies suggest that elderly patients aged >70 years can safely be treated with irinotecan,[11–13] either 350 mg/m^2 once every 3 weeks,[14] or with irinotecan (180 mg/m^2 once every 2 weeks) and 5-FU/leucovorin[13] provided that they are in an overall good condition. Elderly patients may derive the same benefit from irinotecan therapy without experiencing more toxicity compared to younger patients.[14]

BODYWEIGHT

Some patients considered for irinotecan chemotherapy may be either overweight or cachectic. These are both physiological changes that affect volume of distribution, plasma protein concentration and organ function (e.g. cardiac output, renal and hepatic clearance).

In 36 patients who received 100 mg/m^2 irinotecan infused over 90 min, the body mass index (BMI) was shown to be associated with differences in volume of distribution and maximum concentration.[8] To compensate for differences in body composition, irinotecan is usually dosed according to body surface area (BSA, mg/m^2) calculated using actual weight. However, there is a growing body of evidence that indicates that dosage calculation according to BSA does not always adequately correct for these kind of physiological changes that affect the pharmacokinetic behavior of drugs.[15,16] Alternative weight formulas and size descriptors may be used to calculate BSA in obese patients, including ideal body weight or lean body mass. Another common alternative is the use of dose capping, in which the maximum dose is

calculated using a BSA of 2.0 m^2. However, a recent paper reports that the absolute clearance of irinotecan is not significantly different in obese patients compared to lean patients (p= 0.17), and that the use of alternative body size descriptors does not result in a substantial improvement of obtaining the target exposure to irinotecan, as compared to BSA based on actual body weight.[17]

GENDER

Male and female patients may differ with respect to the pharmacokinetic behavior of drugs. Among other factors, this difference is related to a relatively high lean body mass and higher organ perfusion in men. Although early studies indicated no significant association of gender with grade 3 or 4 toxicities,[9,18] more recent findings suggest that gender is an independent predictor of the pharmacokinetic behaviour of irinotecan. Both the maximum plasma concentration and the AUC of irinotecan and SN38 are lower in women.[8] In one study, women experienced a 4-fold lower risk of grade 3–4 diarrhea compared to men (p= 0.01),[5] but other studies found no significant differences in the frequency of grade 3 or 4 neutropenia by gender.[3] Remarkably, the European/Dutch product label states that women are more likely to experience late-onset diarrhea.[1]

PERFORMANCE STATUS

A baseline WHO/ECOG performance status (PS) of ≥1 was associated with an increased risk of first cycle grade 3 or 4 diarrhea in a 3-weekly regimen of irinotecan (p= 0.0004)[19] and with the decrease in white blood cell count in a study of the weekly regimen.[20] In a study of 254 patients receiving biweekly irinotecan (200 mg/m^2), a PS of ≥1 was associated with grade 4 neutropenia.[21] Although this is not a unique feature of irinotecan, the observed association between PS and toxicity stresses the importance of a careful PS assessment prior to initiation of irinotecan chemotherapy.

EXTENT OF DISEASE, PRIOR CHEMOTHERAPY AND RADIATION

In general, patients who have received prior radiotherapy of the abdomen or pelvis have an increased risk of delayed-onset diarrhea (p= 0.046). Besides this, the time elapsed since progression on previous chemotherapy (p= 0.02), the time since diagnosis of metastases (p= 0.034) and the number of organs involved (p= 0.004) were all predictive of irinotecan toxicity.[19] Other tumor burden markers such as low baseline hemoglobin (p< 0.001) and high white blood cell count (p= 0.014), were independent predictors for grade 3–4 neutropenia and diarrhea, respectively. In one of the early studies, patients who had received prior pelvic radiotherapy more frequently experienced grade 4 leukopenia (p= 0.04), but not grade 3 or 4 diarrhea.[5] In a combined analysis of trial data used for irinotecan approval, patients with prior abdomino-pelvic irradiation were more than 4 times as likely to experience grade 3 or 4 neutropenia compared to those who did not receive irradiation in that area (p= 0.04).[3] The relationship between pelvic radiotherapy and neutropenia can be explained by a decreased bone marrow reserve.

RENAL FUNCTION

The in vivo clearance of irinotecan is a multi-step process (Fig. 1). First, the prodrug irinotecan (which has little anti-tumor activity) is converted to its active metabolite, SN38, by carboxylesterases. Alternative routes lead to the formation of APC [7-ethyl-10-[4-N- (5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin), a recently discovered metabolite called M2 and to NPC (7-ethyl-10-(4-amino-1-piperidino)-carbonyloxycamptothecin), which is also metabolized to SN38. Conjugation of SN38 takes place in various tissues by enzymes of the UDP-glucuronosyltransferase (UGT) family.[22] After conjugation, SN38 is excreted into the bile as its inactive glucuronide SN38-G. β-Glucuronidases produced by intestinal flora deconjugate SN38-G, which can then be reabsorbed into the circulation, resulting in an enterohepatic cycle.[23] Only small amounts of irinotecan and its metabolites are excreted in the urine. Therefore, dose adjustment does not seem necessary in patients with reduced renal function. However, in one study, increased serum creatinin was found associated with an increased risk of grades 3 or 4 diarrhea ($p= 0.0001$).[19] In another study, patients with elevated serum creatinin of 1.5–3.5 mg/dL and normal liver function received a 225 mg/m^2 dose of irinotecan every 3 weeks. These patients had similar irinotecan and SN38 clearance and AUCs compared to patients with normal liver and kidney function, who had received prior irradiation of the pelvis.[24] These data suggest that patients with moderately elevated creatinin may not have an increased risk of toxicity when receiving 75% of normal dose, although according to the product label irinotecan use in these patients is not recommended.

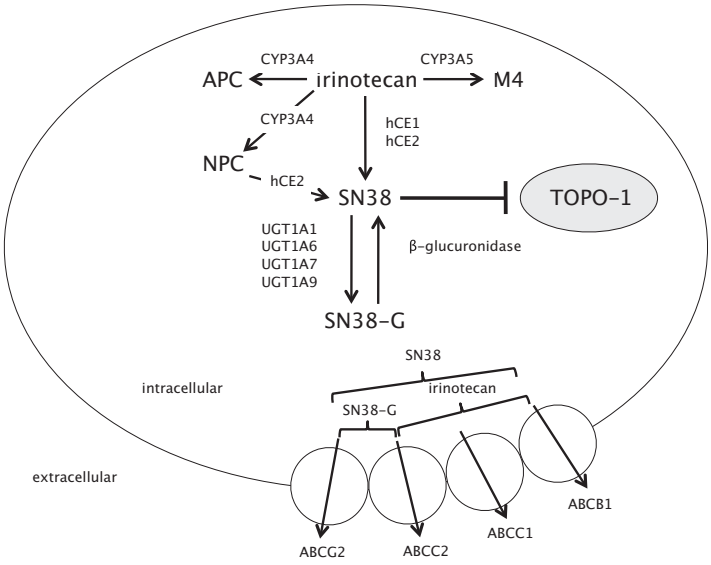

Figure 1

Schematic representation of the metabolic pathway and transport mechanisms of irinotecan and its metabolites (modified after 44). APC, NPC, M4 and SN38; metabolites of irinotecan. hCE; human carboxylesterase. SN38-G; glucuronidation product of SN38. GSTT; glutathione S-transferase T enzyme, hypothetically involved in irinotecan metabolism. TOPO-1; topo-isomerase 1, SN38 target enzyme. OATP1B1; organic anion transporting peptide 1B1. ABCB1, ABCC1, ABCC2, ABCG2; transporting peptides of the ABC family.

