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Predictive Value of UGT1A1 Polymorphisms in Irinotecan-Induced Toxicity and Therapeutic Efficacy in Colorectal Cancer Patients

Qianqian Yu[1], Zhihuan Li[2], Xiaoqi Nie[1], Lu Wang[1], Chen Gong[1], Bo Liu[1], Xin Liao[3], Ben Zhao[1], Qianxia Li[1], Mingsheng Zhang[1], Hong Qiu[1], Xianglin Yuan[1]*

[1]Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China.
[2]Dongguan Enlife Stem Cell Biotechnology Institute, Dongguan 523000, Guangdong, China
[3]Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

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***Correspondence:**
Dr. Xianglin Yuan. Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, P.R. China; Telephone No: 00862783663342; Fax No: 00862783663342; E-mail: xlyuan1020@163.com.

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ABSTRACT

Irinotecan-based chemotherapy is a fundamental cytotoxic regimen for advanced colorectal cancer. The disposition of irinotecan is known to vary in a fashion partially depending on genetic variations in the drug metabolic pathways. UDP-glucuronosyltransferase (UGT)1A1 is a predominant enzyme that converts the active metabolite of irinotecan to the inactive form via a glucuronidation process. Several *UGT1A1* polymorphisms are linked to SN-38 glucuronidation and irinotecan-related adverse events, while the predictive role of *UGT1A1* polymorphisms regarding therapeutic outcome is controversial. In this review, we will evaluate the impact of *UGT1A1* genotypes on irinotecan-induced toxicity and therapeutic efficacy in colorectal cancer patients receiving irinotecan-based treatment.

Introduction

Colorectal cancer (CRC) is the third most frequent neoplasm and the second leading cause of cancer-related death world-wide[1]. Around 25% of patients present with metastatic or inoperable disease at initial diagnosis, and more than 50% of patients will receive therapeutic regimens involving cytotoxic agents during the course of their illness[2,3]. Chemotherapy consisting of 5-fluorouracil (5-FU) in combination with either oxaliplatin or irinotecan remains the fundamental treatment for metastatic or recurrent CRC. In terms of irinotecan-based schedules, 45-65% of patients failed to respond to treatment and the use of irinotecan is accompanied by a comparably high incidence of severe adverse events[4-7]. As individualized therapy guided by genotyping has been prevalent, efforts are needed to discover confirmative molecular biomarkers for optimizing and personalizing treatment procedures.

Irinotecan exerts its anti-proliferative cytotoxic effects by inhibiting topoisomerase I required for DNA replication and transcription through active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Clinical pharmacological evidence demonstrated that irinotecan-related toxicity and efficacy is associated with objects' exposure to SN38[8]. SN-38 is finally metabolized to an inactive form SN-38 glucuronide (SN38G) by UDP-glucuronosyltransferase (UGT)1A enzymes encoded by the *UGT1A* gene family[9]. The predominant enzyme is UGT1A1, which is also involved in the metabolism of bilirubin[10]. Polymorphisms in *UGT1A1* genes may contribute to changes in UGT1A1 enzyme activity, resulting in variability of irinotecan pharmacokinetics[11]. Several

UGT1A1 polymorphisms are reported to be associated with irinotecan-related toxicity and efficacy[12-16]. Despite the conflicting results derived from different studies, potential predictive effects of these loci are still promising.

UGT1A1 Polymorphisms Relationship to Toxicity

The risk of irinotecan-induced toxicity, predominantly neutropenia and diarrhea, increases with the polymorphism of genes involved in irinotecan metabolic pathway[17]. Genetic polymorphisms in the *UGT1A1* gene, such as *UGT1A1*28* and *UGT1A1*6*, were reported to be associated with decreased UGT1A1 expression or reduced enzymatic activity[18,19] and were usually suggested to be risk factors for severe diarrhea and neutropenia[20]. In the United States, Japan, and some other countries, the recommendation was included in irinotecan product label that a reduction in the starting dose of irinotecan be considered for patients harboring homozygous *UGT1A1 *28 (*28/*28* genotype*)* or *6 (*6/*6* genotype*)* allele, or heterozygous for both *UGT1A1 *28* and *6* alleles (*28/*6* genotype)[21,22].

