Case Series

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(7) 1–10

DOI: 10.1177/03000605221110697
journals.sagepub.com/home/imr
SAGE

Irinotecan dose reduction in metastatic colorectal cancer patients with homozygous *UGT1A1*28* polymorphism: a single-center case series

Hsiang-Lin Tsai[1,2], Po-Jung Chen[1], Yen-Cheng Chen[1,3], Ching-Chun Li[1], Tsung-Kun Chang[1], Wei-Chih Su[1], Tzu-Chieh Yin[1,4,5], Ching-Wen Huang[1,2] and Jaw-Yuan Wang[1,2,3,6,7,8]

Abstract

Objective: The *UGT1A1*28* polymorphism reduces *UGT1A1* enzymatic activity, which may increase the risk of severe toxicity in patients who receive standard-dose irinotecan, such as severe neutropenia and diarrhea. This real-world study assessed the optimal irinotecan dose in terms of efficacy and toxicity in metastatic colorectal cancer (mCRC) patients homozygous for the *UGT1A1*28* polymorphism and receiving FOLFIRI plus bevacizumab or cetuximab as first-line therapy.

Methods: We analyzed toxicity and treatment outcomes in seven mCRC patients who were homozygous for *UGT1A1*28* and received FOLFIRI plus bevacizumab or cetuximab, with an initial irinotecan dose of 120 mg/m^2.

[1]Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung
[2]Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung
[3]Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung
[4]Division of General and Digestive Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung
[5]Department of Surgery, Kaohsiung Municipal Tatung Hospital, Kaohsiung Medical University, Kaohsiung
[6]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung
[7]Center for Cancer Research, Kaohsiung Medical University, Kaohsiung
[8]Ministry of Health and Welfare Pingtung Hospital, Pingtung

Corresponding author:
Jaw-Yuan Wang, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807.
Email: cy614112@ms14.hinet.net; jawyuanwang@gmail.com

Results: Six of the seven patients tolerated 120 mg/m^2 irinotecan without requiring dose reductions in subsequent cycles. The overall response and disease control rates were 43.0% (3/7) and 71.4% (5/7), respectively. The median progression-free survival and overall survival were 11.0 and 33.0 months, respectively. Only one severe adverse event, grade III neutropenia (2.5%), was observed.

Conclusions: mCRC patients homozygous for the *UGT1A1*28* allele can tolerate irinotecan at an initial dose of 120 mg/m^2 with favorable oncological outcomes and toxicity profiles. Further prospective studies are warranted to optimize irinotecan-based chemotherapy in these patients.

Keywords

Case series, irinotecan dose-reduction, homozygous UGT1A1*28, metastatic colorectal cancer, poor metabolizer, FOLFIRI

Date received: 9 November 2021; accepted: 13 June 2022

Introduction

Irinotecan is a chemotherapeutic agent used in combination with folinic acid (leucovorin) and 5-fluorouracil (5-FU) as a first-line treatment for metastatic colorectal cancer (mCRC); this regimen is known as FOLFIRI. Irinotecan exerts its cytotoxicity by inhibiting topoisomerase I during DNA replication through its active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Hepatic and extrahepatic phase II UDP-glucuronosyltransferase (UGT) drug-metabolizing enzymes—*UGT1A1*, *UGT1A7*, and *UGT1A9*—convert SN-38 into the inactive form SN-38 glucuronide (SN-38G).[1] Numerous studies have examined associations between alleles of these genes and severe irinotecan toxicities, particularly diarrhea and neutropenia.[2–4] The polymorphism *UGT1A1*28* has been associated with severe irinotecan-induced diarrhea and neutropenia;[4–6] which caused the U.S. Food and Drug Administration to recommend dose reduction in patients with low *UGT1A1* activity. More than 30% of patients homozygous for *UGT1A1*28* (TA 7/7) in Western and East Asian populations were reported to have severe neutropenia and diarrhea (grade III/IV).[7,8]

