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

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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/m².
Results: Six of the seven patients tolerated 120 mg/m² 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/m² 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

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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). Numerous studies have examined associations between alleles of these genes and severe irinotecan toxicities, particularly diarrhea and neutropenia. The polymorphism UGT1A1*28 has been associated with severe irinotecan-induced diarrhea and neutropenia; 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). 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. A previous dose-finding study suggested that the recommended irinotecan dose of 180 mg/m² in the FOLFIRI regimen was low for mCRC patients with the UGT1A1*1/*1 or UGT1A1*28/*1 genotypes. In contrast, the 180 mg/m² dose has been shown to be too high in patients harboring homozygous UGT1A1*28 alleles, and the dose reduction should be approximately 20%. In our previous study, we demonstrated that the maximum tolerated irinotecan dose in mCRC patients with the homozygous UGT1A1*28 allele was 120 mg/m². 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/m². 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/m², as mentioned in our previous study. If grade 3/4 adverse events (AEs) occurred, the irinotecan dose was decreased to 100 mg/m², 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.

The reporting of this study conforms to the CARE guidelines. 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 FOLFIRI 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 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/m² 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/m² after one cycle of therapy due to grade III neutropenia; the others maintained the 120 mg/m² 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/m² 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

| Case No. | Sex   | Age (years) | ECOG performance | 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     | NA     |
| 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.
profile might benefit from an increased irinotecan dose to maximize antitumor activity.\textsuperscript{21–24} The \textit{UGT1A1*28} polymorphism is relatively rare in Asian populations.\textsuperscript{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\%).\textsuperscript{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 \textit{UGT1A1*28} allele.” However, the precise dose reduction in this population is not known.\textsuperscript{14} In 2008, Liu \textit{et al.} reported that an initial irinotecan dose of 180 mg/m\textsuperscript{2} in 26 patients (20 with \textit{UGT1A1*1/*28} and 6 with \textit{UGT1A1*28/*28}) led to severe neutropenia in 53.8\% and severe diarrhea in 26.9\%.\textsuperscript{18} Two studies have demonstrated that initial irinotecan doses of 150 mg/m\textsuperscript{2} and 140 mg/m\textsuperscript{2} in three and 12 patients, respectively, who were homozygous for \textit{UGT1A1*28/*28} led to severe neutropenia in 100\% and 28.6\% of the patients, respectively.\textsuperscript{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\textsuperscript{2}. Hoskins \textit{et al.} indicated that the risk of severe hematologic toxicity is higher among patients with the \textit{UGT1A1*28/*28} genotype than among those with the \textit{UGT1A1*1/*28} or \textit{UGT1A1*1/*1} genotypes at medium (150–250 mg/m\textsuperscript{2}) or high (250–350 mg/m\textsuperscript{2} or higher) irinotecan doses but not at lower doses (100–125 mg/m\textsuperscript{2}).\textsuperscript{25} A 2022 prospective, multicenter, non-randomized study in the Netherlands had patients intended for treatment with irinotecan pretherapeutically genotyped for \textit{UGT1A1*28}. Homozygous variant carriers (\textit{UGT1A1*28/*28}) attended and received an irinotecan dose of 120 mg/m\textsuperscript{2} as the starting dose, which was not associated with severe neutropenia or severe diarrhea.

### Table 2: Clinical data of the seven enrolled \textit{UGT1A1*28/*28} patients.

| Case No | Primary site | mCRC type | Metastatic sites | First-line regimen | Initial irinotecan dose | Final irinotecan dose |
|---------|--------------|-----------|------------------|--------------------|-----------------------|----------------------|
| 1       | Transverse colon | Metachronous | Liver; lungs | FOLFIRI + bevacizumab | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |
| 2       | Sigmoid colon | Synchronous | Liver; peritoneum; Para-Aortic Lns | FOLFIRI + bevacizumab | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |
| 3       | Cecum | Synchronous | Peritoneum; Para-Aortic Lns | FOLFIRI + bevacizumab | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |
| 4       | Sigmoid colon | Metachronous | Liver | FOLFIRI | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |
| 5       | Sigmoid colon | Synchronous | Para-Aortic LNs | FOLFIRI + Cetuximab | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |
| 6       | R-S junction | Metachronous | Para-Aortic LNs | FOLFIRI + leucovorin + fluorouracil + irinotecan | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |
| 7       | R-S junction | Synchronous | Liver; lungs | FOLFIRI + Cetuximab | 120 mg/m\textsuperscript{2} | 120 mg/m\textsuperscript{2} |

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

| Case No. | Best response | Progression-free survival | Overall survival | Hematologic AEs (grade) | Non-hematologic AEs (grade) |
|----------|---------------|---------------------------|-----------------|------------------------|-----------------------------|
| 1        | PD            | 4 months                  | 28 months       | Anemia (II) Neutropenia (II) | Anemia (II) Neutropenia (II) |
| 2        | SD            | 20 months                 | 20 months       | Anemia (II) Neutropenia (III) | Fatigue (I) Nausea (II) |
| 3        | SD            | 29 months                 | 29 months       | Anemia (I) Neutropenia (I) | Fatigue (I) Nausea (I) |
| 4        | PR            | 8 months                  | 40 months       | Neutropenia (II) | Fatigue (I) Nausea (I) |
| 5        | PR            | 28 months                 | 28 months       | Anemia (II) Neutropenia (II) Thrombocytopenia (I) | Fatigue (I) Nausea (I) |
| 6        | PD            | 5 months                  | 29 months       | Anemia (I) Neutropenia (I) | Fatigue (I) Nausea (I) |
| 7        | PR            | 11 months                 | 33 months       | Anemia (II) Neutropenia (II) | Fatigue (II) Nausea (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.
chemotherapy, PFS, or OS. Thus, UGT1A1*28 genotyping can be used to identify patients who require irinotecan dose reductions, which reduces dose-limiting neutropenia without affecting its efficacy. 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.

Several studies have addressed the issue of UGT1A1 polymorphisms and initial irinotecan dose, 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/m², 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.

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.
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.

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