HEPATIC FUNCTION

A decreased liver function is usually associated with changes in AST, ALT, γ-GT and serum bilirubin levels. In a pharmacokinetic study of irinotecan, the AUC ratio of SN38 to irinotecan was higher if AST, ALT and/or bilirubin were elevated.[18] A poor liver function, as indicated by the ICG (indocyanine green) retention test was found predictive of a higher AUC of SN38 in another study.[8] These findings indicate that conjugation of SN38 is limited in patients with li-ver impairment. Since the AUC of SN38 has been associated with the incidence and severity of irinotecan toxicity, this may imply that patients with impaired liver function have a higher risk of developing toxicity. Indeed, patients with higher baseline bilirubin (≥68% ULN) experienced a higher risk of developing grades 3 or 4 neutropenia during first cycle in a series of phase II trials ($p < 0.001$).[19]

Elevated serum bilirubin levels not only indicate reduced hepatic functioning but may themselves influence the pharmacokinetic behavior of irinotecan and SN38. Both compounds are bound to plasma protein (e.g. albumin) and may be displaced by bilirubin. As a result of this competition, the unbound fractions of both irinotecan and SN38 are enhanced, resulting in a higher systemic exposure of the drug. Besides a potential increase of antitumor effects, this may enhance the toxic effects of, mainly, SN38. Indeed, grade 3 or 4 intestinal toxicities were associated with a higher biliary index (defined as AUCiri *(AUCSN38 /AUCSN38-G)) in a study of 40 patients ($p = 0.001$).[18] As a result of higher serum SN38 levels, a larger amount of unconjugated SN38 is excreted into the bile. Moreover, as bilirubin and SN38 are conjugated to their respective glucuronides by the same enzyme in the liver (uridine diphosphate glucuronosyl transferase, UGT) high levels of unconjugated serum bilirubin may be predictive for irinotecan toxicity.[25] Serum total bilirubin levels (unconjugated + conjugated bilirubin) were associated with absolute neutrophil counts (ANC) at nadir following 3-weekly irinotecan treatment ($p < 0.0001$).[26]

Although an association between baseline bilirubin levels and late diarrhea has not been observed in studies of the weekly dosage schedule, patients with moderately enhanced bilirubin (1.0–2.0 mg/dL) receiving weekly irinotecan did experience an increased risk (estimated Odds Ratio of 2.9) of grade 3 or 4 neutropenia in the first cycle ($p < 0.001$).[3] The increased risk of grade 3 or 4 neutropenia was not seen in the 3-weekly regimen.[27] Patients with high conjugated bilirubin levels (1.0–5.5 mg/dL) had significantly lower irinotecan and SN38 clearance ($p < 0.05$), and a normal AUC of SN38 while receiving 35–50% of usual irinotecan dosage.[24]

DRUG ADMINISTRATION SCHEDULE

Frequently used dosage schedules of irinotecan include 350 mg/m^2 once every 3 weeks or 125 mg/m^2 in a weekly regimen (single agent therapy); in case of combination therapy with fluorouracil (5-FU) plus leucovorin (LV) usually 125 or 180 mg/m^2 doses of irinotecan are administered every week or every other week, respectively. Administration of irinotecan with bolus infusional 5-FU/LV on 4–5 consecutive days (e.g. the Mayo Clinic schedule) resulted in high incidences of severe neutropenia (29%) and treatment related deaths (5%).[28] This led to the early termination of two randomized phase III trials.[29] Another study, comparing one infusion of irinotecan (350 mg/m^2 every 21 days; group A) with the same dosage divided

over two infusions (on days 1 and 10 or 11 every 21 days; group B), showed similar antitumor effects (group A: 25% and group B: 27% overall response rates) but higher incidence of late-onset diarrhea in patients of the second group (group A: 44% and group B: 66%).[30] In a study comparing irinotecan doses of 70 mg/m^2 weekly with 300 mg/m^2 3-weekly, 29% of patients on the weekly regimen experienced grade 3 diarrhea, compared to 14% of patients receiving 3-weekly irinotecan (p=0.103).[31] Interestingly, elderly patients who are at increased risk of toxicity should receive a lower starting dose of irinotecan in 3-weekly regimens but not in weekly regimens,[3] although the weekly regimen may be even more toxic according to these studies.

SMOKING

Smoking exposes the individual to several compounds that interact with drug-metabolizing enzymes, e.g. induction of cytochrome P-450 (CYP) enzymes by polycyclic aromatic hydrocarbons (PAHs). CYP isoforms 3A4 and 3A5 are involved in the formation of APC and NPC from irinotecan (the alternative metabolic pathway in the formation of SN38). PAHs are also found to induce enzymes of the UGT family.[32–34] In a study of 190 patients, smokers were found to have a higher clearance of irinotecan (p= 0.001), lower systemic exposure (AUC) to SN38 (p< 0.001) and a higher metabolic conversion of SN38 to its glucuronide (p= 0.006). In addition, smokers experienced less hematologic toxicity (grade 3 or 4 leukopenia p= 0.006, neutropenia p< 0.001) and there was a tendency towards lower incidence of grade 3 or 4 diarrhea in smokers.[35] However, it is still unclear whether smoking affects the antitumor effects of irinotecan.

In addition to enzymatic changes, smoking may also cause induction of ATP-binding cassette (ABC) drug transporters. This induction may result in an enhanced elimination of irinotecan and its metabolites, and therefore in a reduced systemic drug exposure. ABCB1 protein expression was enhanced in smokers compared to non-smokers in a study of 94 non-small-cell lung cancer (NSCLC) patients (p< 0.001).[36] It is yet unclear during which period the induction of CYP enzymes and drug transporters will remain present after smoking cessation. A patient who discontinues smoking immediately prior to or during irinotecan treatment may therefore experience a lower risk of toxicity compared to never-smoking patients.

CO-MEDICATION AND DIETARY SUPPLEMENTS

Medicines or dietary supplements may theoretically influence irinotecan or SN38 pharmacokinetics by one of the following mechanisms: competition for plasma protein binding, competition for (extra)hepatic enzymes or drug transporters, induction or inhibition of enzymes or drug transporters, and disruption of the enterohepatic cycle. Studies in rats indicate that valproic acid, phenobarbital and cyclosporin influence the pharmacokinetic behavior of irinotecan or SN38.[37,38] Phenytoin, phenobarbital and carbamazepine are inducers of CYP3A4 and this may explain a reduced systemic exposure to irinotecan and SN38.[3] In contrast, ketoconazole and other CYP3A4 inhibitors may cause an increased exposure to irinotecan and SN38.[39] Although not routinely used in combination with irinotecan, high-dosed sorafenib (400 mg bid) showed increased irinotecan and SN38 exposure, probably

by inhibiting SN38 glucuronidation.[40] Irinotecan on its turn may influence the metabolism of citalopram, potentially causing increased risk of rhabdomyolysis.[41] Neomycin and other antimicrobials impair enterohepatic cycling of SN38-G by reducing the amount of bacteria in the intestine and hence β-glucuronidase production necessary for deglucuronidation of SN38-G.[23]

Cancer patients frequently use herbal medicines when receiving conventional chemotherapy, for example St.John's Wort or milk thistle.[42] In vivo studies have shown that St. John's Wort reduces the SN38 AUC by 42% (p= 0.033), resulting in less myelosuppression.[43] Milk thistle only slightly changed the AUC ratio of SN38 to irinotecan, but did not have clinically important effects on the pharmacokinetic behavior of irinotecan or its metabolites.[44] Finally, the use of cannabis (taken once daily orally as tea) was shown not to influence the pharmacokinetic parameters of 600 mg irinotecan (fixed-dose) administered every 3 weeks. Nevertheless, a lower decrease in white blood cell and absolute neutrophil counts were observed (p= 0.04 andp= 0.03, respectively), which however did not translate into a lower incidence of neutropenia in cannabis users.[45] The effects with regard to irinotecan metabolism and toxicity caused by cannabis inhalation, or higher oral cannabis dosages, need further investigation.

PHARMACOGENETIC FACTORS ASSOCIATED WITH IRINOTECAN TOXICITY: METABOLIC AND TARGET ENZYMES

There is a large body of evidence suggesting that genetic differences may play an important role in the pharmacokinetic and pharmacodynamic behavior of drugs. Genetic differences may be especially important if a drug is metabolised by a specific predominant pathway, without many alternative routes. This is the case with irinotecan: metabolism of the active metabolite SN38 takes place mainly by the enzyme family of uridine diphosphate glucuronosyl transferases, UGTs. Pharmacogenetic studies of irinotecan ('irinogenetics' as they are alternatively called) therefore generally focus on polymorphisms in this group of enzymes. Other enzymatic conversions of irinotecan include metabolism by CYP3A enzymes and carboxylesterases. A schematic overview of these metabolic pathways is shown in Fig. 1.