Though most studies support the utility of *UGT1A1*28* and *6* as predictors of irinotecan-induced toxicity in clinical practice, some investigations disagree with the predictive identity, partially due to the great genetic diversity between different ethnic groups and inter-subjects. Roughly 8-20% of the Caucasian population is *UGT1A1 *28* homozygosity, in contrast to <3% occurrence in Asian while 13-23% in African subjects[23,24]. *UGT1A1*6* is a frequent variant in Asian populations with a minor allele frequency (MAF) of 10–23%, but not a common one in Caucasians (MAF<3%) and African populations (MAF<1%)[25]. As high as 35% Caucasians suffer severe neutropenia, and the incidence is 15-30% in Asian; the rate of diarrhea is 10-30% in Caucasian population, comparing to 5-19% in Asian crowd[14,23,24,26-31].

Subgroup analysis of the meta-analysis conducted by Zhang *et al*.[32] based on Asian trials demonstrated an increased risk of neutropenia in advanced CRC patients carrying *UGT1A1*6* allele than those with the wild-type genotype (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.07–2.47); and patients homozygous for *UGT1A1*6* had an even higher risk of neutropenia than wild-genotype patients with an OR of 2.55 (95% CI, 1.21-5.36). The meta-analysis by Cheng *et al*.[33] revealed that among Asian cancer patients treated with irinotecan, heterozygous variant of *UGT1A1*6* showed no significant relationship with severe diarrhea, while the homozygous variant performed an elevated risk of severe diarrhea (OR, 3.51; 95 % CI, 1.41–8.73). Subgroup analysis was not performed in the form of tumor types. The relationship between *UGT1A1*6* genotypes and irinotecan-induced toxicity is shown in Table 1.

The meta-analysis conducted in Caucasian CRC patients by Liu *et al*.[31] showed that subjects with *UGT1A1*28/*28* genotype had more than fourfold (OR, 4.79; 95% CI, 3.28-7.01) and *UGT1A1*1/*28* genotype had approximately twofold (OR, 1.90; 95% CI, 1.44-2.51) increases in the risk of severe neutropenia respectively compared to wild-type genotype; and *UGT1A1*28/*28* genotype had an OR of 1.84 (95% CI, 1.24-2.72) for an increased risk of severe diarrhea, while *UGT1A1*1/*28* genotype showed no significant correlation with diarrhea. Similar significance persisted in subgroups (high/medium dose or low dose, cutoff value = 150 mg/m^2; with 5-FU or without 5-FU) of the analysis between genotypes and neutropenia. The higher incidence of diarrhea in homozygous *UGT1A1*28* patients was limited to groups in which irinotecan was given at higher doses or combined with 5-FU. In line with the result of Liu *et al*., *UGT1A1*28* polymorphism was found to be an indicator for neutropenia and diarrhea susceptibility in the meta-analysis by Yang *et al*.[34] which compromising both Caucasian and Asian trials. The relationship between *UGT1A1*28* genotypes and irinotecan-induced toxicity is shown in Table 1.

In TRIBE trial, mCRC patients from Italy were treated with first-line 5-FU- and irinotecan-based chemotherapy regimens (i.e., FOLFIRI or FOLFOXIRI) plus bevacizumab. Adverse events were prospectively collected at each treatment cycle. Homozygous *UGT1A1*28* genotype was found in 39/436 patients (8.9%). *UGT1A1*28/*28* genotype (OR, 4.29; 95% CI, 1.97-9.32) and *UGT1A1*1/*28* genotype (OR, 1.63; 95% CI, 1.02-2.60) were associated with an increased risk of severe neutropenia as compared to *UGT1A1*1/*1* genotype. No significant correlation with severe diarrhea was found. This result shows the potential role of *UGT1A1*28* in irinotecan-containing schedule tailoring[35].

Our previous study[36], based on a prospective multicenter longitudinal trial of metastatic CRC patients treated with irinotecan-based therapy, showed that patients carrying *UGT1A1*28* allele had more than two-fold higher risk of severe diarrhea compared with *UGT1A1*1/*1* patients (OR, 2.673; 95% CI, 1.039–6.876), with an incidence of 11.3% in *UGT1A1*1/*1* genotype and 26.2% in patients carrying *UGT1A1*28* allele, respectively. However, our evaluation did not reveal any association between severe neutropenia and *UGT1A1*28* genotypes (data shown in Table 1). We speculated that the null association might be due to the failure of recording lowest counts of neutrophils in patients with relatively poor compliance or inconvenience in seeking medical advice during their unhospitalization. In addition, anticipated neutropenia might also be covered up by preventive interventions such as granulocyte colony stimulating factor (G-CSF) treatments, which were even recommended by doctors concerned after completing the

