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

Qianqian Yu1, Zhihuan Li2, Xiaoqi Nie1, Lu Wang1, Chen Gong1, Bo Liu1, Xin Liao3, Ben Zhao1, Qianxia Li1, Mingsheng Zhang1, Hong Qiu1, Xianglin Yuan1*

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

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. 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. 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. 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-hydroxy camptothecin (SN-38). Clinical pharmacological evidence demonstrated that irinotecan-related toxicity and efficacy is associated with objects’ exposure to SN38. 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. The predominant enzyme is UGT1A1, which is also involved in the metabolism of bilirubin. Polymorphisms in UGT1A1 genes may contribute to changes in UGT1A1 enzyme activity, resulting in variability of irinotecan pharmacokinetics. Several
**UGT1A1 Polymorphisms are reported to be associated with irinotecan-related toxicity and efficacy**. 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. 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 and were usually suggested to be risk factors for severe diarrhea and neutropenia. 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). 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. *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%). 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.

Subgroup analysis of the meta-analysis conducted by Zhang *et al.* 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.* 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.* 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/m²; 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.* 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. Our previous study 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...
One study of lung cancer took the regimen IRI, IRI + cisplatin or docetaxel with irinotecan dose of 50 to 60 mg/m² every four weeks.

Weekly regimens were considered equal dosage as biweekly schedule when summarized in the table.

Among the seven studies, one study of gynecologic cancer took the regimen IRI + cisplatin with irinotecan dose of 60 mg/m² (d1, 8, 15).

In the first course of chemotherapy, 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.

---

### 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 (125-350mg/m², two/three weeks) | UGT1A1*6 and neutropenia | *6/*6 or *1/*6 vs. *1/*1 | 1.62 (1.07, 2.47) |
|                  |                |                                    |                                     |                           |          |            |
| Cheng et al. [31] 2014 | Gastrointestinal/gynecologic cancer, IV or U | Asian, 7 ¹ | FOLFIRI; IRI + Cape or S-1 or cisplatin; IRI ± C225 or Beva (130-375mg/m², two/three weeks ²) | UGT1A1*6 and diarrhea | *6/*1 vs. *1/*1 | 1.44 (0.84, 2.49) |
| 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; IF/L/mlF; IRI ± Beva (125-350mg/m², two/three weeks ³) | UGT1A1*28 and neutropenia | *28/*28 vs. *1/*1 | 4.79 (3.28, 7.01) |
| 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; IF/L/mlF; IRI ± Beva (125-350mg/m², two/three weeks ³) | UGT1A1*28 and diarrhea | *28/*28 vs. *1/*1 | 1.84 (1.24, 2.72) |
| Yang et al. [34] 2018 | mainly CRC III-IV, GC, LC, EC | Caucasian, 16 Asian, 14 ⁴ | FOLFIRI/ mFOLFIRI ± cC225/ Beva; FOLFIRI/FLIRI; IRI + Cape or FU or OX or cisplatin ± Beva; UFT-Lv-IRI- OX; IF/L/mlF; IRI ± Beva (mainly 100-350mg/m², two/three weeks ⁵) | UGT1A1*28 and neutropenia | *28/*28 vs. *1/*1 | 3.50 (2.23, 5.50) |
| Yang et al. [34] 2018 | mainly CRC III-IV, GC, LC, EC | Caucasian, 16 Asian, 9 ⁴ | FOLFIRI/ mFOLFIRI ± cC225/ Beva; FOLFIRI/FLIRI; IRI + Cape or FU or OX or cisplatin ± Beva; UFT-Lv-IRI- OX; IF/L/mlF; IRI ± Beva (mainly 100-350mg/m², two/three weeks ⁵) | UGT1A1*28 and diarrhea | *28/*28 vs. *1/*1 | 1.69 (1.20, 2.40) |