URIDINE DIPHOSPHATE GLUCURONOSYL TRANSFERASE 1A FAMILY

The human UDP-glucuronosyltransferase (UGT) 1A is a family of enzymes that play an important role in the conjugation of endogenous and exogenous compounds to glucuronides. At least nine functional isoforms of UGT1A exist, which are all encoded by the same gene. The various isoforms are splice-variants of a single mRNA product of this gene, and consist of a unique first exon, followed by 4 exons that are the same in each UGT1A isoform ('shared exons'). Each of these isoforms is presumably individually regulated,[46,47] and they have a specific distribution pattern throughout the body.[48] UGT1A1 is expressed in liver and bladder; the liver also expresses large amounts of UGT1A3 and UGT1A4. UGT1A6 and UGT1A9 are expressed by the liver as well, but also extrahepatically in the kidney and

bladder.[48] An in vitro study revealed that the conversion of SN38 to SN38-G is catalyzed not only by UGT1A1, but to the same extent by UGT1A6 and UGT1A9.[22] UGT1A7 catalyses this reaction even better compared to UGT1A1, but this extrahepatic isoform is only expressed at low levels. Other UGT isoforms did not show in vitro glucuronidation of SN38.[22,49] An overview of UGT1A genetic polymorphisms relevant in SN38-glucuronidation has been published recently.[50]

UGT1A1

By far the most well-known polymorphism studied with regard to irinotecan toxicity is an insertion/deletion polymorphism of TA-nucleotides designated UGT1A1*28. This genetic variant is located in the promoter region of UGT1A1 that controls transcription of the UGT1A1 gene. The number of TA-repeats in the UGT1A1 gene promoter may vary between 5 and 8, and each variant is designated by a separate code: TA5-*36, TA6-*1, TA7-*28 and TA8-*37. In individuals carrying the TA7 allele (especially those being homozygous for this variant) the UGT1A1 expression is reduced up to 70%.[51] As a result, glucuronidation of various compounds is impaired, for instance bilirubin. An enhanced unconjugated serum bilirubin level, one of the symptoms of Gilbert's syndrome, is frequently associated with UGT1A1*28.[52] Gilbert's syndrome is the most common hereditary cause of increased bilirubin levels, and is found in up to 5% of the population. If patients homozygous for UGT1A1*28 are treated with irinotecan, glucuronidation of SN38 is impaired, leading to enhanced risk of toxicity. Several studies show that neutropenia occurs more frequently and ANCs at nadir are lower in patients with two TA7 alleles.[53,54] Although most studies use ANC or neutropenia as an endpoint, also febrile neutropenia (which is a clinically more relevant endpoint, as it results in hospitalisation and is potentially lethal) seems to be more frequent in the TA7/7 genotype.[55] Moreover, in a combined analysis, the incidence of grade 3 or 4 hematological toxicity in patients homozygous for *28 was increased at high and moderate irinotecan dosage (p= 0.008 andp= 0.005, respectively), whereas no association was found in patients receiving low irinotecan doses (p= 0.41).[2] These findings suggest that patients with two TA7 alleles are relatively susceptible to the effects of dose reductions or dose increments. The association of the UGT1A1*28 gene variant with severe diarrhea is somewhat less clear, and studies show either an association[56,57] or no association [58–61] with the homozygote genotype. In a recent meta-analysis, no association between the risk of diarrhea and irinotecan dose was found among patients with the TA7/7 genotype.[2] Analyses of combined hematological and gastrointestinal toxicity show an association with the *28 polymorphism.[53,54,62–64] Based on the findings of four pharmacogenetic trials that have found an increased prevalence of irinotecan-induced toxicity in patients homozygous for *28, the irinotecan product label has been changed to recommend a reduced starting dose in those patients.[53,56,62,63]

Other polymorphisms in the UGT1A1 gene include *6 (211G > A), *27 (686C > A), *29 (1099C > G) and *7 (1456T > G). According to in vitro studies, the enzyme activity of the UGT1A1*6 variant is about one-third of that of the *1 allele. However, the *27 and *6 genotypes are primarily reported in patients of Asian descent, as opposed to *28 which is found both in Caucasian and Asian patients (about 10% and less than 5% are *28 homozygotes, respectively).[65]

The UGT1A1*6 variant allele is associated with Gilbert's syndrome in Asians.[66,67] In homozygous patients receiving irinotecan, a trend towards lower conversion of SN38 to SN38-G and relatively high serum bilirubin levels are observed;[68] as a consequence, homozygous *6 carriers experience a higher incidence of grade 4 neutropenia (p= 0.025), but not of diarrhea.[69] Not all studies confirm the association of this genetic variant with grade 3 or 4 toxicity.[62] In general, it is difficult to determine the effects of the individual UGT1A1 variants because they often occur simultaneously with other UGT1A polymorphisms. For example, the UGT1A1*6 polymorphism was reported to be in linkage disequilibrium with UGT1A7 and UGT1A9 polymorphisms in Japanese patients with cancer.[70] Linkage disequilibrium between UGT1A1 and UGT1A9 single nucleotide polymorphisms (SNPs) was also observed in Caucasian subjects.[71]

Furthermore, a SNP in the promoter region at nucleotide 3156 (G > A) was determined in 93 high-risk stage III colon cancer patients receiving irinotecan. The 3156A variant was found more strongly associated with severe hematological toxicity and with severe neutropenia compared to UGT1A1*28, but not with gastrointestinal toxicity.[59] The 3156A SNP was associated with the ANC at nadir (p= 0.022).[53] Finally, the *60 variant (nucleotide 3279, resulting in decreased transcriptional activity[72]) was studied in a Korean trial of irinotecan in NSCLC patients, but no association with either the pharmacokinetics or toxicity of irinotecan was found.[69]

UGT1A6

Similarly to the UGT1A1 gene variants, unique genotype codes have been assigned to the UGT1A6 polymorphisms: UGT1A6*1, *2, *3 and *4. Each variant encodes for a certain haplotype with respect to amino acids 7, 181 and 184. No significant associations were found between UGT1A6 genotypes and the incidence of irinotecan toxicity.[58]

UGT1A7

A number of haplotypes has been assigned to the UGT1A7 gene, defined as UGT1A7*1–4. Each haplotype relates to differences in the nucleotides encoding for amino acids 115, 129, 131 and 208.[58] UGT1A7 enzyme activities are lower for individuals with the *3 or *4 genetic variants.[73] A strong association was found between the low activity genotypes (*2 and *3) and lack of gastrointestinal toxicity (p= 0.003).[58] In a study of NSCLC patients, the systemic exposure to SN38 was increased in patients with the *2 or *3 genotype, with a relatively low AUC of SN38-G in these individuals (p= 0.006). In line with these observations, grade 3 diarrhea (p= 0.028) and grade 4 neutropenia (p= 0.052) were more common in patients with *2 and *3.[69] However, no association of these polymorphisms with toxicity was detected in Japanese patients treated with irinotecan.[74] Recently it was found that most individuals homozygous for UGT1A1*28 simultaneously carry a functional promoter variant (-57T > G) of the UGT1A7 gene, reducing promoter activity to 30%.[75]

UGT1A9

Polymorphisms in promoter and intronic nucleotides of UGT1A9 have been identified at positions 118,87, 143, 152, 201, 219 and 313. Of these, only the 118 T10 repeat polymorphism (UGT1A9*22) was associated with increased incidence of grade 3–4 toxicity in a study of colorectal cancer patients receiving irinotecan (p= 0.002).[58] Conversely, NSCLC patients homozygous for the 10T-repeat sequence experienced a lower risk of grade 3 diarrhea (p= 0.037) and a lower systemic exposure to SN38 (p= 0.046).[69] Other UGT1A9 SNPs include *5 (at nucleotide position 766) and *3 (at position 98), both of which show a very low SN38 glucuronidation capacity.[76,77] UGT1A9*3 was found in only one of 94 Caucasian patients with malignant solid tumors. Although this particular patient did not suffer from diarrhea or neutropenia, there are insufficient data to draw definite conclusions about the pharmacological effects of this SNP as yet.[78] Another genetic variant of potential interest is the intronic 399C > T, as it was found to influence the pharmacokinetics of SN38 and SN38-G in Asian cancer patients.[79,80]

GLUTATHIONE-S-TRANSFERASE T

Glutathione-S-transferase T (GSTT) is an enzyme involved in the conjugation of endogenous and exogenous compounds to glutathione (GSH). This conjugation results in higher water solubility and hence facilitated excretion of the compound. It is yet unknown if irinotecan or its metabolites are subject to this elimination route. However, one study has shown some evidence that GSTT-null genotype patients receiving 5-FU/ irinotecan/LV regimens have a greater probability (57%) of developing grade 3 gastrointestinal toxicity, compared to patients with the GSTT-present genotype (23%, p= 0.053).[81]

