

UGT1A1 polymorphisms in cancer: impact on irinotecan treatment

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Abstract: Mutations in the *UGT1A1* gene have been implicated in Gilbert syndrome, which shows mild hyperbilirubinemia, and a more aggressive childhood subtype, Crigler–Najjar syndrome. To date, more than 100 variants have been found in the *UGT1A1* gene. Among them, *UGT1A1**28 and *UGT1A1**6 have been reported to be associated with severe toxicities in patients treated with irinotecan-based chemotherapy by increasing the dose of SN-38 (7-ethyl-10-hydroxycamptothecin), an active form of irinotecan. Many association studies and meta-analyses have demonstrated the contribution of *UGT1A1**28 and *UGT1A1**6 polymorphisms to the toxicities caused by irinotecan-based therapy. The aim of this review was to evaluate the impact of these variants upon the toxicities and the efficacy of irinotecan-based chemotherapy.

Keywords: UGT1A1, irinotecan, chemotherapy, toxicity, response, survival

Introduction

Irinotecan hydrochloride, inhibiting topoisomerase I, is one of the key anticancer drugs in chemotherapy for several cancers such as colorectal cancer, lung cancer, gastric cancer, and gynecologic cancers.^{1–4} The patients treated with irinotecan occasionally experience severe neutropenia and delayed diarrhea; however, the occurrence of these adverse reactions has been unpredictable and largely unexplained.⁵ An active metabolite of irinotecan, SN-38 (7-ethyl-10-hydroxycamptothecin), is glucuronidated by uridine diphosphate glucuronosyltransferase 1As (UGT1As), such as UGT1A1, and is inactivated by forming the SN-38 glucuronide (SN-38G). Among these UGT1A enzymes, UGT1A1 protein has the highest ability to glucuronidate SN-38.⁶ Various studies have demonstrated a relationship between *UGT1A1* genotypes affecting SN-38 pharmacokinetics and the experienced toxicity.⁷ The transport pathway of irinotecan is shown in Figure 1. In addition to *UGT1A1* polymorphism, polymorphisms of carboxylesterase (*CES*) and ATP-binding cassette (*ABC*) genes have been reported to affect the metabolism of irinotecan.^{8,9} In this review, the impact of *UGT1A1* genotypes on irinotecan treatment will be discussed.

UGT1A1 polymorphisms and disease susceptibility

Mutations in the *UGT1A1* gene have been implicated in Gilbert's syndrome, which shows mild hyperbilirubinemia, and a more aggressive childhood subtype, Crigler–Najjar syndrome.^{10,11} A common cause of decreased UGT1A1 activity is the insertion of a TA in the TATA box at the promoter region of the *UGT1A1* gene, which was named as *UGT1A1**28.¹⁰ Individuals with homozygous *UGT1A1**28 had higher levels of serum bilirubin compared with those with heterozygous *UGT1A1**28 or the wild-type allele.¹⁰