Clinical research

| TRIBE [35] | CRC, IV | Italy, 1 | FOLFIRI + bevacizumab, FOLFIRI + bevacizumab | UGT1A1*28 and neutropenia | *28/*28 vs. *1/*1 | 4.29 (1.97, 9.32) |
| TRIBE [35] | CRC, IV | Italy, 1 | FOLFIRI + bevacizumab, FOLFIRI + bevacizumab | UGT1A1*28 and diarrheas | *28/*28 vs. *1/*1 | 1.11 (0.63, 1.95) |
| Yu et al. [36] 2018 | CRC, IV | Chinese, 1 | FOLFIRI, IRI+Cape, IRI (125-180mg/m², two/three weeks) | UGT1A1*28 and diarrheas | *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/m², two/three weeks) | UGT1A1*28 and diarrheas | *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 S-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/m² 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 + cisplatin or docetaxel with irinotecan dose of 50 to 60 mg/m² every four weeks.
d: One study of lung, stomach and colon cancer took the regimen IRI + platinum, IRI + others, FOLFIRI with irinotecan dose of 50 to 100 mg/m².
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. UGT1A1*28 and UGT1A1*6 variants contribute to reduced UGT1A1 expression or decreased enzymatic activity, and are linked to SN-38 glucuronidation, therefore, it is pharmacologically plausible that UGT1A1 genotype is connected with tumor response.

A meta-analysis comprising fifteen Asian trials was conducted by Chen et al. 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. Results from the meta-analysis by Liu et al. 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. 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. 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) or an unfavorable index for overall survival (OS). 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. 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, 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.    | subgroup: advanced CRC | Asian, 11                        | FOLFIRI; IFL; IRI; IRI+Cape (mainly 180-200mg/m², 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.    | subgroup: advanced CRC | Asian, 2                         | FOLFIRI; IFL; IRI; IRI+Cape (mainly 180mg/m², 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.    | subgroup: NSCLC or ES-SCLC | Asian, 4                         | IP; EP; IRI (60-80mg/m², 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. | advanced GC | Japanese, 1 (208 pts)           | IRI (150mg/m², two weeks)            | Third line (retrospective design) | UGT1A1*6/*28 and TTF | *28/*28 or *6/*6 or *28/*6 | TTF: 1.3 months (95% CI, 0.3–1.9) |
|                |                |                                   |                                     |                 |                          |                           |                                          |
| Yamaguchi et al. | advanced GC | Japanese, 1 (208 pts)           | IRI (150mg/m², two weeks)            | Third line (retrospective design) | UGT1A1*6/*28 and OS | Others vs. *1/*6 or *6/*6 | HR: 1.525 (1.033–2.251)         |
|                |                |                                   |                                     |                 |                          |                           |                                          |
| Yu et al.      | mCRC           | Chinese, 1 (159 pts)            | FOLFIRI, IRI+Cape, IRI (125-180mg/m², two/three weeks) | First-line (prospective design) | UGT1A1*28 and ORR UGT1A1*28 and DCR | *1/*28 or *28/*28 vs. *1/*1 | OR: 0.444 (0.194, 1.018)        |
|                |                |                                   |                                     |                 |                          |                           |                                          |
| Yu et al.      | mCRC           | Chinese, 1 (164 pts)            | FOLFIRI, IRI+Cape, IRI (125-180mg/m², two/three weeks) | First-line (prospective design) | UGT1A1*28 and PFS | *1/*1 (ref.) | PFS: 9.8 months (95% CI, 8.6–10.9) |
|                |                |                                   |                                     |                 |                          |                           |                                          |
| Yu et al.      | mCRC           | Chinese, 1 (164 pts)            | FOLFIRI, IRI+Cape, IRI (125-180mg/m², two/three weeks) | First-line (prospective design) | UGT1A1*28 and OS | *1/*1 (ref.) | OR: 0.508 (0.209, 1.239)        |
| Toffoli et al. | mCRC           | North-east Italy, 1 (238 pts)   | mFOLFIRI, FOLFIRI (180mg/m², two weeks) | First-line (prospective design) | UGT1A1*28 and PD+SD UGT1A1*28 and PD | *1/*28 or *28/*28 vs. *1/*1 | OR: 0.92 (0.53, 1.56)          |
| Toffoli et al. | mCRC           | North-east Italy, 1 (238 pts)   | mFOLFIRI, FOLFIRI (180mg/m², two weeks) | First-line (prospective design) | UGT1A1*28 and TTP UGT1A1*28 and OS | *1/*28 or *28/*28 vs. *1/*1 | OR: 0.73 (0.55, 0.98)          |

