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REVIEW

Pharmacogenetics of irinotecan: An ethnicity-based prediction of irinotecan adverse events

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Abstract

Irinotecan is now regarded as the most active drug for the treatment of colorectal cancer. However, one of the most difficult issues oncologists face is deciding the optimal dose for an individual patient, as each individual shows different outcomes even at the same dose with regard to treatment related adverse events, ranging from no toxicity to a lethal event. Inherited genetic polymorphism of a single gene or multiple genes (haplotype or linkage disequilibrium) involved in SN-38 glucuronidation, a predominant route of irinotecan detoxification, is now recognized as a significant factor that can alter the incidence of side effects. Attempts to explore such inherited genetic variability have been focused on elucidating interindividual as well as interethnic differences. Genotyping studies in relation to adverse events in an individual or in a group of similar ethnicity should contribute to establishing individual-oriented or ethnicity-oriented irinotecan treatment regimens. This review highlights current single- or multi-tired approaches for the elucidation of genetic predispositions of patients to severe toxicities, especially among Asians. The purpose of this is to contribute to minimizing toxicity by dose modifications, with the consequent aim of maximizing dose intensity and efficacy, an ultimate goal of irinotecan-individualized therapy.

INTRODUCTION

The incidence of colorectal cancer is high worldwide[1]. Regrettably, colorectal cancer is a disease with high mortality, being the second (in Europe)[2] or third (in USA)[3] leading cause of cancer related death. The fact that surgery can not always extirpate the recurrence of this disease has prompted researchers to establish active multimodal treatment options against advanced colorectal cancer. A recent meta-analysis has provided evidence that chemotherapy achieves significantly prolonged median survival time (12 mo) when compared with the best supportive care alone (8 mo)[4].

Irinotecan, a water-soluble, semi-synthetic derivative of plant alkaloid camptothecin, has been approved for the treatment of various kinds of gastrointestinal cancers including those of the stomach and colon. Irinotecan is a prodrug; its hydrolysis by carboxylesterases produces active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), which is 100- or 1000- times more potent than irinotecan as a topoisomerase I inhibitor. Irinotecan has been recognized as one of the pivotal agents of randomized trials against advanced colorectal cancer in this century, and a further prolongation of median survival time (23 mo) by irinotecan in combination with folic acid and fluorouracil

(FOLFIRI regimen)[5] has led to approval for its use in the first line treatment for metastatic colorectal cancer. However, principal dose limiting toxicities of irinotecan are severe delayed diarrhea and/or leukoneutropenia[6], and these toxicities sometimes preclude treatment continuation. Moreover, the probability and profile of toxicities can not be predicted on an individual basis at the time of prescription. The narrow therapeutic index, the given regimen or dose which is overly toxic and/or less effective to some segment of patients, prevents the overall improvement of treatment outcomes. Therefore, the prediction and selection of patients who may experience severe toxicities before drug exposure are urgently needed.

There is a growing body of evidence suggesting that the effectiveness and toxicity of any drug may be at least in part influenced by a genetic polymorphism responsible for drug metabolism. Pharmacogenetic knowledge could stratify patients for expected responses and adverse events, thus leading to more optimal prescriptions and preventing treatment discontinuation of an otherwise effective anticancer agent. Uridine diphosphate glucuronosyltransferases (UGTs) are the principal enzymes for irinotecan detoxification and have attracted much interest in pharmacogenetic research because of their extensive gene polymorphism that can alter irinotecan metabolism. UGTs convert SN-38 to an inactive metabolite SN-38 glucuronide (SN-38G) and convert SN-38 to a more water-soluble form, thereby facilitating excretion into bile and urine. However, the hepatobiliary excreted SN-38G can be deglucuronidated into SN-38 by endogenous bacterial beta-glucuronidase in the intestine, allowing SN-38 to be reabsorbed from the intestine and to enter into enterohepatic circulation. The SN-38 in the intestinal epithelial cell causes delayed-type diarrhea as a manifestation of local toxic effects of SN-38 on the intestinal mucosa. Since glucuronidation of SN-38 theoretically lessens irinotecan induced adverse events, any inherited variability of UGT genes that involves increased or decreased UGT activity may alter concentrations of SN-38 and SN-38G,and, consequently, affect irinotecan-induced toxicities.