The prevalence of homozygous *UGT1A1*28* is significantly greater in African (12%–27%) and Caucasian populations (5%–15%) and is much lower (1.2%–5%) in Southeast Asian and Asia–Pacific populations, including Taiwan.[9–11] A previous dose-finding study suggested that the recommended irinotecan dose of 180 mg/m^2 in the FOLFIRI regimen was low for mCRC patients with the *UGT1A1*1/*1* or *UGT1A1*28/*1* genotypes.[12,13] In contrast, the 180 mg/m^2 dose has been shown to be too high in patients harboring homozygous *UGT1A1*28* alleles, and the dose reduction should be approximately 20%.[14] In our previous study, we demonstrated that the maximum tolerated irinotecan dose in mCRC patients with the homozygous *UGT1A1*28* allele was 120 mg/m^2.[15] However, real-world experience in administering the optimal irinotecan dose in Asian mCRC patients with homozygous *UGT1A1*28* under the FOLFIRI regimen plus targeted agents is lacking due to the limited number of such patients.

In this study, we retrospectively examined the prevalence of *UGT1A1*28* polymorphisms in seven mCRC patients who received an initial irinotecan dose of 120 mg/m^2. We also analyzed the characteristics correlated with this polymorphism as well as toxicity and treatment outcomes from irinotecan-based chemotherapy plus targeted agents.

Methods

Between January 2018 and December 2020, we enrolled mCRC patients who were homozygous for the *UGT1A1*28* polymorphism and had received FOLFIRI plus bevacizumab or cetuximab as first-line therapy. The initial irinotecan dose for those with homozygous *UGT1A1*28* polymorphisms was 120 mg/m^2, as mentioned in our previous study.[15] If grade 3/4 adverse events (AEs) occurred, the irinotecan dose was decreased to 100 mg/m^2, with no adjustment to 5-FU. We reviewed medical charts and records to collect data on treatment outcomes. Clinical samples were obtained with informed consent from each patient, and the institutional review board of our hospital approved our study protocol [KMUHIRB-2012-03-03(II)].

The reporting of this study conforms to the CARE guidelines.[16] We analyzed demographic data (age, sex, Eastern Cooperative Oncology Group [ECOG] performance status, *RAS* genotype, *BRAF* genotype, and microsatellite instability [MSI] status) and clinical variables (primary tumor site, mCRC type, metastatic sites/numbers, initial/final irinotecan dose, efficacy, and toxicity). Progression-free survival (PFS), overall survival (OS), best overall response, and toxicity were evaluated under first-line FOFIRI plus bevacizumab or cetuximab treatment. PFS was defined as the time between treatment initiation and date of disease progression or death (whichever came first). OS was defined as the time between treatment initiation and date of all-cause death. The best overall response was defined as the best of all responses during first-line treatment. Computed tomography or magnetic resonance imaging were used to assess target and non-target lesions and to confirm the presence or absence of new lesions for best response evaluations. The Response Evaluation Criteria in Solid Tumor[17] were used to evaluate best responses, and toxicities were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03; http://ctep.cancer.gov/reporting/ctc.html).

In the Pan-Asian-adapted European Society for Medical Oncology consensus guidelines, recommendation 7a states that *DPD* testing before 5-FU administration remains an option but is not routinely recommended; recommendation 7b states that *UGT1A1* genotyping remains an option that is recommended for patients with a suspicion of *UGT1A1* deficiency due to low conjugated bilirubin or for patients where an irinotecan dose of >180 mg/m^2 is planned. Patients with a favorable *UGT1A1* genotype (homozygous wild-type [**1/*1*] and heterozygous [**1/*28*]) can be treated with high-dose irinotecan without significant AEs. However, detecting *UGT1A1*6* to adjust the irinotecan dose is not currently recommended.

Results

Between January 2018 and December 2020, 156 patients were diagnosed with mCRC at our hospital. Among them, seven (4.5%; four men and three women) were homozygous for the *UGT1A1*28* polymorphism and were enrolled into this observational study. The final analysis was performed during April 2022. At the cut-off time for analysis, the median follow-up duration was 29.0 months (range: 20.0–42.0 months).