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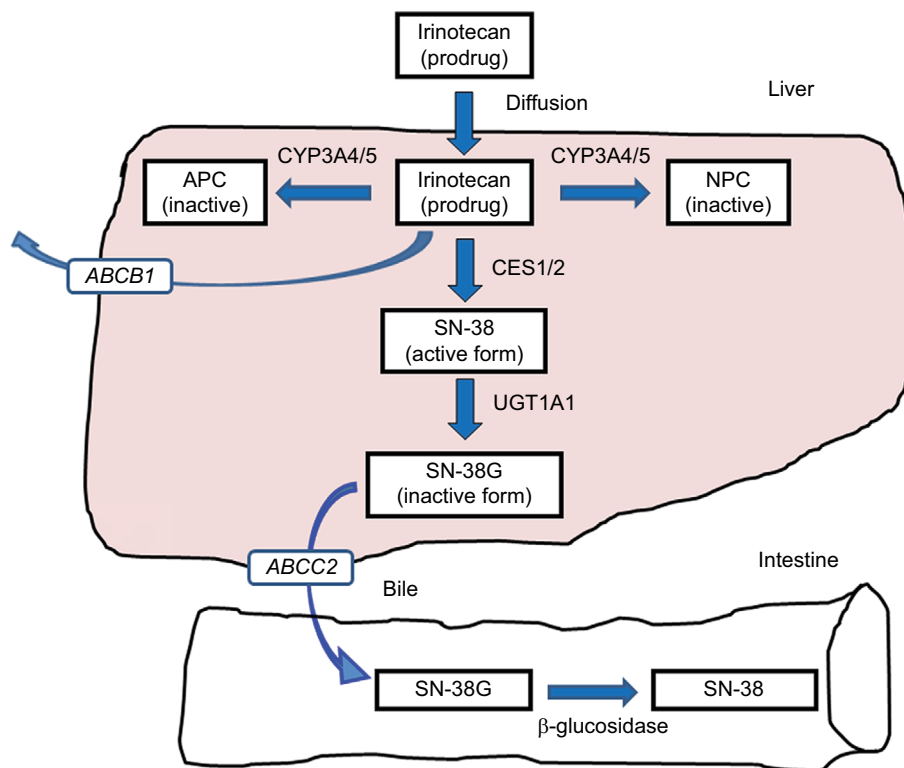


Figure 1 Transport pathway of irinotecan.

Notes: A prodrug, irinotecan, is moved into hepatic cells by passive effusion. Activation to an active form, SN-38, is mediated by CES1/2. Deactivation to an inactive form, SN-38G (glucuronidated SN-38), is mainly mediated by UGT1A1. A part of SN-38G is hydrolyzed to SN-38 by bacterial β -glucosidase. Moreover, irinotecan is degraded to APC and NPC metabolites by CYP3A4/5. Irinotecan and metabolites are transported by P-glycoprotein, a protein of the cell membrane that pumps foreign substances out of cells, which is encoded by *ABCB1* gene. Biliary excretion of SN-38G is mainly mediated by the MRP2/ABCC2.

Abbreviations: APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin; CES1/2, carboxylesterases 1 and 2; CYP3A4/5, cytochrome P450 isoforms 3A4 and 3A5; MRP2/ABCC2, multidrug resistance associated protein-2; NPC, 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin; SN-38, 7-ethyl-10-hydroxycamptothecin; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Gilbert's syndrome, also known as constitutional hepatic dysfunction or familial nonhemolytic jaundice, is an inherited disorder of the liver resulting in an overabundance of bilirubin. Most of the patients with Gilbert's syndrome are asymptomatic; however, they sometimes present with episodes of mild intermittent jaundice due to predominantly unconjugated hyperbilirubinemia. Crigler–Najjar syndrome is a rare, but more severe, disorder of bilirubin metabolism and is divided into two distinct forms (types I and II) based upon the severity of the disease. Gilbert's syndrome is part of a continuous spectrum of altered glucuronidation that extends to the fatal Crigler–Najjar disease.

Gilbert's syndrome is primarily linked to *UGT1A1**28 variants, but other variants in the promoter and coding regions are also involved in the predisposition of the disease.¹² To date, more than 100 variants have been identified in the *UGT1A1* gene.¹³ Among these polymorphisms, the clinically important variants are listed in Table 1.^{14–19}

Recently, a large population-based cohort study, the Rotterdam Study,²⁰ investigated the association between *UGT1A1* genotype and incidence of coronary heart

disease (CHD). However, in this study, neither bilirubin nor *UGT1A1**28 genotype was associated with development of CHD. Another large trial evaluating 1,780 unrelated individuals aged more than 24 years suggested that homozygous *UGT1A1**28 alleles and higher serum level of bilirubin were related with lower risk of cardiovascular disease (CVD).²¹ Serum bilirubin has a protective effect on CVD and CVD-related disease. It seems that individuals with Gilbert syndrome and *UGT1A1**28 allele and having moderate elevation of serum bilirubin could have a lower risk of CHD and CVD.