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/m².
b: Concordance 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 antitumor activity. We further investigated the connection between genotypes, survival outcome and dose reduction in the previous study. 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 UGT1A1*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. 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. 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. An initial reduction of irinotecan is recommended for patients with UGT1A1 *6/*6, *6/*28, and *28/*28 genotypes in Japan.

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, for patients prefer maximizing quality of life, genotyping might allow lower dosing for those harboring UGT1A1*28 homozygotes.

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, dihydropriimidine 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). 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.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394-424.
2. McPhail S, Johnson S, Greenberg D, et al. Stage at diagnosis and early mortality from cancer in England. Br J Cancer. 2015; 112 Suppl 1: S109-115.
3. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016; 66(4): 271-289.
4. Boni V, Zarate R, Villa JC, et al. Role of primary mRNA polymorphic variants in metastatic colon cancer patients treated with 5-fluorouracil and irinotecan. Pharmacogenomics J. 2011; 11(6): 429-436.
5. Fischer von Weikersthal L, Schallhorn A, Staub M, et al. Phase III trial of irinotecan plus infusional 5-fluorouracil/folinic acid versus irinotecan plus oxaliplatin as first-line treatment of advanced colorectal cancer. Eur J Cancer. 2011; 47(2): 206-214.
6. Vamvakas I, Kakolyris S, Kouroussis C, et al. Irinotecan (CPT-11) in combination with infusional 5-fluorouracil and leucovorin (de
7. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 for the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004; 22(2): 229-237.

8. Cai X, Cao W, Ding H, et al. Analysis of UGT1A1*28 genotype and SN-38 pharmacokinetics for irinotecan-based chemotherapy in patients with advanced colorectal cancer: results from a multicenter, retrospective study in Shanghai. J Cancer Res Clin Oncol. 2013; 139(9): 1579-1589.

9. Iyer L, King CD, Whittington PF, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isofrom 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest. 1998; 101(4): 847-854.

10. Yu QQ, Qiu H, Zhang MS, et al. Predictive effects of bilirubin on response of colorectal cancer to irinotecan-based chemotherapy. World J Gastroenterol. 2016; 22(16): 4250-4258.

11. Denlinger CS, Blanchard R, Xu L, et al. Pharmacokinetic analysis of irinotecan plus bevacizumab in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2009; 65(S1): 97-105.

12. Chen X, Liu L, Guo Z, et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment outcome in Asians with Lung Cancer: a meta-analysis. Cancer Chemother Pharmacology. 2017; 79(6): 1109-1117.

13. Zhang X, Yin JF, Zhang J, et al. UGT1A1*6 polymorphisms are correlated with irinotecan-induced neuropenia: a systematic review and meta-analysis. Cancer Chemotherapy and Pharmacology. 2017; 80(1): 135-149.

14. Tofolì G, Cezchin 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(19): 3061-3068.

15. Shulman K, Cohen I, Barnett-Griness O, et al. Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients. Cancer. 2011; 117(14): 3156-3162.

16. Xu C, Tang X, Qu Y, et al. UGT1A1 gene polymorphism is associated with toxicity and clinical efficacy of irinotecan-based chemotherapy in patients with advanced colorectal cancer. Cancer Chemotherapy and Pharmacology. 2016; 78(1): 119-130.

17. Dean L. Irinotecan therapy and UGT1A1 genotype. Medical genetics summaries [Internet]: National Center for Biotechnology Information (US), 2018.