Table 1: Association between UGT1A1 genotypes and irinotecan-induced toxicity

Reference year	Disease, stage	Population (race, number of study)	Regimen (irinotecan dose, schedule)	Polymorphism and toxicity	Genotype	OR (95%CI)
Meta-analysis						
Zhang et al. [32] 2017	Subgroup: CRC, III-IV	Asian, 6	FOLFIRI; IRI + Cape or S-1; IRI ± C225 or Beva (≥150mg/m^2, two/three weeks)	UGT1A1*6 and neutropenia	*6/*6 or *1/*6 vs. *1/*1 *6/*6 vs. *1/*1 *1/*6 vs. *1/*1	1.62 (1.07, 2.47) 2.55 (1.21, 5.36) 1.50 (0.96, 2.35)
Cheng et al. [33] 2014	Gastroin-testinal/ gynecologic cancer, IV or U	Asian, 7 [a]	FOLFIRI; IRI + Cape or S-1 or cisplatin; IRI ± C225 or Beva (130-375mg/m^2, two/three weeks [b])	UGT1A1*6 and diarrhea	*6/*1 vs. *1/*1 *6/*6 vs. *1/*1	1.44 (0.84, 2.49) 3.51 (1.41, 8.73)
Liu et al. [31] 2014	CRC, III-IV	Caucasian, 14	FOLFIRI/ mFOLFIRI; TEGAFIRI; FLIRI; IRI + Cape or S-1 or FU or OX or raltitrexed; UFT- Lv-IRI- OX; IFL/mIFL; IRI ± Beva (125-350mg/m^2, two/three weeks [b])	UGT1A1*28 and neutropenia	*28/*28 vs. *1/*1 *1/*28 vs. *1/*1 *28/*28 vs. *1/*28 or *1/*1	4.79 (3.28, 7.01) 1.90 (1.44, 2.51) 3.44 (2.45, 4.82)
Liu et al. [31] 2014	CRC, III-IV	Caucasian, 13	FOLFIRI/ mFOLFIRI; TEGAFIRI; FLIRI; IRI + Cape or S-1 or FU or OX or raltitrexed; UFT-Lv-IRI-OX; IFL/mIFL; IRI ± Beva (125-350mg/m^2, two/three weeks [b])	UGT1A1*28 and diarrhea	*28/*28 vs. *1/*1 *1/*28 vs. *1/*1 *28/*28 vs. *1/*28 or *1/*1	1.84 (1.24, 2.72) 1.20 (0.93, 1.56) 1.71 (1.18, 2.47)
Yang et al. [34] 2018	mainly CRC III-IV; GC, LC, EC	Caucasian,16 Asian, 14 [c d]	FOLFIRI/ mFOLFIRI ±C225/ Beva; FOLFOXIRI; FLIRI; IRI + Cape or FU or OX or cisplatin ±Beva; UFT-Lv-IRI-OX; IFL/mIFL; IRI ± Beva (mainly100-350mg/m^2, two/three weeks [b])	UGT1A1*28 and neutropenia	*28/*28 vs. *1/*1 *1/*28 vs. *1/*1	3.50 (2.23, 5.50) 1.91 (1.45, 2.50)
Yang et al. [34] 2018	mainly CRC III-IV; GC, LC, EC	Caucasian,16 Asian, 9 [c]	FOLFIRI/ mFOLFIRI ±C225/ Beva; FOLFOXIRI; FLIRI; IRI + Cape or FU or OX or cisplatin ±Beva; UFT-Lv-IRI-OX; IFL/mIFL; IRI ± Beva (mainly 100-350mg/m^2, two/three weeks [b])	UGT1A1*28 and diarrhea	*28/*28 vs. *1/*1 *1/*28 vs. *1/*1	1.69 (1.20, 2.40) 1.45 (1.07, 1.97)
Clinical research						
TRIBE [35]	CRC, IV	Italy, 1	FOLFOXIRI + bevacizumab, FOLFIRI + bevacizumab	UGT1A1*28 and neutropenia	*28/*28 vs. *1/*1 *1/*28 vs. *1/*1	4.29 (1.97, 9.32) 1.63 (1.02, 2.60)
TRIBE [35]	CRC, IV	Italy, 1	FOLFOXIRI + bevacizumab, FOLFIRI + bevacizumab	UGT1A1*28 and diarrhes	*28/*28 vs. *1/*1 *1/*28 vs. *1/*1	1.11 (0.63, 1.95) 0.20 (0.04, 1.09)
Yu et al. [36] 2018	CRC, IV	Chinese, 1	FOLFIRI, IRI+Cape, IRI (125-180mg/m^2, two/three weeks)	UGT1A1*28 and neutropenia	*1/*28 or *28/*28 vs. *1/*1	1.240 (0.554, 2.776)
Yu et al. [36] 2018	CRC, IV	Chinese, 1	FOLFIRI, IRI+Cape, IRI (125-180mg/m^2, two/three weeks)	UGT1A1*28 and diarrhea	*1/*28 or *28/*28 vs. *1/*1	2.673 (1.039, 6.876)