Recent advances in irinotecan pharmacogenetics have provided evidence that there is an interindividual as well as interethnic variability of UGT gene polymorphism, suggesting that incidences and profiles of irinotecan toxicities should be considered on an individual as well as on an ethnic basis. Interethnic variability raises the possibility that a safer, more successful irinotecan regimen for a certain ethnic group does not necessarily provide the same results for other races. Therefore, pharmacogenetics comparing each ethnicity can aid in the development of ethnic-specific irinotecan regimens.

This review highlights current knowledge on UGT polymorphism affecting irinotecan metabolism, especially in Asian people. The application of this knowledge to clinical use should contribute to establishing individualized dose modifications of irinotecan as well as ethnic-specific irinotecan usage, which will offer a minimal chance of severe toxicity, leading to an increase in dose intensity and resultant improved efficacy.

UGT

The UGT superfamily is classified into two families (UGT1 and 2) and 3 subfamilies (UGT1A, UGT2A, and UGT2B). According to the nomenclature system, the first Arabic numeral represents the family (e.g. UGT1), followed by a letter designating the subfamily (e.g. UGT1A) and a second Arabic numeral denoting the individual enzyme (e.g. UGT1A1)[7]. The UGT1 gene, mapped on chromosome 2q37, generates nine functional (UGT1A1, UGT1A3-1A10) and four pseudogenes (UGT1A2p, UGT1A11p, UGT1A12p, and UGT1A13p) by splicing individual exon 1 to the common downstream exons 2 to 5[8]. Each individual UGT1A gene exhibits a specific tissue distribution[9]. Since the first nine unique exons each confer the substrate specificity[7] and is preceded by a promoter, polymorphism in the exon 1 or in the upstream promoter area affects the substrate metabolism by the respective UGT1A enzyme. On the other hand, polymorphism in common exons 2 to 5 is relatively uncommon. SN-38 is a substrate for several UGT1A isoforms, such as UGT1A1, UGT1A4, UGT1A6, UGT1A7, and UGT1A9[7]; among them, UGT1A1 is thought to be the most predominant catalyst in its metabolism[10]. Therefore, the polymorphism of genes encoding UGT1A1 *(UGT1A1)* is one of the most critical factors in irinotecan efficacy and toxicity, and therefore has been most extensively studied.

UGT1A1

More than 50 genetic variations of *UGT1A1* have been currently identified[11], each of which leads to different degrees of functional variation. Among them, functionally important candidates of *UGT1A1* polymorphism both in Caucasians and Asians are *UGT1A1*6, UGT1A1*28, UGT1A1*36,* and *UGT1A1*37*, the latter three corresponding to the variable number of TA repeats in the promoter lesion. The wild type *UGT1A1* is designated as *UGT1A1*1.*

DIFFERENT NUMBERS OF TA REPEAT (*UGT1A1*28*, *UGT1A1*36*, AND *UGT1A1*37*)

Polymorphism in the TATAA element of the 5'-promoter region causes increased or decreased numbers of TA repeats. Wild type *UGT1A1* contains six TA repeats [A(TA)$_6$TAA], whereas genes containing five, seven, and eight TA repeats are respectively designated as *UGT1A1*36* (TA$_5$)[12], *UGT1A1*28* (TA$_7$)[13], and *UGT1A1*37* (TA$_8$)[12]. The transcriptional activity of the promoter appears to be inversely correlated with the number of TA repeats, i.e. the TA$_7$ or TA$_5$ promoter exhibits respectively a decreased or increased