***UGT1A1**28 allele and efficacy of irinotecan-based therapy**

Emerging data on the role of genetic variants in the *UGT1A1* gene confirm that the *UGT1A1**28 allele is associated with severe toxicities in irinotecan-based chemotherapy.²² Additionally, it seems that patients with the allele were also associated with better outcome, despite severe toxicities.²² A study by Toffoli et al,²² conducted in 238 patients with metastatic colorectal cancers, showed that

Table 1 *UGT1A1* allelic variants and their biologic impact

Denomination	Variants ¹⁴	Allele frequency (ethnicity) ^{15,16}	Expression level	Enzymatic activity	Clinical consequence
<i>UGT1A1</i> *1	(TA) ₆ TA	Common allele	100%	100%	None
TATA box polymorphisms					
<i>UGT1A1</i> *28	c.-39_-40 ins TA: (TA) _n TA	29–45% (Caucasians); 42–51% (Africans); 16% (Asians)	Reduced	Reduced	Gilbert's syndrome, Crigler–Najjar syndrome ¹⁷
Polymorphisms in the promoter region					
<i>UGT1A1</i> *60	c.-3279 T>G	23–39% (Caucasian); 15% (African Americans); 17% (Asians)	Reduced	Unchanged	Gilbert's syndrome, Crigler–Najjar syndrome ¹⁸
Polymorphisms in exon I					
<i>UGT1A1</i> *6	c.211 G>A p.Gly71Arg	15–20% (Asians)	Unchanged	Reduced	Gilbert's syndrome, Crigler–Najjar syndrome ¹⁹
<i>UGT1A1</i> *27	c.686 C>A p.Pro229Gln	5–28% (Asians)	Unchanged	Reduced	Gilbert's syndrome, Crigler–Najjar syndrome ¹⁹

*28/*28 cases had a better response rate and progression-free survival compared with *1/*1 cases. However, most of the other studies evaluating survival according to *UGT1A1* genotypes failed to show the significance of *UGT1A1* variants in terms of survival. A meta-analysis by Dias et al,^{23,24} evaluating 10 studies using irinotecan-based chemotherapy, revealed that there was no significant efficacy in terms of response rate, progression-free survival, and overall survival. Additionally, another meta-analysis by Liu et al²⁵ also confirmed that the *UGT1A1* genotype could not be a predictor for response rate and survival. These results might reflect a lower dose intensity of irinotecan in patients with *28/*28 or *1/*28 alleles, due to severe toxicities. Representative studies evaluated in these meta-analyses are listed in Table 2.^{22,26–36}

***UGT1A1**28 allele and the toxicities of irinotecan-based therapy**

Many studies have evaluated toxicities in patients treated with irinotecan-based therapy according to *UGT1A1**28 genotypes.^{22,26–36} Table 2 summarizes representative studies evaluating the incidence of neutropenia and diarrhea. In terms of neutropenia, approximately half of these studies suggested a significant contribution of *28/*28 alleles to severe toxicities. A study by Kweekel et al²⁹ analyzing high-dose irinotecan regimens (250 or 350 mg/m²) revealed that patients with *28 allele had a significantly higher rate of febrile neutropenia compared with *1/*1 cases.