CARBOXYLESTERASES

The human carboxylesterases hCE1 and mainly hCE2 are involved in the activation of irinotecan to its active metabolite, SN38.[82] Apart from this main pathway of activation, a small fraction of irinotecan is converted into NPC which is subsequently metabolised by hCEs to form SN38. A number of genetic polymorphisms and haplotypes have been identified in the hCE2 gene, but these were not correlated to differences in hCE2 activity or irinotecan hydrolysis.[83] In a study of 65 cancer patients, no association was found between irinotecan pharmacokinetics and the hCE2 polymorphism 1647C > T.[84]

CYTOCHROME P450 ENZYMES

The cytochrome P450 enzyme 3A4 was shown to be involved in the conversion of irinotecan into NPC or APC, which are both inactive compounds. Midazolam clearance (a measure of CYP3A4 activity) was highly correlated with irinotecan clearance (p< 0.001).[85] A recently identified metabolite, M4, is formed via CYP 3A5.[86] However, these are minor metabolic pathways and there is not much evidence that genetic variants in either CYP 3A4 or CYP3A5 have a substantial influence in the overall pharmacokinetics or toxicity profile of irinotecan. Indeed, the 6986A > G SNP in the CYP3A5 gene was not associated with the occurrence of severe hematological symptoms, severe neutropenia or gastrointestinal side effects of irinotecan.[59] Several other studies found similar results for other genotypes of the CYP3A4 and 3A5 genes.[87]

TOPO-ISOMERASE-I

SN38 is an active inhibitor of topo-isomerase-I (TOPO-1), an enzyme responsible for unfolding DNA during transcription or replication. In tissue samples of tumors with acquired resistance to irinotecan point mutations in the TOPO-1 gene or decreased TOPO-1 expression have been observed.[88,89] Variation in the number of TOPO-1 alleles was found to influence TOPO-1 gene expression and potentially confer intrinsic resistance to irinotecan.[90] However, there are yet no data suggesting that SNPs in TOPO-1 or copy number variants may cause differential susceptibility toward irinotecan toxicity.

PHARMACOGENETIC FACTORS ASSOCIATED WITH IRINOTECAN TOXICITY: TRANSPORTER PROTEINS

Irinotecan and its metabolites SN38 and SN38-G are transported out of the cell by members of the ATP-binding cassette transporter family (Fig. 1). The proteins that have been studied with respect to irinotecan transport are encoded by the ABCB1 gene (P-glycoprotein or multi-drug resistance (MDR) 1); ABCC1 (multi-drug resistance protein 1, MRP1); ABCC2 (canalicular multispecific organic anion transporter, C-MOAT or MRP2) and ABCG2 (breast cancer resistance protein, BCRP). Recent evidence suggests that the organic anion transporting peptide OATP1B1 (gene: SLCO1B1) plays a role in the pharmacokinetics of irinotecan as well.

ABC-TRANSPORTERS

ABCB1

The SNPs 1236C > T, 2677G > A/T and 3435C > T are commonly described in the ABCB1 gene and are linked to a high degree. Patients carrying the 1236T allele showed an increased exposure (AUC) of both irinotecan and SN38 ($p= 0.038$ and $p= 0.031$, respectively).[84] In a study of Japanese colorectal cancer patients, an ABCB1 haplotype harboring 1236T, 2677T and 3435T was associated with lower renal clearance of irinotecan and its metabolites ($p< 0.05$).[91]

Recently, the 3435C > T SNP was studied in 179 cancer patients treated with irinotecan, but no associations were found with severe gastrointestinal or hematological toxicity.[59] This may not be surprising as the ABCB1 2677G > T and 3435C > T SNPs were not significantly related to the pharmacokinetic behavior of irinotecan and its metabolites.[84] However, a study of NSCLC patients with the 3435TT genotype showed a significantly lower AUC of SN38G ($p= 0.010$) and higher clearance of SN38G compared to 3435CC patients ($p= 0.011$).[92] In addition, grade 3 diarrhea in this study was more frequent in 3435TT ($p= 0.047$) and grade 4 neutropenia was more common in 2677GG individuals ($p= 0.030$).

ABCC2

ABCC2 appears to be the principal transporter involved in hepatobiliary secretion of irinotecan, SN38 and SN38-G. Various ABCC2 polymorphisms have been described, that may influence ABCC2 activity or irinotecan pharmacokinetics.[93] Pharmacogenetic analysis of 6 ABCC2 SNPs showed that patients with the ABCC2*2 haplotype had a lower risk of severe irinotecan-induced diarrhea, if they did not carry a UGT1A1*28 allele (p= 0.005).[60] However, in patients either homozygous or heterozygous for the UGT1A1*28 genotype, this effect was not found. In another study, the 3972T > C variant was identified as factor influencing irinotecan pharmacokinetics.[94] In a study in NSCLC patients, the ABCC2 SNPs 24C > T and 3972C > T were found to be related to tumor response, but not toxicity.[92] There are to date no studies indicating that SNPs in other ABCC transporters (ABCC1, ABCC4) may influence irinotecan toxicity in vivo.

ABCG2

In vivo and *in vitro* data suggest that ABCG2 plays an important role in the cellular transport of irinotecan and its metabolites. For example, cell lines that overexpress ABCG2 are resistant to irinotecan and SN38.[95] In addition, patients treated with irinotecan show enhanced expression of ABCG2 in the tumor. Resistance toward irinotecan was found to be correlated to a SNP in the ABCG2 gene (421C > A).[96] Grade 4 neutropenia and grade 3 diarrhea were not found to be associated with this SNP in NSCLC patients receiving irinotecan.[92] No significant changes in the pharmacokinetics of irinotecan were found in relation to the 421C > A polymorphism.[97]

SLCO1B1

The organic anion transporting peptides OATP1B1, OATP2B1 and OATP1B3 are located on the basolateral membrane of human hepatocytes. Of these, only the organic anion transporting peptide OATP1B1, which is encoded by the SLCO1B1 gene, was found to be involved in the transport of SN38 but not of its glucuronide or irinotecan.[98] Polymorphic variants of this peptide include *1b (388A > G) and *5 (521T > C); (*1a indicating the wild-type protein). *In vitro* experiments have shown that the combination of both variants (designated *15) confers a 50% lower intracellular uptake of irinotecan, which may contribute to interpatient variability of toxic effects.[98] In a study of NSCLC patients treated with irinotecan and cisplatin, patients with the OATP1B1*5 genotype showed a higher systemic exposure to SN38 and a lower clearance of this compound. Similar results were found for the 11187G > A SNP, but not the *1b polymorphism.[99] Another pharmacokinetic study reveals that irinotecan clearance is 3-fold reduced and systemic exposure to irinotecan is enhanced in patients with the *15 haplotype.[100] A case report describes serious toxicities in a lung cancer patient homozygous for the *15 allele.[101] The effects of these SNPs with respect to irinotecan- induced toxicity require further analysis.

Risk factor	effect	recommendation	refs
Age ≥ 65	Increased toxicity risk	3-weekly regimen SA: reduced starting dose 300 mg/m^2 weekly regimen SA: no dose adjustment all regimens: intensive monitoring	3
Abnormal body weight	Difference in exposure	use BSA based on actual body weight	17
Prior abdominopelvic radiation	Increased toxicity risk	all SA regimens: reduced starting dose (300 mg/m^2 once every 3 weeks; 100 mg/m^2 in a weekly regimen)	3
Performance status (PS) ≥2	Increased toxicity risk	PS=2: consider reduced starting dose in SA regimen and monitor closely PS>2: irinotecan is not recommended, choose other therapy	3
Elevated bilirubin	Decreased SN38 metabolism	bilirubin>2mg/dL or >3*ULN: irinotecan is not recommended, choose therapy with another agent bilirubin 1.0-2.0 mg/dL or 1.5-3.0*ULN: reduced starting dose (SA therapy) and weekly hematological monitoring; consider irinotecan combination therapy or different agent	3
Elevated AST/ALT	Decreased irinotecan metabolism	AST/ALT 5-20*ULN: Irinotecan is not recommended, but one study indicates that 60mg/^{2} (normal bilirubin) or 40 mg/m^2 (bilirubin 1.5-3.0*ULN) weekly may be tolerated. Preferably select therapy with different agent. AST/ALT >20*ULN: irinotecan is not recommended, select another agent	3, 101
Reduced renal function	Decreased irinotecan excretion	Serum creat 1.5-3.5mg/dL: consider reduced (75%) starting dose in (3-weekly) SA therapy, or select different agent/regimen; monitor closely Serum creat > 3.5mg/dL: irinotecan is not recommended due to lack of data	3, 24
Smoking	increased SN38 elimination	Smoking cessation during irinotecan treatment may enhance toxicity. No prophylactic dose adjustments recommended	35
Comedication	Difference in exposure	CYP3A4 inducers: discontinue at least 2 weeks prior to irinotecan treatment CYP3A4 inhibitors: discontinue at least 1 week prior to irinotecan treatment	3
UGT1A1*28 homozygote genotype	Decreased SN38 metabolism	SA regimen: reduced starting dose, or choose combination therapy combination regimen: no dose adjustment all regimens: consider prophylactic CSF treatment	3

Table 2

Summary of recommendations for risk factors. SA, single agent therapy.