The median patient age was 67.0 years (range: 55.0–77.0 years). The ECOG status of all seven enrolled patients was 1. Two patients had *RAS* mutations, and all had wild-type *BRAF*. Only three patients' MSI status was analyzed (Table 1). Five patients received FOLFIRI plus bevacizumab, whereas the other two received FOLFIRI plus cetuximab as first-line therapy. Only one enrolled patient needed to reduce the irinotecan dose to 100 mg/m^2 after one cycle of therapy due to grade III neutropenia; the others maintained the 120 mg/m^2 dose throughout the treatment course (Table 2).

Table 3 presents data on efficacy and AEs. Three patients were categorized as having partial responses (43%), and the disease control rate was 71.4%. The median PFS and OS were 11.0 months (Figure 1a) and 33.0 months (Figure 1b), respectively. AEs were divided into hematologic and non-hematologic events. For hematologic events, six anemia events (42.8%) occurred, but none were severe (grade III or higher). Seven neutropenia events (50.0%) occurred, but only one (7.1%) was severe (grade III). Only one grade I thrombocytopenia event (7.1%) was observed. No severe non-hematologic AEs occurred. Only two events of diarrhea were reported (7.7%, both grade I). Other non-hematologic events included fatigue, impaired renal function, alopecia, impaired liver function, nausea, oral mucositis, anorexia, and dermatitis. The non-hematologic AEs and grading for each patient are shown in Table 3.

Discussion

This observational study assessed real-world experiences of using a modified irinotecan dose in Asian mCRC patients homozygous for the *UGT1A1*28* polymorphism and receiving FOLFIRI plus bevacizumab or cetuximab. Our results demonstrated that an irinotecan dose of 120 mg/m^2 might be associated with a lower incidence of severe irinotecan-related toxicities in these patients but with comparable oncological outcomes.[18]

Identifying genetic variants that predispose patients to severe AEs of chemotherapeutic agents is critically important. Many studies have investigated the pharmacogenetic tailoring of irinotecan-based chemotherapy. Despite these efforts, the most reliable predictor of severe neutropenia remains the *UGT1A1*28/*28* genotype, which leads to lower SN-38G, greater exposure to SN-38, and an approximately two-fold greater risk of toxicity; this genotype can thus be used to identify patients who would benefit from reduced irinotecan doses.[19,20] Patients with a favorable genetic

Table 1. Demographic data of the seven enrolled *UGT1A1*28/*28* patients.

Case No.	Sex	Age (years)	ECOG performance status	*RAS* gene type	*BRAF* gene type	dMMR
1	Female	67	1	Mutated	Wild-type	NA
2	Male	60	1	Wild-type	Wild-type	NA
3	Male	64	1	Wild-type	Wild-type	MSS/MSI-L
4	Male	55	1	Wild-type	Wild-type	MSS/MSI-L
5	Female	77	1	Mutated	Wild-type	MSS/MSI-L
6	Male	72	1	Wild-type	Wild-type	NA
7	Female	69	1	Wild-type	Wild-type	NA

UGT1A1: UDP-glucuronosyltransferase 1A1; ECOG: eastern cooperative oncology group; dMMR: deficient mismatch repair; NA: non-analyzed.

Table 2. Clinical data of the seven enrolled *UGT1A1*28/*28* patients.

Case No	Primary site	mCRC type	Metastatic No.	Metastatic sites	TNM stage	First-line regimen	Initial irinotecan dose	Final irinotecan dose
1	Transverse colon	Metachronous	2	Liver; lungs	rycT3N0M1b	FOLFIRI + bevacizumab	120 mg/m^2	120 mg/m^2
2	Sigmoid colon	Synchronous	3	Spleen; lungs; peritoneum	cT4aN2bM1c	FOLFIRI + bevacizumab	120 mg/m^2	100 mg/m^2
3	Cecum	Synchronous	2	Peritoneum; Para-Aortic Lns	rycT3N1bM1c	FOLFIRI + bevacizumab	120 mg/m^2	120 mg/m^2
4	Sigmoid colon	Metachronous	1	Liver	rycT3N1aM1a	FOLFIRI + bevacizumab	120 mg/m^2	120 mg/m^2
5	Sigmoid colon	Synchronous	1	Para-aortic LNs	cT4aN1aM1a	FOLFIRI + bevacizumab	120 mg/m^2	120 mg/m^2
6	R-S junction	Metachronous	1	Para-aortic LNs	rycT3N2aM1a	FOLFIRI + Cetuximab	120 mg/m^2	120 mg/m^2
7	R-S junction	Synchronous	2	Liver; lungs	cT3N2bM1b	FOLFIRI + Cetuximab	120 mg/m^2	120 mg/m^2