Several studies evaluating 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) regimen also reported significantly higher incidence of severe neutropenia in cases with *28/*28 alleles.^{26,28,32–34} Some reports suggested significant association between diarrhea and *28/*28 alleles.^{27,31,33} Several meta-analyses have examined the impact of the *28 allele on the

toxicities of irinotecan-based therapy. A study by Hoskins et al,³⁷ evaluating 821 cases, revealed that severe hematological toxicities were more frequently observed in *28/*28 patients, when the irinotecan doses were high (>250 mg/m²) or intermediate (150–250 mg/m²). However, the risk was not elevated in patients treated with low doses of irinotecan (<150 mg/m²).³⁷ Another study by Hu et al³⁸ reported that the *28/*28 genotype was associated with an increased risk of neutropenia not only at medium (response rate [RR] =2.0, 95% confidence interval [CI] =1.6–2.5, *p*<0.01) or high doses (RR =7.2, 95% CI =3.1–16.8, *p*<0.01) of irinotecan but also at low doses (RR =2.4, 95% CI =1.3–4.4, *p*<0.01) from the results of meta-analyses evaluating 1,998 patients. Additionally, a study by Liu et al³⁹ confirmed that patients with *28/*28 genotype had higher incidence of neutropenia compared with *1/*1 or *1/*28 genotype cases, in addition to suggesting that patients with *1/*28 genotype had significantly higher rate of severe neutropenia compared with *1/*1 genotype cases (odds ratio [OR] =1.84, 95% CI =1.24–2.72, *p*<0.01).

***UGT1A1**6 allele and efficacy or toxicities of irinotecan-based therapy**

The most frequent and important variant in the Asian population is *UGT1A1**6, which is rarely found among Caucasians. Representative studies evaluating *UGT1A1**6 and clinical outcomes in patients treated with irinotecan-based therapy are listed in Table 3.^{40–50}

Most of these studies were mainly focused on the toxicities of the regimens,^{40,42,44–46,49,50} and quite a few studies reported the clinical outcomes such as response rate and survival.^{39,47,48} Some studies reported that there were no significant associations between *6 alleles and the efficacy,

Table 2 Severe toxicities according to *UGT1A1**28 genotyping

Study	No of patients	Regimens	Irinotecan dose (mg/m ²)	Neutropenia G3–4, %		Diarrhea G3–4, %		Efficacy
				Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	
				*28/*28 vs *1/*1	*1/*28 vs *1/*1	*28/*28 vs *1/*1	*1/*28 vs *1/*1	
Rouits et al ²⁶	73	FOLFIRI, mFOLFIRI	85/1w, 180/2w	23.33 (3.08–177.04)	6.22 (1.58–24.47)	2.70 (0.39–18.92)	1.69 (0.44–6.43)	–
Marcuello et al ²⁷	95	IRI-Tomodex, etc	80/w, 180/2w, 350/3w	–	–	11.00 (2.27–53.37)	2.36 (0.85–6.57)	RR, no difference (NS)
Toffoli et al ²²	250	FOLFIRI, mFOLFIRI	180/2w	2.08 (0.60–7.28)	1.99 (0.91–4.38)	0.86 (0.10–7.49)	2.52 (0.93–6.81)	RR 40% (*1/*1), 42% (*1/*28), 67% (*28/*28) (p=0.03)
Côté et al ²⁸	89	FOLFIRI	180/2w	6.40 (1.20–34.20)	1.88 (0.58–6.11)	–	–	DFS 52% (*1/*1), 42% (*1/*28), 87% (*28/*28) (p=0.06, NS)
Kweekel et al ²⁹	218	IRI, IRI-Cape	250 or 350/3w	–	–	IRI 11.14 (0.89–140.12) IRI-Cape 2.08 (0.53–8.14)	IRI 1.63 (0.51–5.21)	–
Braun et al ³⁰	326	IRI, IRI-5Fu	300–350/3w, 180/2w	IRI 1.73 (0.16–18.40) IRI-5Fu 1.07 (0.22–5.25)	IRI 1.28 (0.52–3.13) IRI-5Fu 2.82 (0.69–11.58)	IRI 1.20 (0.12–11.91) IRI-5Fu 2.75 (0.49–15.38)	IRI-Cape 1.06 (0.46–2.46)	–
Ferraldeschi et al ³¹	92	FOLFIRI, IRI-Cape, etc	180/2w, 250 or 350/3w	2.53 (0.40–16.15)	2.14 (0.66–7.03)	14.00 (1.09–179.00)	IRI 0.48 (0.08–2.74) IRI-5Fu 1.24 (0.32–4.77)	–
McLeod et al ³²	212	IFL, IROX	100–125/1w, 200/3w	IFL 3.04 (0.44–20.91) IROX 11.28 (2.51–50.70)	IFL 1.71 (0.40–7.26) IROX 1.66 (0.47–5.88)	IFL 1.94 (0.47–8.01) IROX 1.88 (0.50–7.05)	3.32 (0.33–33.25)	RR of IROX, lower in *28/*28 (p=0.02)
Martinez-Balibrea et al ³³	149	FOLFIRI, FUJIRI	80/1w, 180/2w	4.00 (1.12–14.32)	1.67 (0.67–4.20)	4.96 (1.49–16.55)	IFL 0.97 (0.37–2.52) IROX 1.08 (0.45–2.63) 1.38 (0.63–3.04)	RR, PFS, OS, no difference (NS)
Glimelius et al ³⁴	136	FLIRI, Lv-5Fu-IRI	180/2w	6.88 (1.70–27.75)	1.75 (0.55–5.56)	1.42 (0.15–13.79)	1.85 (0.47–7.25)	RR, no difference (NS)
Shulman et al ³⁵	214	TEGAFIRI, XELIRI, etc	80/w, 180/biweekly	5.43 (1.50–19.67)	1.53 (0.48–4.85)	0.66 (0.22–1.95)	0.59 (0.30–1.18)	–
Lamas et al ³⁶	100	IRI-Cape, FOLFIRI	100 or 125/w, 180/biweekly	0.80 (0.09–7.25)	2.49 (0.85–7.29)	0.28 (0.01–5.22)	0.57 (0.14–2.29)	–