RECOMMENDATIONS FOR PERSONALIZED MEDICINE

An overview of the literature shows that determinants of dose-limiting toxicities of irinotecan (neutropenia and severe late-onset diarrhea) include both clinical parameters and pharmacogenetic factors. The fact that most associations are derived from retrospective studies makes it difficult to translate these findings to the clinic. Moreover, more than one risk factor may be present in an individual patient and it is yet unclear how the described risk factors interact. In the following section, we propose recommendations for separate risk factors (Table 2).

REDUCED HEPATIC FUNCTION, ENHANCED BILIRUBIN

Irinotecan administration is not recommended in patients with serum bilirubin levels of >2 mg/dL[3] or >3 times the upper limit of normal (ULN);[1] alternative chemotherapy should be considered. However, in one study patients with total bilirubin of 3.1–5.0 times ULN and otherwise normal AST/ALT were shown to tolerate irinotecan doses of 50 mg/m^2 weekly.[102] Patients with moderately increased bilirubin levels (1.0– 2.0 mg/dL[3]) or bilirubin levels 1.5–3.0 times ULN[1] should receive a lower starting dose in case of irinotecan single-agent therapy (100 mg/m^2 in a weekly regimen, 300 mg/m^2 once every 3 weeks[3] or even 200 mg/m^2 once every 3 weeks).[1,103,104] Patients with total bilirubin of 1.5–3.0 times ULN and enhanced AST/ALT (5.1–20.0 ULN) tolerated 40 mg/m^2 doses of irinotecan in a weekly regimen, whereas patients with normal serum bilirubin and enhanced AST/ALT were able to receive 60 mg/m^2 weekly.[102] Patients with moderately enhanced bilirubin levels treated with irinotecan single-agent therapy should be monitored every week with respect to hematological parameters in order to allow for dose adjustments. Alternative chemotherapy or decreased dose of irinotecan in irinotecan combination therapy should be considered for these patients.

CO-MEDICATION AND DIETARY SUPPLEMENTS

CYP3A4 inducing drugs such as the anticonvulsants phenytoin, phenobarbital and carbamazepine substantially reduce the exposure to irinotecan and SN38, and should be substituted by non-inducing anticonvulsant medication at least 2 weeks prior to the first dose of irinotecan. Apart from anticonvulsants, any other CYP3A4 inducing drug should be discontinued before irinotecan chemotherapy (e.g. St. John's Wort, rifampicin). CYP3A4 inhibitors, such as ketoconazole, should be discontinued at least one week before the first dose of irinotecan, as the inhibition results in increased exposure to irinotecan and SN38. If co-administration with ketoconazole (or other potent CYP3A4 inhibitors) is necessary, the irinotecan dose may need to be reduced up to 4-fold.[39]

The recommended treatment of irinotecan-induced late diarrhea is loperamide and in severe cases fluid/electrolyte replacement. In case of fever (in combination with diarrhea) also antibiotics are used (e.g. ciprofloxacillin).[29] Studies have investigated the use of budesonide and octreotidein patients with loperamide refractory diarrhea,[105–107] but in this review we will focus on the prevention and not treatment of late diarrhea.

A number of compounds have been tested for the prevention of late diarrhea, such as active charcoal, thalidomide,[108] neomycin and the Kampo medicine Hangeshashin-to. In the neomycin diarrhea prevention study, no clear benefit could be observed with respect to the occurrence of diarrhea grades 2 or 3, but grade 2 nausea was significantly more common in neomycin users.[109] The combination of neomycin with bacitracin reduced the incidence and severity of irinotecan- induced diarrhea in a study with colorectal cancer patients.[110] Similar results were obtained with the administration of active charcoal.[111] In a Japanese study of patients with advanced NSCLC, the prophylactic administration of Hangeshashin-to reduced the severity of late diarrhea, but not the amount of stools or number of days with diarrhea.[112] Oral alkalization in combination with ursodeoxycholic acid and defecation control significantly reduced the incidence of diarrhea ≥ grade 2 and other gastrointestinal effects in lung cancer patients receiving irinotecan. It also resulted in less severe hematological side effects, while at the same time tumor response rates were similar compared to control subjects. Patients with this prophylactic treatment tolerated higher doses of irinotecan.[113] Cyclosporin blocks the transporter proteins MDR1 and MRP2, reducing biliary excretion of SN38 and SN38-G. According to one theory, the gastrointestinal side effects of irinotecan are induced by biliary SN38/SN38-G excretion. By blocking the intestinal transporter proteins, the lumen may suffer less side effects of irinotecan. The use of cyclosporin (5 mg/kg bid on 3 consecutive days) therefore has prophylactic potential; indeed, relatively low incidences of gastrointestinal side effects were observed in colorectal cancer patients receiving irinotecan.[114] Cyclosporin, or the combination of cyclosporin with phenobarbital,[115] may improve the therapeutic index of irinotecan, but needs to be investigated further before its value can be established.

UGT1A1 POLYMORPHISM

Patients who are known homozygous carriers of the UGT1A1*28 genetic variants and receive irinotecan as single-agent therapy should receive a reduced starting dose according to the Camptosar product label.[3] This advice is based on studies reporting an increased risk of neutropenia and/or diarrhea in these individuals, which appears to be especially elevated in biweekly or 3-weekly regimens.[2] According to the product label, patients homozygous for *28 initially should initially receive 100 mg/m^2 weekly or 300 mg/m^2 once every 3 weeks. The current dosage advice evokes a number of questions, for example: Will irinotecan dosage reduction in patients homozygous for UGT1A1*28 result in a lower incidence of neutropenia in these individuals? If so, should irinotecan dosage be reduced only at starting dose, or in all cycles? Is it rational to give a reduced starting dose in irinotecan single agent therapy, but not combination therapy? Does a reduced dosage result in equal antitumor efficacy in these individuals? Do UGT1A1*28 homozygotes really need dosage reduction, or do they tolerate the same dosages of irinotecan despite a higher risk of neutropenia? There are to date no independent prospective studies that have addressed these questions into detail.

The relative benefit of the proposed genotype individualization of a starting dose remains unclear. In the European product label, no recommendations are given with respect to the UGT1A1*28 genotype. A summary of studies reporting the combined incidence of grade 3 and 4 diarrhea and neutropenia over all cycles is shown in Table 3. The data derived from these studies show that in order to potentially prevent serious toxicity (diarrhea and/or neutropenia) in one TA7/TA7 patient, a total of 19 patients need to be genotyped (NNTG,

number needed to genotype), and a dose reduction given to those of them who are UGT1A1*28 homozygotes, in order to potentially prevent one case of severe toxicity (Table 3). The NNTG is larger (45) if only a reduced starting dose is prescribed, because not all toxicity occurs in the first cycle. In addition, also TA6/TA6 and TA6/TA7 patients (who constitute roughly 90% of the patient population) will experience toxicity, although less frequently. As a result, the majority of toxic side effects will not be affected by using genotypic information in this way, and it may even give a false sense of safety. This is especially true in non-Caucasian patients, who may also carry the common UGT1A1*6 polymorphism.

In our opinion, there are to date too little data to promote the active genotyping for UGT1A1 or any other genetic polymorphism in the clinical setting. If a patient is a known UGT1A1*28 homozygote, one could individualize therapy in one of the following ways:

(1) adopt starting dose in case of irinotecan single agent therapy;

(2) choose another therapy regimen (irinotecan combination therapy, or select a different agent);

(3) prophylactic use of colony-stimulating factors (CSF).