mCRC: metastatic colorectal cancer; FOLFIRI: leucovorin + fluorouracil + irinotecan; R-S junction: rectosigmoid junction.

profile might benefit from an increased irinotecan dose to maximize antitumor activity.[21–24] The *UGT1A1*28* polymorphism is relatively rare in Asian populations.[9–11] Consistently, our data showed the incidence was 4.5% in our hospital, which is compatible with data from other Southeast Asian and Asia–Pacific populations (1.2%–5%).[10,11]

In 2005, the U.S. Food and Drug Administration revised the Dosage and Administration section on the irinotecan labeling as follows: "When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR (brand name of CPT-11) should be considered for patients known to be homozygous for the *UGT1A1*28* allele." However, the precise dose reduction in this population is not known.[14] In 2008, Liu *et al*. reported that an initial irinotecan dose of 180 mg/m^2 in 26 patients (20 with *UGT1A1*1/*28* and 6 with *UGT1A1*28/*28*) led to severe neutropenia in 53.8% and severe diarrhea in 26.9%.[18] Two studies have demonstrated that initial irinotecan doses of 150 mg/m^2 and 140 mg/m^2 in three and 12 patients, respectively, who were homozygous for *UGT1A1*28/*28* led to severe neutropenia in 100% and 28.6% of the patients, respectively.[8,14] By contrast, in this study, the incidence of severe neutropenia was only 7.1%, and no severe diarrhea was reported with an initial irinotecan dose of 120 mg/m^2. Hoskins *et al*. indicated that the risk of severe hematologic toxicity is higher among patients with the *UGT1A1*28/*28* genotype than among those with the *UGT1A1*1/*28* or *UGT1A1*1/*1* genotypes at medium (150–250 mg/m^2) or high (250–350 mg/m^2 or higher) irinotecan doses but not at lower doses (100–125 mg/m^2).[25] A 2022 prospective, multicenter, non-randomized study in the Netherlands had patients intended for treatment with irinotecan pretherapeutically genotyped for *UGT1A1*28*. Homozygous variant carriers (*UGT1A1*

Table 3. Efficacy and toxicity in the seven enrolled *UGT1A1*28/*28* patients.

Case No.	Best response	Progression-free survival	Overall survival	Survival	Hematologic AEs (grade)	Non-hematologic AEs (grade)
1	PD	4 months	28 months	yes	Anemia (II) Neutropenia (II)	Fatigue (I) Renal function impairment (I) Alopecia (I)
2	SD	20 months	20 months	yes	Anemia (II) Neutropenia (III)	Fatigue (I) Nausea (II) Renal function impairment (I)
3	SD	29 months	29 months	yes	Anemia (I) Neutropenia (I)	Fatigue (I) Nausea (I) Alopecia (I) Renal function impairment (I) Liver function impairment (II)
4	PR	8 months	40 months	yes	Neutropenia (II)	Nausea (I) Liver function impairment (I)
5	PR	28 months	28 months	yes	Anemia (II) Neutropenia (II) Thrombocytopenia (I)	Fatigue (I) Nausea (I) Alopecia (I) Diarrhea (I) Oral mucositis (I)
6	PD	5 months	29 months	no	Anemia (I) Neutropenia (I)	Fatigue (I) Nausea (I) Anorexia (I) Dermatitis (II)
7	PR	11 months	33 months	no	Anemia (II) Neutropenia (II)	Fatigue (II) Nausea (I) Diarrhea (I) Anorexia (I)

