**UGT1A1 Allele Test Not Only Minimizes the Toxicity But Also Maximizes the Therapeutic Effect of Irinotecan in the Treatment of Colorectal Cancer: A Narrative Review**

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**Background:** Irinotecan is a first-line agent in the systematic treatment of colorectal cancer (CRC). Adjusting the dose of irinotecan according to the uridine diphosphate glucuronosyltransferase (UGT) 1A1 genotype reflects the principle of individualized and precision medicine, and may improve the chemotherapy response and survival of CRC.

**Methods:** To summarize the feasibility, efficacy and safety of high dose irinotecan in CRC patients with UGT1A1 wild-type or heterozygous alleles, PubMed, EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials online databases were searched from the date of creation to October 22, 2021.

**Results:** A total of 1,186 related literatures were searched, and 14 studies were included for review according to the inclusion criteria. The results indicated that the maximum tolerated dose of irinotecan in CRC patients with UGT1A1 wild-type or heterozygous variant was significantly higher than the conventional recommended dose. Chemotherapy based on high dose irinotecan improved the clinical efficacy in mCRC patients with UGT1A1*28 wild-type and heterozygous variant, and the toxicity was tolerated, as reflected in most studies.

**Conclusions:** We are optimistic about the application of high dose irinotecan for mCRC patients with UGT1A1*28 wild-type or heterozygous variant, which will provide a relatively clear direction for future research and certain norms for clinical practice.

**Keywords:** UGT1A1, irinotecan, colorectal cancer, systematic review, precision medicine

**INTRODUCTION**

With high morbidity and mortality, colorectal cancer (CRC) is still one of the major diseases threatening human health (1, 2). In 2020, the global incidence of CRC was about 1.88 million, ranking third in the incidence of common cancer, with more than 900 thousand deaths, making it the second leading cause of cancer deaths (3). In the new diagnosis of CRC, 20% of patients have
metastatic disease, and the other 25% of patients with local disease will have metastasis later (4). Irinotecan is one of the first-line agents in the systematic therapy of metastatic colorectal cancer (mCRC) (5), but its high toxicity, including severe neutropenia and diarrhea (6), has become the focus of concern in clinical use.

In recent years, the potential of pharmacogenetics in the treatment of malignant tumors has been fully reflected, which provides strong guidance for the rational application of antitumor drugs (7). Uridine diphosphate glucuronosyltransferase (UGT) 1A1 is a key enzyme for metabolism of the active metabolite SN-38 (8) of irinotecan. Studies have confirmed that UGT1A1 gene polymorphism, with defective alleles *28 and *6 as research hotspots, affects the metabolism of irinotecan and enhances its toxicity (9–11). In clinical practice, it has been agreed to reduce the dose of irinotecan in individuals homozygous and double heterozygous mutations for UGT1A1 *28 or *6 alleles (*28/*28 or *6/*6 or *6/*28) to minimize their toxicity (12), but such treatment may be associated with poorer survival (13, 14).

Compared with patients with UGT1A1 homozygous defect, patients with wild-type or heterozygous alleles are more efficient in metabolizing SN-38, which indicates that they may be able to tolerate the treatment of irinotecan beyond the conventional dose, resulting in better clinical outcomes. However, there seems to be no consensus on the dosage of irinotecan in patients with UGT1A1 wild-type (*1/*1) or heterozygous alleles (such as *1/*28 or *1/*6) (15, 16). In the context of precision and personalized medicine, this is a more reasonable hypothesis. In this study, we systematically reviewed the use of high dose irinotecan in mCRC patients with UGT1A1 wild-type or heterozygous variant to determine whether this was feasible and brought good clinical benefits and acceptable toxicity.

**METHODS**

**Search Strategy**

We systematically searched PubMed, EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) online databases for the period from the time of their inception to October 22, 2021. We targeted studies that selected irinotecan doses in mCRC patients based on UGT1A1 genotype, without restrictions related to region, age or gender. We used Medical Subject Heading (MeSH) terms in PubMed, MEDLINE and CENTRAL, EMTREE terms in EMBASE. We performed keyword searches in the above four databases, and exploded them in EMBASE, MEDLINE, and CENTRAL. The search strategy is provided in the Appendix.