It must be noted however that the effects of none of these strategies have been prospectively tested, whether with respect to antitumor efficacy, survival or toxicity. Although there is no formal indication for routine or prophylactic administration of CSF, it may be considered in individual patients experiencing significant (risk of) neutropenia.[3]

Toxicity (%) in TA6/6+TA6/7	Toxicity (%) in TA7/TA7	p	N	NNTG	Toxicity potentially prevented by dose reduction in TA7/TA7(%)	reference
Over all cycles				**18.8**		
1 (6.3%)	2 (50.0%)	0.028	20	10.0	66.7%	300 mg/m^2 3-weekly [-54]
3 (5.7%)	4 (66.7%)	<0.001	59	14.8	57.1%	350 mg/m^2 3-weekly [-53]
21 (36.2%)	0 (0%)	-0.072	64	>>>	-	125 mg/m^2 weekly [+57]
66 (52.08%)	8 (72.7%)	0.185	138	17.3	10.8%	250 mg/m^2 3-weekly [+55]
32 (41.6%)	3 (100.0%)	0.045	80	26.7	8.6%	350 mg/m^2 3-weekly [-55]
First cycle only				**44.5**		
17 (7.5%)	5 (22.7%)	0.016	250	50.0	22.7%	180 mg/m^2 biweekly [+63]
19 (15.0%)	4 (36.4%)	0.068	138	34.5	17.4%	250 mg/m^2 3-weekly [+55]
11 (14.3%)	0 (0%)	0.481	80	>>>	-	350 mg/m^2 3-weekly [-55]

Table 3

Summary of studies reporting combined hematologic and gastrointestinal toxicity (grade 3 or 4) of irinotecan.Only studies using irinotecan as single agent or in combination with either fluorouracil or capecitabine are considered. Abbreviations: p:p-value for comparison of % toxicity (chi-square test), N: number of patients in study, NNTG: number needed to genotype, +combination therapy with 5FU/LV or capecitabine, -single agent. NNTG is calculated by dividing the number of patients in a study by the number of toxicities in TA7/TA7 patients of that study. The overall NNTG is calculated as the sum of 'NNTG*(number of patients in a study/total number of patients)' of all studies. Only studies with high-dosage irinotecan (≥180 mg/m2) are taken into account in this calculation because of similar toxicity incidence. The % of toxicity potentially prevented in TA7/TA7 is calculated by dividing the number of toxicities in the TA7/TA7 genotype group by the number of all toxicities occurring in the study.

CONCLUSION AND DISCUSSION

In this review we have shown that a large number of factors, both genetic and physiologic, play an important role in the development of toxic side effects of irinotecan. Elderly patients, patients with high performance status, prior radiation or poor hepatic function (e.g. increased bilirubin levels) are at increased risk of developing toxicity, but also patients who use certain co-medications or dietary supplements. In patients presenting with multiple risk factors, even a reduced irinotecan starting dose may not be safe, and other therapeutic options should be considered. A younger patient, homozygous for UGT1A1*28, may tolerate irinotecan without major difficulties, but a middle-aged patient with for example PS = 1 and recurrent disease may not. It is therefore important to obtain more information about the relative importance of toxicity risk factors, before they can effectively be used in a clinical setting.

We are just beginning to understand a small part of the complex pharmacogenetics of irinotecan, and the first attempts to predict toxicity have been promising. However, we need to focus not only on neutropenia (although an objective endpoint, easily measured and showing a clear association with UGT1A1*28) but on all severe toxicity combined (mainly neutropenia and diarrhea). We also need to investigate the effects of the proposed genotypic dose individualization on toxicity and efficacy. Future studies should aim to take into account relevant clinical factors that may otherwise confound a pharmacogenetic association with irinotecan toxicity.

ACKNOWLEDGMENTS

We thank B. Steemers for his assistance with the artwork.

REFERENCES

1. Anonymous. Camptosar product label Europe; 2007.

2. Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 2007;99:1290–5.

3. Anonymous. Camptosar product label USA; 2007.

4. Rougier P, Bugat R, Douillard JY, et al. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 1997;15:251–60.

5. Pitot HC, Wender DB, O'Connell MJ, et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. J Clin Oncol 1997;15:2910–9.

6. Mathijssen RH, Verweij J, Loos WJ, de BP, Nooter K, Sparreboom A. Irinotecan pharmacokinetics–pharmacodynamics: the clinical relevance of prolonged exposure to SN-38. Br J Cancer 2002;87:144–50.

7. Xie R, Mathijssen RH, Sparreboom A, Verweij J, Karlsson MO. Clinical pharmacokinetics of irinotecan and its metabolites in relation with diarrhea. Clin Pharmacol Ther 2002;72: 265–75.

8. Miya T, Goya T, Fujii H, et al. Factors affecting the pharmacokinetics of CPT-11: the body mass index, age and sex are independent predictors of pharmacokinetic parameters of CPT-11. Invest New Drugs 2001;19:61–7.

9. Rothenberg ML, Cox JV, DeVore RF, et al. A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. Cancer 1999;85:786–95.

10. Drengler RL, Kuhn JG, Schaaf LJ, et al. Phase I and pharmacokinetic trial of oral irinotecan administered daily for 5 days every 3 weeks in patients with solid tumors. J Clin Oncol 1999;17:685–96.

11. Comella P, Farris A, Lorusso V, et al. Irinotecan plus leucovorin-modulated 5-fluorouracil I.V. bolus every other week may be a suitable therapeutic option also for elderly patients with metastatic colorectal carcinoma. Br J Cancer 2003;89:992–6.

12. Sastre J, Paz-Ares L, Carcas A, et al. A phase I, dose-finding study of irinotecan (CPT-11) short i.v. infusion combined with fixed dose of 5-fluorouracil (5-FU) protracted i.v. infusion in adult patients with advanced solid tumours. Cancer Chemother Pharmacol 2005;55:453–60.

13. Souglakos J, Pallis A, Kakolyris S, et al. Combination of irinotecan (CPT-11) plus 5-fluorouracil and leucovorin (FOLFIRI regimen) as first line treatment for elderly patients with metastatic colorectal cancer: a phase II trial. Oncology 2005;69:384–90.

14. Chau I, Norman AR, Cunningham D, et al. Elderly patients with fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer derive similar benefit without excessive toxicity when treated with irinotecan monotherapy. Br J Cancer 2004;91:1453–8.

15. Ratain MJ. Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit? J Clin Oncol 1998;16:2297–8.

16. Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. J Clin Oncol 1996;14:2590–611.

17. Sparreboom A, Wolff AC, Mathijssen RH, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol 2007;25:4707–13.

18. Gupta E, Mick R, Ramirez J, et al. Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. J Clin Oncol 1997;15: 1502–10.

19. Freyer G, Rougier P, Bugat R, et al. Prognostic factors for tumour response, progression-free survival and toxicity in metastatic colorectal cancer patients given irinotecan (CPT-11) as second-line chemotherapy after 5FU failure. CPT-11 F205, F220, F221 and V222 study groups. Br J Cancer 2000;83:431–7.

20. Sasaki Y, Hakusui H, Mizuno S, et al. A pharmacokinetic and pharmacodynamic analysis of CPT-11 and its active metabolite SN-38. Jpn J Cancer Res 1995;86:101–10.

21. Comella P, Massidda B, Filippelli G, et al. Safety and efficacy of irinotecan plus high-dose leucovorin and intravenous bolus 5-fluorouracil for metastatic colorectal cancer: pooled analysis of two consecutive southern Italy cooperative oncology group trials. Clin Colorectal Cancer 2005;5:203–10.

22. Ciotti M, Basu N, Brangi M, Owens IS. Glucuronidation of 7-ethyl-10-hydroxy-camptothecin (SN-38) by the human UDP-glucuronosyltransferases encoded at the UGT1 locus. Biochem Biophys Res Commun 1999;260:199–202.

23. Takasuna K, Hagiwara T, Hirohashi M, et al. Involvement of beta-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (CPT-11) in rats. Cancer Res 1996;56:3752–7.

24. Venook AP, Enders KC, Fleming G, et al. A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863. Ann Oncol 2003;14:1783–90.

25. Canal P, Chatelut E, Guichard S. Practical treatment guide for dose individualisation in cancer chemotherapy. Drugs 1998;56:1019–38.

26. Ramchandani RP, Wang Y, Booth BP, et al. The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. J Clin Pharmacol 2007;47:78–86.

27. Meyerhardt JA, Kwok A, Ratain MJ, McGovren JP, Fuchs CS. Relationship of baseline serum bilirubin to efficacy and toxicity of single-agent irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 2004;22:1439–46.

28. Delaunoit T, Goldberg RM, Sargent DJ, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. Cancer 2004;101:2170–6.

29. Rothenberg ML, Meropol NJ, Poplin EA, Van CE, Wadler S. Mortality associated with irinotecan plus bolus fluorouracil/ leucovorin: summary findings of an independent panel. J Clin Oncol 2001;19:3801–7.