OR, odds ratio; CI, confidence interval; CRC, colorectal cancer; IRI, irinotecan; Beva, bevacizumab; Cape, capecitabine; C225, cetuximab; IFL, irinotecan and 5-fluorouracil; U, unknown; UFT, uracil/tegafur; OX, oxaliplatin; GC, gastric cancer; LC, lung cancer; EC, esophageal cancer.
a: Among the seven studies, one study of gynecologic cancer took the regimen IRI + cisplatin with irinotecan dose of 60 mg/m^2(d1, 8, 15) every four weeks.
b: Weekly regimens were considered equal dosage as biweekly schedule when summarized in the table.
c: One study of lung cancer took the regimen IRI, IRI + cisplatin or docetaxel with irinotecan dose of 50 to 60 mg/m^{2}every four weeks.
d: One study of Lung, stomach and colon cancer took the regimen IRI + platinum, IRI + others, FOLRIRI with irinotecan dose of 50 to 100 mg/m^2.

first course of chemotherapy. With respect to diarrhea toxicity, the index was more accessible through phone call following-up surveys and reevaluated by face-to-face questionnaires.

UGT1A Polymorphisms and Treatment Efficacy

Given the predictive value of *UGT1A1* polymorphism in irinotecan-induced toxicity, genetic testing of these loci prior to treatment could tailor irinotecan therapy,

enabling targeted surveillance and preventive measures in order to reduce the risk of chemotherapy-related side effects. Moreover, knowledge of which crowd will benefit (response and/or better survival rates) from the medical procedure could assist implementers in making an informed decision when prioritizing chemotherapy regimens. However, relatively less evidence supports the link between *UGT1A1* genotype and irinotecan treatment efficacy, and the existing data are controversial.

It is reported that 35-55% of patients respond to irinotecan-based first-line chemotherapy, and the disease control rate is about 75%-85%, while both the rates are almost reduced by half when the regimen is taken as a second-line treatment[4-7]. *UGT1A1*28* and *UGT1A1*6* variants contribute to reduced UGT1A1 expression or decreased enzymatic activity[18,19], and are linked to SN-38 glucuronidation, therefore, it is pharmacologically plausible that *UGT1A1* genotype is connected with tumor response[37,38].

A meta-analysis comprising fifteen Asian trials was conducted by Chen *et al*.[39] to investigate the relationship between *UGT1A1*6* alleles and patient response to irinotecan-based chemotherapy. Most studies involved in the meta-analysis failed to find the relationship between *UGT1A1*6* and therapeutic efficacy, possibly due to small sample sizes and mixed analysis of various therapy line (first-, second- and third-line). Poor statistic power might be partially eliminated by meta-analysis, nevertheless, no association was found between *UGT1A1*6* allele and tumor response or survival, either in pooled analysis nor subgroup analysis (shown in Table 2). Hence, *UGT1A1*6* polymorphism is less likely to be a predictor of irinotecan, especially in CRC patients, for tumor response and survival outcome based on these available studies.

Emerging data represented the predictive value of *UGT1A1*28* allele in therapeutic efficacy of irinotecan-based chemotherapy[36]. Results from the meta-analysis by Liu *et al*.[40] revealed that *UGT1A1*1/*28* or *UGT1A1*28/*28* genotype was an unfavorable predictor for overall survival (OS) compared with wild-type genotype. Dias *et al*.[41] considered the evidence in Liu's meta-analysis was not strong enough to support the trend conclusion owing to their insufficient analyses of original data. A meta-analysis included 58 studies by Liu *et al*.[42] demonstrated an increased response rate in patients harboring *UGT1A1*1/*28* or *UGT1A1*28/*28* genotypes, but a null association between *UGT1A1*28* and survival. Although most of the studies involved in these meta-analyses suggested a null association between *UGT1A1*28* polymorphism and survival outcome, four studies showed predictive roles of *UGT1A1*28* in irinotecan-treated patients, as a favorable indicator for progression-free survival (PFS)[14] or an unfavorable index for overall survival (OS)[15,16,43]. These inconsistencies may be partially attributed to diverse schedules of irinotecan, relatively small sample sizes, different study designs, and limited follow-up time.