Abbreviations: CI, confidence interval; RR, response rate; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; NS, not significant; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; mFOLFIRI, modified FOLFIRI; IRI-Tomodex, irinotecan plus tomudex, IRI, irinotecan; IRI-Cape, irinotecan plus capecitabine; IRI-5Fu, irinotecan plus 5-fluorouracil; IFL, irinotecan plus 5-fluorouracil; IROX, irinotecan plus oxaliplatin; FUJIRI, irinotecan plus high-dose 5-fluorouracil; FLIRI, irinotecan plus bolus 5-fluorouracil/leucovorin; Lv-5Fu-IRI, irinotecan, plus bolus/infused 5-fluorouracil/leucovorin; TEGAFIRI, uracil, ftorafur, leucovorin, and irinotecan; XELIRI, capecitabine plus irinotecan.

including response rate and survival.^{40,44,45} Among the studies listed, almost all the studies reported significant relationship between *UGT1A1**6/*6 and severe neutropenia, compared with *1/*1 cases. Additionally, half of the studies suggested significantly higher incidence of severe neutropenia in patients with *UGT1A1**1/*6.^{42,44,48–50} A study evaluating a combination therapy with irinotecan and cisplatin reported an increased risk of severe diarrhea in patients with *1/*6 alleles.³⁹

A meta-analysis evaluating mainly Asian studies reported that patients with *6/*6 alleles had increased incidences of severe neutropenia with both high/medium (OR =3.95, 95% CI =2.05–7.64, *p*<0.01) and low doses (OR =9.64, 95% CI =2.05–45.28, *p*<0.01) of irinotecan. This trend was also observed in patients with *1/*6 alleles compared with *1/*1 cases: OR =4.42 for low dose, and OR =1.55 for high/intermediate dose of irinotecan.⁵¹