Best response: the best response on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1 during first-line treatment on 1st line setting; AEs: adverse events, graded as per the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.3; PD: progressive disease; SD: stable disease; PR: partial response.

poor metabolizers) were treated with an initial 30% dose reduction. This article demonstrated that *UGT1A1* genotype-guided dosing significantly reduces the incidence of febrile neutropenia in *UGT1A1* poor metabolizers treated with irinotecan, resulting in therapeutically effective systemic drug exposure that is ultimately cost-saving.[26] *UGT1A1* genotype-guided dosing of irinotecan should be considered the new standard-of-care to improve patient safety.

Whether dose reduction affects treatment outcomes should also be examined. Liu *et al.* claimed that although the need for an irinotecan dose reduction was significantly greater in patients who had the genetic variant, it did not affect the response rate to irinotecan-based

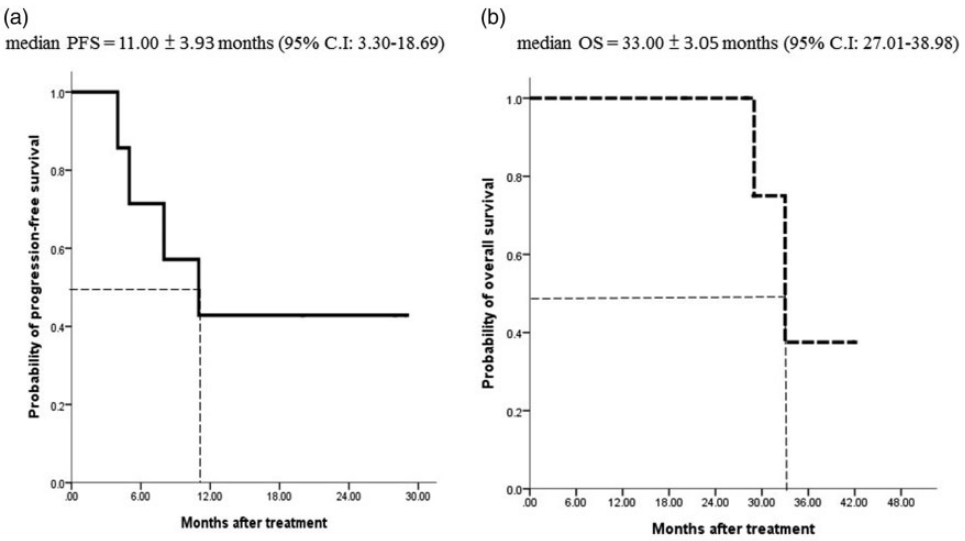

Figure 1. Cumulative survival rates of seven mCRC patients with a homozygous *UGT1A1*28* polymorphism using the Kaplan–Meier method. (a) The median progression-free survival was 11.0 months and (b) the median overall survival was 33.0 months.
UGT1A1: UDP-glucuronosyltransferase 1A1.

chemotherapy, PFS, or OS.[17] Thus, *UGT1A1*28* genotyping can be used to identify patients who require irinotecan dose reductions, which reduces dose-limiting neutropenia without affecting its efficacy.[13,27] However, Personeni *et al.* reported that a dose reduction did not prevent the onset of severe neutropenia in patients with gastrointestinal malignancies carrying the *UGT1A1*28/*28* genotype. They also concluded that there is a relationship between the percentage of drug reduction and neutropenia. Genetic testing is therefore indicated to identify the group of patients at higher risk of hematological toxicity.[28]

Several studies have addressed the issue of *UGT1A1* polymorphisms and initial irinotecan dose,[29,30] but most of these studies were conducted in Caucasian populations or had other limitations such as small numbers of patients with the rare variant alleles, retrospective design, or the inclusion of patients with various cancer types. This was also a retrospective study with a small number of patients due to the rare frequency of this genotype in Taiwan. Nevertheless, taking our data together with those of previous studies, we contend that irinotecan dose reduction is possible in mCRC patients with the *UGT1A1*28* polymorphism without affecting its efficacy.