A retrospective study focusing on gastric cancer treated with irinotecan as third-line therapy by Yamaguchi *et al*.[44] demonstrated a significant association between combined genotyping of *UGT1A1*28* and **6* and OS outcome in univariate analysis, in which carrying variant allele is an unfavorable indicator for OS (hazard ratio [HR], 1.525; 95% CI, 1.033-2.251) compared with no carriers, but the significance faded away when adjusted in multivariate model (data shown in Table 2). If validated in prospective designed study, the combined indicator of *UGT1A1*28* and **6* is promising in facilitating stratification of gastric patients for individualized third-line treatment options.

In our previous study[36], which was prospectively designed to investigate the role of *UGT1A1*28* polymorphism in therapeutic efficacy in Chinese metastatic CRC patients treated with irinotecan-based first-line chemotherapy, PFS and OS were co-primary end points, meanwhile, objective response rate (ORR) and disease control rate (DCR) were also evaluated. *UGT1A1*28* carriers tended to have a reduced likelihood of objective response (ORR=22.7%) compared with the wild-type genotype (ORR=39.1%; OR, 0.444; 95% CI, 0.194-1.018; p=0.055). No significant difference was observed in groups divided by genotypes with respect to DCR. *UGT1A1*28* variant genotype was predictive of worse PFS (median=7.5 months; HR, 1.803; 95% CI, 1.217-2.671) and OS (median=13.3 months; HR, 1.979; 95% CI, 1.267 to 3.091) compared with wild-type genotype (median PFS=9.8 months; median OS=20.8 months) (seen in Table 2). Since patients with *UGT1A1*28* allele showed an unfavorable therapeutic response and susceptibility to irinotecan-induced toxicity (see Table 1), it is not recommended to carry out irinotecan-based regimen as first-line procedure in mCRC patients with *UGT1A1*28* variant.

Opposite to the role in our study, *UGT1A1*28* polymorphism seemed to be associated with increased clinical benefit and tumor response in the study by Toffoli *et al.* Patients bearing homozygous *UGT1A1*28* were less likely to experiencing disease progression (OR, 0.19; 95% CI, 0.04-0.89), and had a significantly reduced risk of progression or stable disease compared with the wild-type genotype (OR, 0.32; 95% CI, 0.12-0.86). Analysis of time to progression (TTP) revealed a significant decrease in patients harboring *UGT1A1*28/*28* (HR, 0.52; 95% CI, 0.31-0.90) and *UGT1A1*1/*28* genotypes (HR, 0.73; 95% CI, 0.55 to 0.98) compared with the wild-type genotype. With respect to OS, no significant survival advantage was observed in *UGT1A1*28* carriers. Data were shown in Table 2.