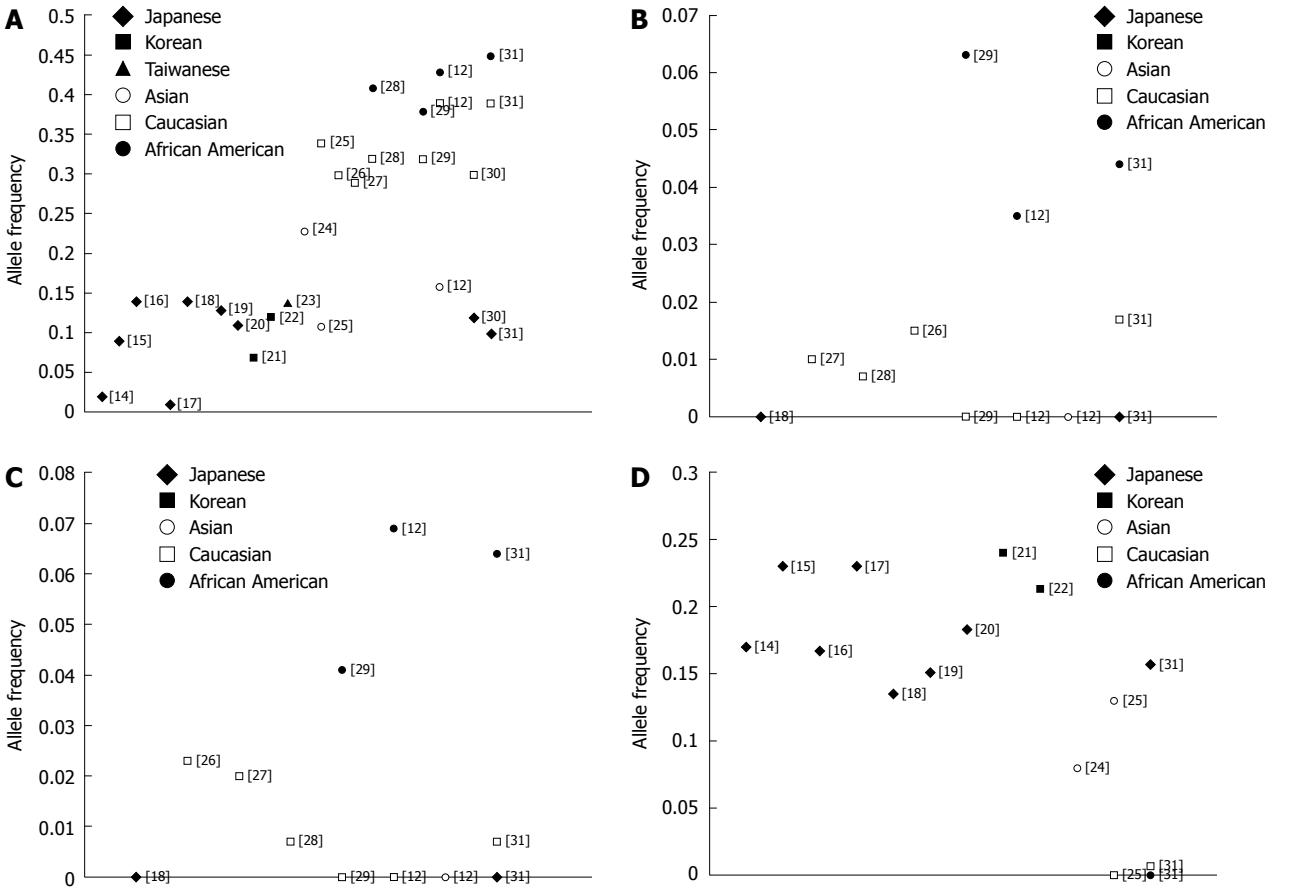

Figure 1 Allele frequency of each ethnicity. A: *UGT1A1*28*; B: *UGT1A1*36*; C: *UGT1A1*37*; D: *UGT1A1*6*.

transcriptional activity as compared with wild type TA_6[12].