Table 3 Severe toxicities according to *UGT1A1**6 genotyping

Study	No of patients	Regimens	Irinotecan dose	Neutropenia G3–4 (%)		Diarrhea G3–4 (%)		Efficacy
				Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	
				*6/*6 vs *1/*1	*1/*6 vs *1/*1	*6/*6 vs *1/*1	*1/*6 vs *1/*1	
Jada et al ⁴⁰	45	IRI	375/3w	–	–	7.75 (0.40–149.70)	1.11 (0.11–11.49)	
Sai et al ⁴¹	49	IRI	60/1w, 100, 125, 150/2w	28.00 (0.92–851.54)	8.00 (0.82–78.47)	–	–	
Takano et al ⁴²	30	IRI-cisplatin	60/1w	–	11.20 (1.73–72.30)	–	16.00 (1.45–176.45)	–
Seo et al ⁴³	39	FOLFIRI	150/2w	–	0.97 (0.24–3.90)	–	0.56 (0.10–3.08)	RR, OS, no difference (NS)
Onoue et al ⁴⁴	133	IRI-platinum, FOLFIRI	<60, >100	7.78 (1.36–44.50)	4.27 (1.71–10.62)	–	–	–
Satoh et al ⁴⁵	73	IRI	150/2w	9.33 (1.96–44.49)	0.85 (0.16–4.51)	18.18 (0.68–483.94)	–	–
Okuyama et al ⁴⁶	39	FOLFIRI	150/2w	4.04 (0.15–108.57)	1.93 (0.44–8.42)	–	–	–
Wang et al ⁴⁷	130	FOLFIRI, IFL	180/2w 125/1w	0.59 (0.06–5.54)	0.97 (0.44–2.13)	4.47 (0.16–30.12)	1.99 (0.77–5.13)	PFS, OS, no difference (NS)
Gao et al ⁴⁸	276	FOLFIRI, XELIRI	180/2w	4.07 (1.50–11.04)	2.02 (1.06–3.86)	1.98 (0.40–9.77)	0.90 (0.27–2.95)	RR, no difference (NS)
Gao et al ⁴⁹	133	IRI-cisplatin, FOLFIRI, etc	180/2w	6.40 (1.30–31.60)	3.34 (1.43–7.79)	2.25 (0.23–21.86)	1.13 (0.27–4.75)	–
Ichikawa et al ⁵⁰	1,376	FOLFIRI, IRIS, etc	150/2w 125/2w	3.34 (2.19–5.10)	1.64 (1.21–2.17)	1.91 (NS)	0.84 (NS)	–

Abbreviations: CI, confidence interval; RR, response rate; PFS, progression-free survival; OS, overall survival; NS, not significant; IRI, irinotecan; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; IFL, irinotecan plus 5-fluorouracil; XELIRI, capecitabine plus irinotecan; IRIS, irinotecan plus S-I.

Genotype-based dose modification studies

Accumulated evidence suggests that optimal doses of irinotecan according to *UGT1A1* genotype are needed. Several dose-finding studies have been published; however, most of the studies were dose modifications of the FOLFIRI regimens (Table 4).^{52–56} Three studies evaluating irinotecan doses in FOLFIRI showed that the maximal tolerated dose

(MTD) in patients with *1/*1, *1/*28, and *1/*6 alleles was higher than the standard doses of the FOLFIRI regimen.^{52–54} The MTD in the *1/*1 patients was also higher than that of patients with *1/*28 and *1/*6 alleles, and the MTD in patients with *28/*28, *6/*6, and *28/*6 alleles was lower than the current standard doses of the FOLFIRI regimen.^{53,54} In the Asian population, incorporation of *UGT1A1**6 in addition to *UGT1A1**28 would be needed for the safety