Table 2: Association between UGT1A1 genotypes and therapeutic efficacy

Reference year	Tumor	Population (race, number of study)	Regimen (irinotecan dose, schedule)	Line of therapy	Polymorphism and outcome	Genotype	OR/HR (95% CI) Or median survival (95% CI)
Meta-analysis							
Chen et al. [38] 2017	subgroup: advanced CRC	Asian, 11	FOLFIRI; IFL[a]; IRI; IRI+Cape (mainly 180-200mg/m^2, two weeks)	First, second, third line and U	UGT1A1*6 and ORR	*1/*1 vs. *1/*6 or *6/*6	OR: 0.73 (0.51, 1.05)
Chen et al. [38] 2017	subgroup: advanced CRC	Asian, 2	FOLFIRI; IFL; IRI; IRI+Cape (mainly 180mg/m^2, two weeks)	First, second and third line	UGT1A1*6 and TTP	*1/*1 vs. *1/*6 or *6/*6	HR: 0.79 (0.52, 1.18)
Chen et al. [38] 2017	subgroup: NSCLC or ES-SCLS	Asian, 4	IP; EP; IRI (60-80mg/m^2, three/four weeks)	U	UGT1A1*6 and ORR	*1/*1 vs. *1/*6 or *6/*6	OR: 1.09 (0.55, 2.15)
Clinical research							
Yamaguchi et al. [43] 2019	advanced GC	Japanese, 1 (208 pts)	IRI (150mg/m^2, two weeks)	Third line (retro-spective design)	UG-T1A1*6/*28 and TTF	*28/*28 or *6/*6 or *28/*6 *1/*28 or *1/*6 [b] *1/*1	TTF: 1.3 months (95% CI, 0.3–1.9) 2.3 months (95% CI, 1.3–3.7) 2.4 months (95% CI, 1.6–3.6)
Yamaguchi et al. [43] 2019	advanced GC	Japanese, 1 (208 pts)	IRI (150mg/m^2, two weeks)	Third line (retro-spective design)	UG-T1A1*6/*28 and OS	Others vs. *1/*1	HR: 1.525 (1.033–2.251) [c] HR: 1.306 (0.684–2.492) [d]
Yu et al. [36] 2018	mCRC	Chinese, 1 (159 pts)	FOLFIRI, IRI+Cape, IRI (125-180mg/m^2, two/three weeks)	First-line (pro-spective design)	UGT1A1*28 and ORR UGT1A1*28 and DCR	*1/*28 or *28/*28 vs. *1/*1 *1/*28 or *28/*28 vs. *1/*1	OR: 0.444 (0.194, 1.018) OR: 0.508 (0.209, 1.239)
Yu et al. [36] 2018	mCRC	Chinese, 1 (164 pts)	FOLFIRI, IRI+Cape, IRI (125-180mg/m^2, two/three weeks)	First-line (pro-spective design)	UGT1A1*28 and PFS	*1/*1 (ref.) *1/*28 or *28/*28	PFS: 9.8 months (95% CI, 8.6-10.9) PFS: 7.5 months (95% CI, 5.5-9.6) HR: 1.803 (1.217, 2.671)
Yu et al. [36] 2018	mCRC	Chinese, 1 (164 pts)	FOLFIRI, IRI+Cape, IRI (125-180mg/m^2, two/three weeks)	First-line (pro-spective design)	UGT1A1*28 and OS	*1/*1 (ref.) *1/*28 or *28/*28	OS: 20.8 months (95% CI, 18.7-23.0) OS: 13.3 months (95% CI, 10.3-16.2) HR: 1.979 (1.267, 3.091)
Toffoli et al. [14]	mCRC	North-east Italy, 1 (238 pts)	mFOLFIRI, FOLFIRI (180mg/m^2, two weeks)	First-line (pro-spective design)	UGT1A1*28 and PD+SD UGT1A1*28 and PD	*1/*28 vs. *1/*1 *28/*28 vs. *1/*1 *1*28 or *28/*28 vs. *1/*1 *1/*28 vs. *1/*1 *28/*28 vs. *1/*1 *1*28 or *28/*28 vs. *1/*1	OR: 0.92 (0.53, 1.56) OR: 0.32 (0.12, 0.86) OR: 0.77 (0.46, 1.31) OR: 0.77 (0.42, 1.39) OR: 0.19 (0.04, 0.89) OR: 0.65 (0.36, 1.16)
Toffoli et al. [14]	mCRC	North-east Italy, 1 (238 pts)	mFOLFIRI, FOLFIRI (180mg/m^2, two weeks)	First-line (pro-spective design)	UGT1A1*28 and TTP UGT1A1*28 and OS	*1/*28 vs. *1/*1 *28/*28 vs. *1/*1 *1/*28 vs. *1/*1 *28/*28 vs. *1/*1	HR: 0.73 (0.55, 0.98) HR: 0.52 (0.31, 0.90) HR: 0.84 (0.58, 1.21) HR: 0.81 (0.45, 1.44)

OR, odds ratio; HR, hazard ratios; CI, confidence interval; mCRC, metastatic colorectal cancer; NSCLC, non-small-cell lung cancer; ES-SCLC, extensive stage small-cell lung cancer; IRI, irinotecan; IP, irinotecan and cisplatin; EP, etoposide and cisplatin; IFL, irinotecan and 5-fluorouracil; Cape, capecitabine; U, Unknown; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; TTP: time to progression; TTF, time to treatment failure; pts, patients; GC, gastric cancer; PD, progression disease; SD, stable disease.

a: In one study, the dose of irinotecan in IFL regimen is 125mg/m^2.

b: Concurrence of *UGT1A1*1/*28* and **1/*6* is not included in this genotype.

c: Univariate analysis.

d: Multivariate analysis.