The allele frequency of *UGT1A1*28* varies among individuals from various geographic areas, being the highest among African Americans (0.38-0.45), followed by Caucasians (0.29-0.39), while it is much lower in Asians (0.02-0.14) (Figure 1A)[12,14-31]. Even among Asians, the occurrence of the *UGT1A1*28* homozygote varies across the continent, at frequencies ranging from < 5% in Southeast Asia to around 20% in the Indian subcontinent[32]. The five (*UGT1A1*36*) and eight (*UGT1A1*37*) TA repeats are rarely found in Caucasians and Asians[12,18,27,31], while they occur more frequently in persons of African descent, although the frequencies, ranging from 0.04 to 0.07, remain low[12,18,27,31,32] (Figure 1B and 1C). Among these three polymorphisms (*UGT1A1*28, *36,* and **37*), *UGT1A1*28* has been investigated most extensively.

Observations presented in the literature clearly illustrate that homo- and/or heterozygous *UGT1A1*28* ($TA_{7/7}$ or $TA_{6/7}$) carriers experience severe grade 3/4 neutropenia[27,33-35] or severe diarrhea[36,37], or both[38] more frequently than wild type (TA6/6) carriers. Subsequently, several diagnostic tests for the *UGT1A1*28* genotype for irinotecan dosing have been developed[39,40]. A recent review[41] has described four currently available methods of *UGT1A1*28* testing which, when combined provide 100% sensitivity and 100% specificity. Although the link between *UGT1A1*28* and diarrhea seems less evident[41,42], the United States Food and Drug Administration recommends in the package insert for irinotecan that *UGT1A1*28* homozygous patients should receive a lower starting dose of irinotecan as they are more likely to experience neutropenia than patients who have one or two copies of the wild type allele. This demonstrates that the application of pharmacogenetics to clinical practice for cancer treatment is a reality, at least for Caucasians.

According to further research, however, conflicting results have been reported from several studies including meta analysis, where the association between homozygous *UGT1A1*28* and hematological toxicities is null[15,26] or positive only at medium (biweekly 180 mg/m^2) or higher (triweekly 200-350 mg/m^2) doses of irinotecan[42], the latter study being suggestive of a dose dependent association. Other investigators reported similar findings that *UGT1A1*28* is not relevant to patients treated with low dosage irinotecan[43]. These dosage considerations imply that there is no need for patients receiving lower doses of irinotecan to be genotyped. Furthermore, although *UGT1A1*28* was only the significant risk factor among Japanese patients for severe leukopenia and/or diarrhea (odds ratio 7.2-fold)[44], the wide range of 95% CI (2.5-22.3) indicates the difficulty in determining the individual risk by *UGT1A1*28* alone. From these findings, the number of TA repeats is considered to be a significant predictor of severe toxicity, especially hematological, but the risk prediction by TA repeat is modified by irinotecan dosage and applicable only to a certain segment of patients. This

suggests that additional genetic factors could also explain the toxicity risk.

UGT1A1*6

*UGT1A1*6* is a single nucleotide substitution of G by A at base position 211, resulting in the amino acid change of glycine to arginine [211G>A (G71R)][45]. Higher levels of SN-38, a lower extent of glucuronidation, and higher bilirubin levels were found in the *UGT1A1*6* homozygous carriers than in wild type carriers[18,24,46,47], suggesting that *UGT1A1*6* is a low activity allele. In sharp contrast to the racial differences for *UGT1A1*28* frequency, *UGT1A1*6* occurs most frequently in Asians at a rate that reaches the same as that of *UGT1A1*28*, while it is absent or very rare in Caucasians or African Americans (Figure 1D)[14-22,24,25,31]. As observed in *UGT1A1*28,* populations from different geographic Asian regions also exhibited differences in the *UGT1A1*6* allele frequency: the Chinese population had a three to five-fold higher GA substitution as compared with Malays and Indians[24].