18. Beutler E, Gelbart D, Demina A. Racial variability in the UDP-glucuronyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci U S A. 1998; 95(14): 8170-8174.

19. Jinno H, Tanaka-Kagawa T, Hanikoa N, et al. Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan (CPT-11), by human UGT1A1 variants, G71R, P229Q, and Y486D. Drug Metab Dispos. 2003; 31(1): 108-113.

20. Campbell M, Stephenson MD, Bateman E, et al. Irinotecan-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. Pharmacogenomics. 2017; 17(1): 21-28.

21. Fresenius Kabi USA L. IRINOTECAN HYDROCHLORIDE: irinotecan hydrochloride injection, solution [package insert]. Available from: https://dailyemed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee45f127-8450-4455-a945-a115707f1d39#e5447ef4-2043-4809-85c7-db6a9f483f63 [Internet]. December 31, 2019.

22. Fujita K, Kubota Y, Ishida H, et al. Irinotecan, a key chemotherapeutic drug for metastastic colorectal cancer. World J Gastroenterol. 2015; 21(43): 12233-12248.
40. Liu X, Cheng D, Kuang Q, et al. Association between UGT1A1*28 polymorphisms and clinical outcomes of irinotecan-based chemotherapies in colorectal cancer: a meta-analysis in Caucasians. PLoS One. 2013;8(3):e58489.

41. Dias MM, Pignon JP, Karapetis CS, et al. The effect of the UGT1A1*28 allele on survival after irinotecan-based chemotherapy: a collaborative meta-analysis. Pharmacogenomics J 2014; 14(5):424-431.

42. Liu XH, Lu J, Duan W, et al. Predictive Value of UGT1A1*28 Polymorphism In Irinotecan-based Chemotherapy. J Cancer. 2017; 8(4): 691-703.

43. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG 50124. J Clin Oncol. 2009; 27(15):2530-2535.

44. Yamaguchi T, Iwasa S, Shoji H, et al. Association between UGT1A1 gene polymorphism and safety and efficacy of irinotecan monotherapy as the third-line treatment for advanced gastric cancer. Gastric Cancer. 2019; 22(4): 778-784.

45. [DPWG]. RDPAKPWG. Pharmacogenetic Guidelines [Internet]. Netherlands. Irinotecan – UGT1A1. Available from: http://kennisbank.knmp.nl [Access is restricted to KNMP membership]. May 2017.

46. Araki K, Fujita K, Ando Y, et al. Pharmacogenetic impact of polymorphisms in the coding region of the UGT1A1 gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci. 2006; 97(11): 1255-1259.

47. Han FF, Guo CL, Yu D, et al. Associations between UGT1A1*6 or UGT1A1*6/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. Cancer Chemother Pharmacol. 2014; 73(4): 779-788.

48. Toffoli G, Sharma MR, Mangon E, et al. Genotype-Guided Dosing Study of FOLFIRI plus Bevacizumab in Patients with Metastatic Colorectal Cancer. Clin Cancer Res. 2017; 23(4): 918-924.

49. Philip JM, Mineur L, De la Fouchardiere C, et al. High Resectability Rate of Initially Unresectable Colorectal Liver Metastases After UGT1A1-Adapted High-Dose Irinotecan Combined with LV5FU2 and Cetuximab: A Multicenter Phase II Study [ERBIFORT]. Ann Surg Oncol. 2016; 23(7): 2161-2166.

50. Innocenti F, Schilsky RL, Ramirez J, et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. J Clin Oncol. 2014; 32(22): 2328-2334.

51. Paez D, Tobena M, Fernandez-Plana J, et al. Pharmacogenetic clinical randomised phase II trial to evaluate the efficacy and safety of FOLFIRI with high-dose irinotecan (HD-FOLFIRI) in metastatic colorectal cancer patients according to their UGT1A1 genotype. Br J Cancer. 2019; 120(2): 190-195.