It is often considered that premature drug suspension and dose reduction as well as administration delays due to toxicity can decrease anti-tumor activity. We further investigated the connection between genotypes, survival outcome and dose reduction in the previous study [36]. *UGT1A1*28* carriers tended to have an elevated likelihood of dose reduction compared with no carriers, although not statistically significant (OR, 2.156; 95% CI, 0.984–4.725; p=0.055). Dose reduction was significantly associated with decreased PFS (p<0.001) and represented a trend towards decreased OS (p=0.060). Therefore, dose reduction affected PFS, but whether it had an impact on OS needed further study. Additionally, subgroup analysis of patients treated without dose reduction showed that *UGT1A1*28* allele was still an unfavorable predictor of PFS and OS. Since patients with *UGT1A1*28* allele had more susceptibility to adverse effects (see Table 1) and less clinical benefits than wild-type genotype, it is not recommended to carry out irinotecan-based regimen as first-line procedure in mCRC patients with *UGT1A1*28* variant.

Conclusion and Clinical Application of Potential Biomarkers

Genetic diversity exists among ethnics and individuals. *UGT1A1*6* allele is frequently observed in Asian population, while rarely found in Caucasian population. *UGT1A1*28* is an extremely common variant in Caucasian, and of a lower frequency in Asian. *UGT1A1*28* and *UGT1A1*6* (mainly in Asian) polymorphisms are promising predictors for irinotecan-induced toxicity in CRC patients receiving irinotecan-based chemotherapy. *UGT1A1*28* variant is of some relevance to clinical advantage or disadvantage, but there are no sufficient evidence to support its role in therapeutic efficacy predicting.

Genetic testing could provide important insights for making individualized therapeutic strategies. In the USA, routine genotyping tests are performed typically for *UGT1A1 *1/*1*, **1/*28*, and **28/*28* genotypes. It is recommended by the United States of America Food and Drug Administration (FDA) that when irinotecan is administered as a single-agent, a reduction in the starting dose by at least one level should be considered for patients with U*GT1A1*28/*28* genotypes, and subsequent dose modifications should be made based on individual tolerance. However, the precise dose reduction in this crowd is not clear[21]. The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) suggests starting with 70% of the standard dose for *UGT1A1*28* homozygote carriers, and increasing following dose according to neutrophil counts if the patient tolerates the initial dose well[45]. In Asian populations, both *UGT1A1*28* and **6* are taken into consideration when making irinotecan dose adjustment, and concurrence of *28 and *6, even when heterozygous, alters the disposition of irinotecan remarkably, potentially increasing susceptibility to toxicity[46,47]. An initial reduction of irinotecan is recommended for patients with *UGT1A1 *6/*6*, **6/*28*, and **28/*28* genotypes in Japan[22].

However, due to the lack of prospective data, it is yet unknown whether initial dose reduction leads to an altered antitumor effect, and whether the routine dose is sufficient for objects without variant homozygotes. The use of genetic testing for dose modification might be performed in selective cases: when the patient calls for aggressive treatment (e.g. shrinking the tumor for excision), genotyping might allow higher dosing for individuals with *UGT1A1*1/*1* or **1/*28* genotypes[48-51]; for patients prefer maximizing quality of life, genotyping might allow lower dosing for those harboring *UGT1A1*28* homozygotes[15,23].

To date, given the inconsistent result of the predictive effect of *UGT1A1* on therapeutic efficacy, recommendations are given mainly based on the toxicity data of irinotecan and *UGT1A1* genotypes. Furthermore, as 5-Fu is included in the combined chemotherapy protocol, *dihydropyrimidine dehydrogenase deficiency (DPYD)* polymorphism also needs to be considered in the predictive indicator. A few allelic variants of *DPYD* involved in the synthesis of non-functional or poorly functional enzymes expose patients to an increased risk of 5-FU-related adverse events (e.g. thrombocytopenia and stomatitis)35. Current genetic testing helps to identify patients with high risk of developing irinotecan-induced toxicity, and enables informed dosing, targeted surveillance and prophylactic measures. Further investigations are needed for building an optimal genetic prediction model with the potential to both reduce the burden of toxicity and improve survival.

Conflict of interest

The authors declare that they have no conflict of interest.

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