Accordingly, the incidence of grade 3/4 neutropenia was *UGT1A1*6*-dependent in Asians[15,21,24,48]. Considering that *UGT1A1*6* is a polymorphism with the same frequency as *UGT1A1*28* among Asian people, and that the *UGT1A1*6* and *UGT1A1*28* allele are independent polymorphisms affecting decreased glucuronidation[19], genotyping both *UGT1A1*6* and *UGT1A1*28* is recommended as a genetically predictive marker for irinotecan-related toxicities in Japanese and probably in Asian patients[16,49]. The importance of analyses for both *UGT1A1*6* and *UGT1A1*28* is confirmed by the pharmacogenetic studies. Japanese cancer patients having *UGT1A1*6* and/or *UGT1A1*28* were proved to have significantly low "area under concentration-time course" ratios of SN38G to SN38, suggesting the necessity of typing *UGT1A1*6* in addition to *UGT1A1*28*[19,49]. Very recently, a prospective study was carried out in Japan to examine the distributions of *UGT1A1*28* and *UGT1A1*6* (n = 300) and proved that the risk allele (*UGT1A1*28* and/or *UGT1A1*6*), which exists in 10% of Japanese patients, might lead to an increased risk of irinotecan toxicity[50].

UGT1A SUBFAMILY POLYMORPHISM AND TOXICITY

UGT1A1 polymorphism is most closely correlated with neutropenia, whereas the link between the low activity alleles and the diarrhea seems weaker. The intestinal toxicity is explained by an accumulation of SN-38 in the gastrointestinal epithelial cells[51]. Biliary excreted SN-38G is deconjugated to form SN-38 by beta-glucuronidases of the intestinal microflora. Deconjugated SN-38 is transported into epithelial cells and undergoes glucuronidation again there. Any reduction of re-glucuronidation in the epithelial cells will lead to an accumulation of SN-38, an event that may underlie delayed-type diarrhea. This hypothesis is supported by the fact that the co-treatment of irinotecan with orally-administered neomycin effectively ameliorates irinotecan-induced delayed type diarrhea by decreasing fecal beta-glucuronidase activity and the enteral SN-38 level[52]. These findings suggest that inhibiting deconjugation events which occur in the lumen and keeping the reconjugation process appropriately in the gastrointestinal epithelial cells play protective roles against irinotecan-induced diarrhea.

Therefore, it is hypothesized that the capacity to detoxify SN-38 and subsequent excretion of SN-38G into bile may enhance gastrointestinal toxicity because increased intestinal SN-38G would result in increased fecal SN-38. Hence, increased UGT1A activities that serve to protect against adverse events in the bone marrow may yet predispose patients to increased gastrointestinal toxicities. These considerations may pose a dilemma for genetic predisposition regarding inverse associations between hematological and gastrointestinal toxicities, and provide explanations for the unclear association between reduced UGT1A1 activity and irinotecan-induced diarrhea[41].

Since diarrhea is sometimes a critical toxicity that precludes treatment continuation, recent significant efforts have led to the identification of polymorphisms of the UGT1A subfamily genes that could be responsible for gastrointestinal toxicities. As each part of the gastrointestinal tract has its own unique UGT1A expression patterns[9], gastrointestinal toxicities may be determined by the net activity of these UGT1A sub-family enzymes.

Polymorphism of UGT1A7 causes amino acid alteration at positions 129, 131, and 208. Comparing wild type alleles (*UGT1A7*1*; N129/R131/W208), single or combined alterations create *UGT1A7*2* (K129/K131/W208), *UGT1A7*3* (K129/K131/R208), and *UGT1A7*4* (N129/R131/R208), all of which confer a low enzymatic activity[53]. In addition, a single nucleotide polymorphism in the TATA box of the UGT1A7 gene, -57T>G, reduces promoter activity to 30%[54]. In contrast, single base insertion of thymidine in a promoter region of the UGT1A9 gene, designated as *UGT1A9*22* [-118 (T) 9>10], is associated with 2.6-fold greater UGT1A9 transcriptional activity[55]. Recently, the coexistence of *UGT1A1*28* and *UTG1A7* variants has proved to be a significant predictor of early- and late- onset diarrhea[56]. Understanding UGT1A expression in detail is expected to predict irinotecan-induced toxicities. These UGT1A genes will, therefore, become targets in a haplotype analysis as discussed below.