Table 4 Genotype-based dose-finding studies

Study	Chemotherapy	Genotype	Starting dose, mg/m ²	Results, mg/m ²
Toffoli et al ⁵²	FOLFIRI	*1/*1	215	MTD =370
		*1/*28	215	MTD =310
Marcuello et al ⁵³	FOLFIRI	*1/*1	180	MTD =390
		*1/*28	110	MTD =340
		*28/*28	90	MTD =130
Kim et al ⁵⁴	FOLFIRI	*1/*1	240	MTD ≥330
		*1/*28, *1/*6	240	MTD =300
		*28/*28, *6/*6, *6/*28	240	MTD ≥150
Hazama et al ⁵⁵	Irinotecan (every 2w)+ doxifluridine	*1/*1	70	MTD >150; RD =150
		*1/*28	70	MTD =100; RD =70
Lu et al ⁵⁶	FOLFIRI + bevacizumab	*1/*1	180	MTD =260
		*1/*28	180	MTD =240
		*28/*28	120	MTD =210

Abbreviations: MTD, maximal tolerated dose; RD, recommended dose; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan.

of irinotecan-based chemotherapy. All these results suggested that patients with heterozygous *UGT1A1* variants, in addition to those with homozygous *UGT1A1* variants, had lower MTD of irinotecan compared with those with wild-type alleles.

Current recommendation for *UGT1A1* genotyping in daily practice

The US Food and Drug Administration recommends on the irinotecan drug label that patients with the *28/*28 genotype should receive a lower starting dose of irinotecan.⁵⁷ Additionally the recommendation also noted that “the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment”.⁵⁷

According to European Society for Medical Oncology (ESMO) guidelines, testing for *UGT1A1* polymorphisms should be considered only if severe toxicity potentially related to treatment with irinotecan occurs. The ESMO guideline noted that testing for *UGT1A1* is particularly important when irinotecan is used at high doses (300–350 mg/m²) but of less importance when it is administered at lower doses (125–180 mg/m²).⁵⁸

According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines, it is especially desirable to test for a *UGT1A1* genetic polymorphism before administering irinotecan to patients with a high serum bilirubin level, elderly patients, patients whose general condition is poor (eg, performance status 2 [PS2]), and patients in whom severe toxicity (especially neutropenia) developed after the previous administration of irinotecan.⁵⁹ The guidelines also noted that “irinotecan toxicity cannot be predicted with certainty on the basis of the presence of a *UGT1A1* genetic polymorphism alone”, and that “it is essential to monitor patients’ general condition during treatment and to manage adverse drug reactions carefully, irrespective of whether a genetic polymorphism is detected”.

In the USA, single agent irinotecan (350 mg/m², triweekly, monotherapy) is usually used as one of the “irinotecan-based therapies”, so the doses of irinotecan are usually higher than in Europe (180 mg/m², biweekly, combination) or Japan (150 mg/m², biweekly, combination). Although the recommendations for *UGT1A1* genotyping are different according to the doses of irinotecan which are clinically often used in daily practice, clinical usefulness should be always considered in all patients who receive irinotecan-based therapy.

Conclusion

Emerging data confirmed an increased risk of severe toxicities, such as neutropenia, in patients with *UGT1A1**28 and/or *UGT1A1**6 genotype when the patients received irinotecan-based chemotherapy. Homozygous variants and double heterozygous variants showed a higher risk of severe toxicities compared with single heterozygous variants. However, genotype-based studies suggest that MTD is clearly lower in patients with heterozygous *UGT1A1* variants compared with those with wild-type alleles. Further clinical studies that include heterozygous *UGT1A1* variants, in addition to homozygous variants, are needed to evaluate the clinical utility of *UGT1A1* genotyping in patients treated with irinotecan-based therapy. On the other hand, although severe toxicities were clearly evident when the dose of irinotecan was high or intermediate, the incidence of these toxicities was significantly higher even when the dose of irinotecan was lower. Furthermore, clinical significance in terms of tumor response or survival was not found according to *UGT1A1* genotypes. Further investigations, such as genotype-based therapy, are needed for increasing the efficacy and decreasing the toxicities for patients receiving irinotecan-based therapy.

Disclosure

The authors report no conflicts of interest in this work.

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