In conclusion, the *UGT1A1*28* polymorphism may be a crucial determinant for irinotecan dose adjustment to reduce severe AEs in Taiwanese mCRC patients without affecting oncological outcomes. Patients homozygous for *UGT1A1*28* should receive irinotecan at an initial dose of 120 mg/m^2, and the dose may be further individualized depending on the frequency and severity of AEs. In case of no toxicity occurring, irinotecan may also be titrated upwards. Further prospective studies are warranted to optimize irinotecan-based chemotherapy to avoid life-threatening toxicity and maximize efficacy in mCRC patients.

Availability of data and materials

All authors had access to the primary data.

Author contributions

Hsiang-Lin Tsai and Jaw-Yuan Wang performed the studies and drafted the manuscript. Po-Jung Chen, Yeh-Cheng Chen, Ching-Chun Li, Tsung-Kun Chang, Wei-Chih SU, and Ching-Wen Huang participated in data collection. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors report no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors express our gratitude to the following groups or institutions: the Ministry of Science and Technology (MOST 109-2314-B-037-035, MOST 109-2314-B-037-040, MOST 109-2314-B-037-046-MY3) and the Ministry of Health and Welfare (MOHW109-TDU-B-212-134026, MOHW109-TDU-B-212-114006, MOH W110-TDU-B-212-1140026); funding was also granted by the health and welfare surcharge of on tobacco products, and the Kaohsiung Medical University Hospital (KMUH109-9R32, KMUH109-9R33, KMUH109-9R34, KMUH109-9M30, KMUH109-9M31, KMUH 109-9M32, KMUH109-9M33, KMUHS10903, KMUHSA10903, KMUH-DK(C)110010, KMUH-DK(B)110004-3) and KMU Center for Cancer Research (KMU-TC109A04-1) as well as a KMU Center for Liquid Biopsy and Cohort Research Center Grant (KMU-TC109B05), Kaohsiung Medical University. In addition, this study was supported by the Grant of Taiwan Precision Medicine Initiative, Academia Sinica, Taiwan, R.O.C.

ORCID iD

Jaw-Yuan Wang https://orcid.org/0000-0001-6218-3760

References

1. Gagne JF, Montminy V, Belanger P, et al. Common human *UGT1A* polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). *Mol Pharmacol* 2002; 62: 608–617.
2. Cecchin E, Innocenti F, D'Andrea M, et al. Predictive role of *UGT1A1*, *UGT1A7*, and *UGT1A9* genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. *J Clin Oncol* 2009; 27: 2457–2465.
3. Nagar S and Blanchard RL. Pharmacogenetics of uridine diphosphoglucuronosyltransferase (UTG) 1A family members and its role in patient response to irinotecan. *Drug Metab Rev* 2006; 38: 393–409.
4. Toffoli G, Cecchin E, Corona G, et al. The role of *UGT1A1*28* polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; 24: 3061–3068.
5. Hu ZY, Yu Q, Pei Q, et al. Dose-dependent association between *UGT1A1*28* genotype and irinotecan-induced neutropenia: low doses also increase risk. *Clin Cancer Res* 2010; 16: 3832–3842.
6. Hu ZY, Yu Q and Zhao YS. Dose-dependent association between *UGT1A1*28* polymorphism and irinotecan-induced diarrhea: a meta-analysis. *Eur J Cancer* 2010; 46: 1856–1865.
7. Martinez-Balibrea E, Abad A, Martinez-Cardus A, et al. *UGT1A* and *TYMS* genetic variants predict toxicity and response of colorectal cancer patients treated with first-line irinotecan and fluorouracil combination therapy. *Br J Cancer* 2010; 103: 581–589.
8. Satoh T, Ura T, Yamada Y, et al. Genotype-directed, dose-finding study of irinotecan in cancer patients with *UGT1A1*28* and/or *UGT1A1*6* polymorphisms. *Cancer Sci* 2011; 102: 1868–1873.
9. Yong WP, Innocenti F and Ratani MJ. The role of pharmacogenetics in cancer therapeutics. *Br J Clin Pharmacol* 2006; 62: 35–46.