**Inclusion and Exclusion Criteria**

The pieces of literature that met the inclusion criteria were those clinical studies that used higher dose of irinotecan in mCRC patients with UGT1A1 wild-type or heterozygous variant and identified specific doses and outcomes for different genotypes. The exclusion criteria include: 1. Only different genotypes results of UGT1A1 in the population were mentioned, but treatment results were not listed according to genotypes; 2. The sample size of the study was <10; 3. The specific dose of irinotecan in different genotypes of UGT1A1 was not clear or the dose in each genotype was not uniform in the retrospective study; 4. The study only reflected the predictive function of UGT1A1 polymorphism on irinotecan toxicity, and there was no specific dosage record; and 5. The study was on the toxicity or therapeutic responses of conventional doses of irinotecan.

**Study Selection and Data Collection**

We used the search strategy described above to obtain relevant studies, and then selected pieces of literature based on the inclusion and exclusion criteria. Firstly, we performed a preliminary screening by using the title and abstract of a study to exclude obviously unrelated literature. Then, we downloaded the full text of the candidate papers, and finally the clinical studies of high dose irinotecan in the treatment for mCRC patients with UGT1A1 wild-type or heterozygous variant were selected in strict accordance with the screening criteria. Two reviewers independently completed the above screening. For any discrepancy, all reviewers negotiated to reach a consensus.

Two independent reviewers used the data extraction table tested in a pilot study to extract data. If necessary, all reviewers jointly decided whether to include the data. For each included study, the main data extracted were author, year of publication, tumor stage, number of evaluable cases, treatment, recruitment period, duration of follow-up and outcome. The main outcomes included the maximum tolerated dose (MTD) of irinotecan and the therapeutic efficacy and toxicity of high dose irinotecan in mCRC patients with target genotypes. We have excluded data that were not clearly reflected in the papers.

**Data Analysis**

Detailed meta-analysis was not possible due to the wide variation in the included studies. Therefore, a descriptive approach was used to summarize the data.

**RESULTS**

From the four databases, we obtained 1,186 relevant literatures. The software excluded 342 duplicates, and we identified 784 apparently unrelated studies by viewing the title and abstract. The full text was reviewed for the remaining 60 pieces of literature, excluding reviews, pieces of literature with repeated contents, and studies with unclear or low dose of irinotecan in mCRC patients with target genotypes. Finally, 14 studies were included for systematic review and summary analysis (Figure 1).

The included studies, from a variety of countries and ethnicities, mainly reflected the MTD of irinotecan in mCRC patients with UGT1A1 wild-type or heterozygous variant, and the chemotherapy response, survival, and toxicity in patients with target genotypes treated with high dose irinotecan.
MTD of Irinotecan in mCRC Patients With UGT1A1 Wild-Type or Heterozygous Variant

Five phase I clinical trials in Asia, Europe and the United States specifically described the MTD of irinotecan in mCRC patients with UGT1A1 wild-type and heterozygous variant (Table 1) (17–21). UGT1A1 heterozygous variant in two studies from Asian populations included *1/*28 or *1/*6 (19, 20), and the other three studies only included genotype *1/*28 (17, 18, 21). In these five studies, the definition of dose limiting toxicity (DLT) was the same, i.e., hematologic grade 4 toxicity or nonhematologic grade 3 to 4 toxicity, but the definition of MTD generated from DLT was slightly different. The definition of recommended dose in two studies was closer to the conventional definition of MTD (19, 20). Therefore, we proposed to replace MTD with the recommended dose in these two studies.

In general, in the two-week regime of irinotecan combined with 5-FU and leucovorin (FOLFIRI) (17, 18, 20, 21), the MTD of irinotecan in mCRC patients with UGT1A1 wild-type and heterozygous variant was at least greater than 260 mg/m², which was significantly higher than the clinical routine dose of 180 mg/m². In this study, 260 mg/m² was used as the high dose cutoff value of irinotecan in FOLFIRI. Even the combination of biological agent bevacizumab did not change the pharmacokinetics of irinotecan, and its MTD was not significantly affected in the regimen of FOLFIRI combined with bevacizumab (21). In the three-week regimen combined with capcitabine, it was suggested that the TMD of irinotecan in mCRC patients with UGT1A1 wild-type and heterozygous variant was 350 mg/m², which was also significantly higher than the clinical routine dose (22).