HAPLOTYPE ANALYSIS (TABLE 1)

Several polymorphisms occur close together on the same chromosome and are rarely separated by splicing. Hence, they tend to occur simultaneously at a greater frequency than would be predicted by chance, a phenomenon which is known as linkage disequilibrium. The independent analysis of each polymorphism is time consuming, labor intense, and expensive. This further underscores the need for a cluster analysis of

Table 1 Results of haplotype analysis among UGT1A1, UGT1A6, UGT1A7, and UGT1A9

		UGT subfamily	1A1						1A6	1A7	1A7		1A9
		Site	Enhancer	Enhancer	Promoter	Promoter	Exon1	Exon1		Exon1	Exon1	Promoter	Promoter
		Allele	*60			*28	*6	*27	*2	*2	*3		
		Polymorphism	-3279T>G	-3156G>A	-364C>T	insTA	211G>A	686C>A	19T>G 541A>G 552A>C	387T>G 391C>A 392C>A	387T>G 391C>A 392C>A 622T>C	-57T>G	-118(T)9>10
Authors	Ethnicity	Frequency											
Sai *et al*[19]	Japanese	0.146					X						
		0.121	X	X	X	X							
			X			X							
Minami *et al*[16]	Japanese	0.138	X			X		X					
						X							
Kitagawa *et al*[58]	Asian	ND		X		X							
	Caucasian	ND		X		X							
	Japanese	0.097	X			X							
Kaniwa *et al*[31]	African American	0.446	X			X							
	Caucasian	0.389	X			X							
Innocenti *et al*[57]	African American	0.26	X	X		X							
Kohle *et al*[62]	Caucasian	0.285				X			X		X		
		0.15					X				X	X	
Fujita *et al*[17]	Japanese	0.05				X					X	X	
		0.03					X				X		
		0.02				X							X
Carlini *et al*[26]	ND	0.234				X			X		X		
Huang *et al*[61]	Asian + Caucasian	ND					X				X		
Cecchin *et al*[60]a	Caucasian	0.232	X			X							

ND; not described; [a]UGT1A7 (387T>G) and UGT1A7 (622T>C) in addition to UGT1A1*93 and X; Linkage disequilibrium is designated by X.

functional variations, haplotype analysis, which enables the understanding of responsive genetic polymorphisms more effectively and at less expense.

There is a wide variability in haplotype patterns or haplotype frequencies among ethnic groups. Earlier haplotype analyses focused on the polymorphism set within the UGT1A1 gene. In these analyses, *UGT1A1*28* was combined with polymorphisms such as *UGT1A1*60, UGT1A1*27*, -364C>T in the primer lesion, and -3156G>A in the enhancer lesion[16,19,25,31,57,58]. Furthermore, Caucasians and African Americans showed different haplotype patterns[29,57]. In Caucasians, there are three common haplotypes accounting for 72% of all chromosomes, whereas in African Americans, even 5 common haplotypes accounted for only 47% of chromosomes. The top three haplotypes were the same but the frequencies of each haplotype differed between Caucasians and African Americans[29]. Another study[57] has demonstrated that *UGT1A1*60* showed stronger linkage disequilibrium with -3156G>A and *UGT1A1*28* in Caucasians than in African Americans. Taking these results into account, racial variability in haplotype frequencies within *UGT1A1* is presumably responsible for the racial diversity in the efficacy and toxicity of irinotecan.