30. Tsavaris N, Ziras N, Kosmas C, et al. Two different schedules of irinotecan (CPT-11) in patients with advanced colorectal carcinoma relapsing after a 5-fluorouracil and leucovorin combination. A randomized study. Cancer Chemother Pharmacol 2003;52:514–9.

31. Borner MM, Bernhard J, Dietrich D, et al. A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. Ann Oncol 2005;16:282–8.

32. Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 2006;12:2166–71.

33. Collier AC, Tingle MD, Paxton JW, Mitchell MD, Keelan JA. Metabolizing enzyme localization and activities in the first trimester human placenta: the effect of maternal and gestational age, smoking and alcohol consumption. Hum Reprod 2002;17:2564–72.

34. Bock KW, Schrenk D, Forster A, et al. The influence of environmental and genetic factors on CYP2D6, CYP1A2 and UDP-glucuronosyltransferases in man using sparteine, caffeine, and paracetamol as probes. Pharmacogenetics 1994;4:209–18.

35. van der Bol JM, Mathijssen RH, Loos WJ, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 2007;25: 2719–26.

36. Volm M, Mattern J, Samsel B. Overexpression of P-glycoprotein and glutathione S-transferase-pi in resistant non-small cell lung carcinomas of smokers. Br J Cancer 1991;64:700–4.

37. Gupta E, Safa AR, Wang X, Ratain MJ. Pharmacokinetic modulation of irinotecan and metabolites by cyclosporin A. Cancer Res 1996;56:1309–14.

38. Gupta E, Wang X, Ramirez J, Ratain MJ. Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. Cancer Chemother Pharmacol 1997;39:440–4.

39. Kehrer DF, Mathijssen RH, Verweij J, de BP, Sparreboom A. Modulation of irinotecan metabolism by ketoconazole. J Clin Oncol 2002;20:3122–9.

40. Mross K, Steinbild S, Baas F, et al. Results from an in vitro and a clinical/pharmacological phase I study with the combination irinotecan and sorafenib. Eur J Cancer 2007;43:55–63.

41. Richards S, Umbreit JN, Fanucchi MP, Giblin J, Khuri F. Selective serotonin reuptake inhibitor-induced rhabdomyolysis associated with irinotecan. South Med J 2003;96:1031–3.

42. Werneke U, Earl J, Seydel C, Horn O, Crichton P, Fannon D. Potential health risks of complementary alternative medicines in cancer patients. Br J Cancer 2004;90:408–13.

43. Mathijssen RH, Verweij J, de BP, Loos WJ, Sparreboom A. Effects of St. John's wort on irinotecan metabolism. J Natl Cancer Inst 2002;94:1247–9.

44. van Erp NP, Baker SD, Zhao M, et al. Effect of milk thistle (Silybum marianum) on the pharmacokinetics of irinotecan. Clin Cancer Res 2005;11:7800–6.

45. Engels FK, de Jong FA, Sparreboom A, et al. Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. Oncologist 2007;12:291–300.

46. Gong QH, Cho JW, Huang T, et al. Thirteen UDP-glucuronosyltransferase genes are encoded at the human UGT1 gene complex locus. Pharmacogenetics 2001;11:357–68.

47. Strassburg CP, Manns MP, Tukey RH. Expression of the UDP-glucuronosyltransferase 1A locus in human colon. Identification and characterization of the novel extrahepatic UGT1A8. J Biol Chem 1998;273:8719–26.

48. Zhang D, Zhang D, Cui D, et al. Characterization of the UGT activity of human liver microsomes genotyped for the UGT1A1*28 polymorphism. Drug Metab Dispos 2007;35: 2270–80.

49. Hanioka N, Ozawa S, Jinno H, Ando M, Saito Y, Sawada J. Human liver UDP-glucuronosyltransferase isoforms involved in the glucuronidation of 7-ethyl-10-hydroxycamptothecin. Xenobiotica 2001;31:687–99.

50. Nagar S, Blanchard RL. Pharmacogenetics of uridine diphosphoglucuronosyltransferase (UGT) 1A family members and its role in patient response to irinotecan. Drug Metab Rev 2006;38:393–409.

51. Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 1995;333:1171–5.

52. Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UPD-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet 1996;347:578–81.

53. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004;22: 1382–8.

54. Iyer L, Das S, Janisch L, et al. UGT1A*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43–7.

55. Kweekel DM, Gelderblom AJ, Van der Straaten T, et al. UGT1A1*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer – a Dutch Colorectal Cancer Group study. Br J Cancer 2008;99:275-82.

56. Marcuello E, Altes A, Menoyo A, Del Rio E, Gomez-Pardo M, Baiget M. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer 2004;91:678–82.

57. Massacesi C, Terrazzino S, Marcucci F, et al. Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy. Cancer 2006;106:1007–16.

58. Carlini LE, Meropol NJ, Bever J, et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin Cancer Res 2005;11:1226–36.

59. Cote JF, Kirzin S, Kramar A, et al. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin Cancer Res 2007;13:3269–75.

60. de Jong FA, Scott-Horton TJ, Kroetz DL, et al. Irinotecan induced diarrhea: functional significance of the polymorphic ABCC2 transporter protein. Clin Pharmacol Ther 2007;81: 42–9.

61. Stewart CF, Panetta JC, O'Shaughnessy MA, et al. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. J Clin Oncol 2007;25:2594–600.

62. Ando Y, Saka H, Ando M, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921–6.

63. Rouits E, Boisdron-Celle M, Dumont A, Guerin O, Morel A, Gamelin E. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients.Clin Cancer Res 2004;10:5151–9.

64. Toffoli G, Cecchin E, Corona G, et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 2006;24:3061–8.

65. Premawardhena A, Fisher CA, Liu YT, et al. The global distribution of length polymorphisms of the promoters of the glucuronosyltransferase 1 gene (UGT1A1): hematologic and evolutionary implications. Blood Cells Mol Dis 2003;31: 98–101.

66. Yamamoto K, Sato H, Fujiyama Y, Doida Y, Bamba T. Contribution of two missense mutations (G71R and Y486D) of the bilirubin UDP glycosyltransferase (UGT1A1) gene to phenotypes of Gilbert's syndrome and Crigler-Najjar syndrome type II. Biochim Biophys Acta 1998;1406:267–73.

67. Koiwai O, Nishizawa M, Hasada K, et al. Gilbert's syndrome is caused by a heterozygous missense mutation in the gene for bilirubin UDP-glucuronosyltransferase. Hum Mol Genet 1995;4:1183–6.

68. Sai K, Saeki M, Saito Y, et al. UGT1A1 haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. Clin Pharmacol Ther 2004;75:501–15.

69. Han JY, Lim HS, Shin ES, et al. Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J Clin Oncol 2006;24:2237–44.

70. Fujita K, Ando Y, Nagashima F, et al. Genetic linkage of UGT1A7 and UGT1A9 polymorphisms to UGT1A1*6 is associated with reduced activity for SN-38 in Japanese patients with cancer. Cancer Chemother Pharmacol 2007;60: 515–22.

71. Innocenti F, Liu W, Chen P, Desai AA, Das S, Ratain MJ. Haplotypes of variants in the UDP-glucuronosyltransferase1A9 and 1A1 genes. Pharmacogenet Genomics 2005;15: 295–301.

72. Sugatani J, Yamakawa K, Yoshinari K, et al. Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. Biochem Biophys Res Commun 2002;292: 492–7.

73. Gagne JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C. Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl- 10-hydroxycamptothecin (SN-38). Mol Pharmacol 2002;62:608–17.

74. Ando Y, Ueoka H, Sugiyama T, Ichiki M, Shimokata K, Hasegawa Y. Polymorphisms of UDP-glucuronosyltransferase and pharmacokinetics of irinotecan. Ther Drug Monit 2002;24:111–6.

75. Lankisch TO, Vogel A, Eilermann S, et al. Identification and characterization of a functional TATA box polymorphism of the UDP glucuronosyltransferase 1A7 gene. Mol Pharmacol 2005;67:1732–9.

76. Villeneuve L, Girard H, Fortier LC, Gagne JF, Guillemette C. Novel functional polymorphisms in the UGT1A7 and UGT1A9 glucuronidating enzymes in Caucasian and African–American subjects and their impact on the metabolism of 7-ethyl-10- hydroxycamptothecin and flavopiridol anticancer drugs. J Pharmacol Exp Ther 2003;307:117–28.