10. Premawardhena A, Fisher CA, Liu YT, et al. The global distribution of length polymorphisms of the promoters of the glucuronosyltransferase 1 gene (*UGT1A1*): hematologic and evolutionary implications. *Blood Cells Mol Dis* 2003; 31: 98–101.
11. Huang CS, Luo GA, Huang ML, et al. Variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwan. *Pharmacogenetics* 2000; 10: 539–544.
12. Negoro S, Fukuoka M, Masuda N, et al. Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1991; 83: 1164–1168.
13. Tsai HL, Huang CW, Lin YW, et al. Determination of the *UGT1A1* polymorphism as guidance for irinotecan dose escalation in metastatic colorectal cancer treated with first-line bevacizumab and FOLFIRI (PURE FIST). *Eur J Cancer* 2020; 138: 19–29.
14. Miyata Y, Touyama T, Kusumi T, et al. UDP-glucuronosyltransferase 1A1*6 and *28 polymorphisms as indicators of initial dose level of irinotecan to reduce risk of neutropenia in patients receiving FOLFIRI for colorectal cancer. *Int Clin Oncol* 2016; 21: 696–703.
15. Lu CY, Huang CW, Wu IC, et al. Clinical implication of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab combined with FOLFIRI in the first-line setting. *Transl Oncol* 2015; 8: 474–479.
16. Gagnier JJ, Kienle G, Altman DG, et al; CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92: 205–216.
18. Liu CY, Chen PM, Chiou TJ, et al. *UGT1A1*28* polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal cancer. *Cancer* 2008; 112: 1932–1940.
19. Barbarino JM, Haidar CE, Klein TE, et al. PharmGKB summary: very important pharmacogene information for *UGT1A1*. *Pharmacogenet Genomics* 2014; 24: 177–183.
20. Chen S, Laverdiere I, Tourancheau A, et al. A novel *UGT1* marker associated with better tolerance against irinotecan-induced severe neutropenia in metastatic colorectal cancer patients. *Pharmacogenpmics J* 2015; 15: 513–520.
21. 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: 2328–2334.
22. Marcuello E, Paez D, Pare L, et al. A genotype-directed phase I–IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer. *Br J Cancer* 2011; 105: 53–57.
23. Toffoli G, Cecchin E, Gasparini G, et al. Genotype-driven phase I study of irinotecan administrated in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer. *J Clin Oncol* 2010; 28: 866–871.
24. Hsieh YC, Chang TK, Su WC, et al. *UGT1A1* polymorphism for irinotecan dose escalation in patients with BRAF-mutated metastatic colorectal cancer treated with first-line bevacizumab and FOLFIRI. *J Oncol* 2021; 2021: 6686517.
25. Hoskins JM, Marcuello E, Altes A, et al. Irinotecan pharmacogenetics: influence pf pharmacodynamic genes. *Clin Cancer Res* 2008; 14: 1788–1796.
26. Hulshof EC, De With M, De Man FM, et al. *UGT1A1* genotype-guided dosing of irinotecan: a prospective safety and cost analysis in poor metaboliser patients. *Eur J Cancer* 2022; 162: 148–157.

27. Berg AO, Armstrong K, Botkin J, et al. Recommendations from the EGAPP working group: can *UGT1A1* genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? *Genet Med* 2009; 11: 15–20.
28. Personeni N, Giordano L, Michelini A, et al. Implementing pre-therapeutic UGT1A1 genotyping in clinical practice: a real-life study. *J Pers Med* 2022; 12: 204. https://doi.org/10.3390/jpm12020204.
29. Ando Y, Saka H, Ando M, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res* 2000; 60: 6921–6926.
30. Sai K, Saeki M, Saito Y, et al. *UGT1A1* haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administrated Japanese patients with cancer. *Clin Pharmacol Ther* 2004; 76: 501–515.