Subsequently, recent progress in haplotype analyses has led to the accumulation of knowledge about combinations of several genetic variabilities beyond *UGT1A1*, such as functionally significant genetic variations of *UGT1A6*[59], *UGT1A7*[53], and *UGT1A9*[55]. Seventy-five percent of Caucasian patients homozygous for *UGT1A1*28* additionally exhibit a *UGT1A7* variant[54]. Very recently, a combined analysis of *UGT1A1*, *UGT1A7*, and *UGT1A9* polymorphism has revealed better predictions of hematological toxicity[60], suggesting that a haplotype analysis encompassing various genes beyond *UGT1A1* is more predictive of hematological toxicities than merely a single isolated polymorphism. Interestingly, one polymorphism in a particular locus may cause a change in the occurrence of another polymorphism, even if the frequency of the latter polymorphism in itself is small. One example is a finding that *UGT1A1*6* is highly related to *UGT1A7*3* in East Asians. Although *UGT1A7*3* occurs considerably less frequently in East Asians than in whites[61], it occurs much more frequently in individuals when they also carry *UGT1A1*6*, a frequent polymorphism in Asians. In performing a linkage disequilibrium analysis expanding from within the *UGT1A1* gene to the other *UGT1A* subfamily, *UGT1A7* and *UGT1A9* seem to be candidates for haplotype analysis in combination with *UGT1A1*28* (for Caucasians)[26,62] or *UGT1A1*6* (for Asians)[17,61].

FUTURE PERSPECTIVES

The narrow therapeutic index of anticancer drugs due to the variability in toxicities is one of the daunting problems oncologists face. Organ-specific wide distri-

butions of each *UGT1A* subfamily makes research in genetic predisposition for irinotecan-induced toxicities more complex than believed previously. Furthermore, besides UGTs, many other enzymes are also involved in the irinotecan metabolism. Recent attempts have been focused on elucidating genetic variability beyond the UGT system, including the organic anion transporting polypeptide C (OATP1B1) that transports SN-38 from the plasma into the liver[63], the cytochrome P450 3A system that produces an inactive form of irinotecan, and the adenosine triphosphate binding cassette transporter system that mediates drug efflux. Innocenti *et al*[64] have very recently provided evidence that a comprehensive polymorphism analysis of genes involved throughout the process of irinotecan metabolism explains approximately 50% of the neutropenia variation. In addition, possible additive effects of transporters and *UGT1A1* genotype have been demonstrated, although their predictive power for severe neutropenia is still unsatisfactory[65]. Even such comprehensive genotyping can not explain the toxicities with full certainty, implying that nongenetic covariates may be involved and should be taken further into account in future investigations.

With the advent of a combination regimen for colorectal cancer treatment, the next stage of pharmacogenetic research should encompass a wide variety of enzymes participating in the metabolism of drugs or agents used in combination with irinotecan[66]. The candidate enzymes include dihydropyrimidine dehydrogenase, thymidylate synthase, orotate phosphoribosyl transferase, and methylenetetrahydrofolate reductase. All are involved in fluorouracil or folic acid metabolism and each enzyme has its own polymorphism that affects the corresponding enzymatic activity. Another direction for pharmacogenetic research in relation to colorectal cancer chemotherapy is therefore to elucidate net outcomes of enzyme polymorphisms that would alter the efficacy and toxicity of irinotecan-containing combination regimens.

Challenges in solving the problems of unpredictable irinotecan toxicities are supported by the application of such comprehensive pharmacogenetics into clinical practice. Pretherapeutic genetic screening helps to distinguish patients expected to benefit from irinotecan from those who are less capable of detoxifying SN-38 or those who are more prone to suffer from hematological and gastrointestinal toxicities. Those patients genetically predisposed to irinotecan toxicities should undergo dose modifications, although these might also be associated with unsatisfactory tumor response and increased tumor related death. Therefore, pharmacogenetic studies should aim to determine the optimal dose modification only in patients who have a higher chance of irinotecan induced toxicities. This would allow prolonged treatment periods and enlarged dose intensity and should ultimately maximize the efficacy even under the conditions of reduced doses of irinotecan.

As many genes are involved in drug elimination, panels of linkage disequilibrium would need to include all variants of clinical significance in the population or race to be treated. Continued efforts toward discovering irinotecan elimination genotype sets (or haplotype) should be made before truely personalized dosing of irinotecan becomes common practice. The knowledge of pharmacogenetics can potentially aid in this discovery and provide promising tools for cancer therapeutics.

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