77. Jinno H, Saeki M, Saito Y, et al. Functional characterization of human UDP-glucuronosyltransferase 1A9 variant, D256N, found in Japanese cancer patients. J Pharmacol Exp Ther 2003;306:688–93.

78. Paoluzzi L, Singh AS, Price DK, et al. Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. J Clin Pharmacol 2004;44:854–60.

79. Sandanaraj E, Jada SR, Shu X, et al. Influence of UGT1A9 intronic I399C > T polymorphism on SN-38 glucuronidation in Asian cancer patients. Pharmacogenomics J.

80. Girard H, Villeneuve L, Court MH, et al. The novel UGT1A9 intronic I399 polymorphism appears as a predictor of 7-ethyl-10-hydroxycamptothecin glucuronidation levels in the liver. Drug Metab Dispos 2006;34:1220–8.

81. Romero RZ, Morales R, Garcia F, et al. Potential application of GSTT1-null genotype in predicting toxicity associated to 5-fluorouracil irinotecan and leucovorin regimen in advanced stage colorectal cancer patients. Oncol Rep 2006;16: 497–503.

82. Humerickhouse R, Lohrbach K, Li L, Bosron WF, Dolan ME. Characterization of CPT-11 hydrolysis by human liver carboxylesterase isoforms hCE-1 and hCE-2. Cancer Res 2000;60:1189–92.

83. Wu MH, Chen P, Wu X, et al. Determination and analysis of single nucleotide polymorphisms and haplotype structure of the human carboxylesterase 2 gene. Pharmacogenetics 2004;14:595–605.

84. Mathijssen RH, Marsh S, Karlsson MO, et al. Irinotecan pathway genotype analysis to predict pharmacokinetics.Clin Cancer Res2003;9:3246–53.

85. Mathijssen RH, de Jong FA, van Schaik RH, et al. Prediction of irinotecan pharmacokinetics by use of cytochrome P450 3A4 phenotyping probes. J Natl Cancer Inst 2004;96:1585–92.

86. Santos A, Zanetta S, Cresteil T, et al. Metabolism of irinotecan (CPT-11) by CYP3A4 and CYP3A5 in humans. Clin Cancer Res 2000;6:2012–20.

87. Smith NF, Figg WD, Sparreboom A. Pharmacogenetics of irinotecan metabolism and transport: an update. Toxicol In Vitro 2006;20:163–75.

88. Takatani H, Oka M, Fukuda M, et al. Gene mutation analysis and quantitation of DNA topoisomerase I in previously untreated non-small cell lung carcinomas. Jpn J Cancer Res 1997;88:160–5.

89. Tsurutani J, Nitta T, Hirashima T, et al. Point mutations in the topoisomerase I gene in patients with non-small cell lung cancer treated with irinotecan. Lung Cancer 2002;35: 299–304.

90. McLeod HL, Keith WN. Variation in topoisomerase I gene copy number as a mechanism for intrinsic drug sensitivity. Br J Cancer 1996;74:508–12.

91. Sai K, Kaniwa N, Itoda M, et al. Haplotype analysis of ABCB1/ MDR1 blocks in a Japanese population reveals genotype-dependent renal clearance of irinotecan. Pharmacogenetics 2003;13:741–57.

92. Han JY, Lim HS, Yoo YK, et al. Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer. Cancer 2007;110:138–47.

93. Sugiyama Y, Kato Y, Chu X. Multiplicity of biliary excretion mechanisms for the camptothecin derivative irinotecan (CPT-11), its metabolite SN-38, and its glucuronide: role of canalicular multispecific organic anion transporter and P-glycoprotein. Cancer Chemother Pharmacol 1998;42 Suppl.:S44–9.

94. Innocenti F, Undevia SD, Chen PX et al. Pharmacogenetic analysis of interindividual irinotecan (CPT-11) pharmacokinetic (PK) variability: evidence for a functional variant of ABCC2.Journal of Clinical Oncology, 2004. ASCO Annual Meeting Proceedings (post-meeting edition), vol. 22, No. 14S (July 15 Suppl.); 2010.

95. Candeil L, Gourdier I, Peyron D, et al. ABCG2 overexpression in colon cancer cells resistant to SN38 and in irinotecantreated metastases. Int J Cancer 2004;109:848–54.

96. Imai Y, Nakane M, Kage K, et al. C421A polymorphism in the human breast cancer resistance protein gene is associated with low expression of Q141K protein and low-level drug resistance. Mol Cancer Ther 2002;1:611–6.

97. de Jong FA, Marsh S, Mathijssen RH, et al. ABCG2 pharmacogenetics: ethnic differences in allele frequency and assessment of influence on irinotecan disposition. Clin Cancer Res 2004;10:5889–94.

98. Nozawa T, Minami H, Sugiura S, Tsuji A, Tamai I. Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxy-camptothecin: in vitro evidence and effect of single nucleotide polymorphisms. Drug Metab Dispos 2005;33:434–9.

99. Han JY, Lim HS, Shin ES, et al. Influence of the organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharmacokinetics and clinical outcome of patients with advanced non-small cell lung cancer. Lung Cancer 2008;59:69–75.

100. Xiang X, Jada SR, Li HH, et al. Pharmacogenetics of SLCO1B1 gene and the impact of *1b and *15 haplotypes on irinotecan disposition in Asian cancer patients. Pharmacogenet Genomics 2006;16:683–91.

101. Takane H, Miyata M, Burioka N, et al. Severe toxicities after irinotecan-based chemotherapy in a patient with lung cancer: a homozygote for the SLCO1B1*15 allele. Ther Drug Monit 2007;29:666–8.

102. Schaaf LJ, Hammond LA, Tipping SJ, et al. Phase 1 and pharmacokinetic study of intravenous irinotecan in refractory solid tumor patients with hepatic dysfunction. Clin Cancer Res 2006;12:3782–91.

103. Raymond E, Boige V, Faivre S, et al. Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. J Clin Oncol 2002;20:4303–12.

104. Boige V, Taieb J, Hebbar M, et al. Irinotecan as first-line chemotherapy in patients with advanced hepatocellular carcinoma: a multicenter phase II study with dose adjustment according to baseline serum bilirubin level. Eur J Cancer 2006;42:456–9.

105. Lenfers BH, Loeffler TM, Droege CM, Hausamen TU. Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. Ann Oncol 1999;10:1251–3.

106. Barbounis V, Koumakis G, Vassilomanolakis M, Demiri M, Efremidis AP. Control of irinotecan-induced diarrhea by octreotide after loperamide failure. Support Care Cancer 2001;9:258–60.

107. Pro B, Lozano R, Ajani JA. Therapeutic response to octreotide in patients with refractory CPT-11 induced diarrhea. Invest New Drugs 2001;19:341–3.

108. Govindarajan R, Heaton KM, Broadwater R, Zeitlin A, Lang NP, Hauer-Jensen M. Effect of thalidomide on gastrointestinal toxic effects of irinotecan.Lancet2000;356:566–7.

109. de Jong FA, Kehrer DF, Mathijssen RH, et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1*28 genotype screening: a double-blind, randomized, placebo-controlled study. Oncologist 2006;11:944–54.

110. Alimonti A, Satta F, Pavese I, Burattini E, Zoffoli V, Vecchione A. Prevention of irinotecan plus 5-fluorouracil/leucovorin-induced diarrhoea by oral administration of neomycin plus bacitracin in first-line treatment of advanced colorectal cancer. Ann Oncol 2003;14:805–6.

111. Michael M, Brittain M, Nagai J, et al. Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. J Clin Oncol 2004;22:4410–7.

112. Mori K, Kondo T, Kamiyama Y, Kano Y, Tominaga K. Preventive effect of Kampo medicine (Hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. Cancer Chemother Pharmacol2003;51:403–6.

113. Takeda Y, Kobayashi K, Akiyama Y, et al. Prevention of irinotecan (CPT-11)-induced diarrhea by oral alkalization combined with control of defecation in cancer patients. Int J Cancer 2001;92:269–75.

114. Chester JD, Joel SP, Cheeseman SL, et al. Phase I and pharmacokinetic study of intravenous irinotecan plus oral cyclosporin in patients with fluorouracil-refractory metastatic colon cancer. J Clin Oncol 2003;21:1125–32.

115. Innocenti F, Undevia SD, Ramirez J, et al. A phase I trial of pharmacologic modulation of irinotecan with cyclosporine and phenobarbital. Clin Pharmacol Ther 2004;76: 490–502.