Outcome of High Dose Irinotecan in mCRC Patients With UGT1A1 Wild-Type or Heterozygous Variant

There were five single-arm (23–27) trials and four double-arm trials (28–31) on the application of FOLFIRI regimen containing high dose irinotecan under the guidance of genotypes in mCRC patients with UGT1A1 *1/*1 or *1/*28. The characteristics and results of these studies are shown in Tables 2, 3, respectively. The dose of irinotecan was progressively escalated in some studies, and in others the initial dose was ≥260 mg/m².

Single-Arm Trials Results

In the single-arm trials, three studies from Europe directly used high dose irinotecan according to the guidance of UGT1A1 genotypes (23, 25, 26), while two studies from Asia used the dose escalation of irinotecan (24, 27).
TABLE 1 | MTD of irinotecan in mCRC patients with UGT1A1 wild-type or heterozygous variant.

| Source            | Country | Tumor stage | No. of person | Treatment                                                                 | Judgment criteria                                                                 | Outcome |
|-------------------|---------|-------------|---------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------|
| Toffoli et al. (27) | Italy and US | mCRC       | *1/*1; 35; *1/*28, 24 | Dose adjusted irinotecan, day 1; leucovorin, 200 mg/m²; day 1; 5-FU at 400 mg/m² bolus injection, day 1, followed by 2,400 mg/m² infusion. | DLT was defined as hematologic grade 4 toxicity or nonhematologic grade 3–4 toxicity. MTD was defined as the highest dose at which fewer than 2 of 10 patients experienced DLT. | The MTD was 370 mg/m² for *1/*1 patients and 310 mg/m² for *1/*28 patients |
| Marcuello et al. (28) | Spain  | White mCRC or a locally advanced recurrence after surgery | *1/*1, 42; *1/*28, 38; *28/*28, 14 | Dose adjusted irinotecan, day 1; leucovorin, 200 mg/m²; day 1; 5-FU at 400 mg/m² bolus injection, day 1, followed by 600 mg/m²/day×2 days infusion. Repeat every 2 weeks | DLT was defined as hematologic grade 4 toxicity or nonhematologic grade 3–4 toxicity. If 2 out of 3 or 2 out of 6 patients experienced DLT, the level below was considered MTD. | The MTD was 390 mg/m² for *1/*1 patients and 340 mg/m² for *1/*28 patients and 130 mg/m² for *28/*28 patients |
| Kim et al. (18) | Korea | mCRC | 0 DA group: *1/*1; *1/*1; 23; 1 DA group: *1/*28 or *1/*6; 20; 2 DA group: *28/*28, 19; 2 DA group: *1/*28, 20; 2 DA group: *28/*28, 20 | Dose adjusted irinotecan plus capecitabine (2,000 mg/m² days 2–15). Repeat every 3 weeks | DLT was defined as hematologic grade 4 toxicity or nonhematologic grade 3–4 toxicity. The recommended dose was defined as the level below this cutoff. | The recommended dose was 350 mg/m², 350 mg/m² and 200 mg/m² for 0, 1, 2 DA group patients, respectively |
| Kim et al. (20) | Korea | mCRC | 0 DA group: *1/*1; 19; 1 DA group: *1/*28 or *1/*6; 20; 2 DA group: *28/*28, 4; 2 DA group: *28/*6, 4 | Leucovorin, 200 mg²/m; day 1; 5-FU at 400 mg/m² bolus injection, day 1, continuous infusion of 2,400 mg/m² for 46 h, followed by dose adjusted irinotecan. Repeat every 2 weeks | DLT was defined as hematologic grade 4 toxicity or nonhematologic grade 3–4 toxicity. MTD was defined as the dose level at which 2 or more of the 3–6 patients developed DLTS. The recommended dose was defined as 1 dose level under the MTD. | The recommended dose was 300, 270, 150 mg²/m² for 0, 1, 2 DA group patients, respectively |
| Toffoli et al. (23) | US and Italy | Previously untreated mCRC | *1/*1; 25; *1/*28, 23 | Dose adjusted irinotecan, day 1; leucovorin, 200 mg²/m²; day 1; 5-FU at 400 mg/m² bolus injection, day 1, followed by 2,400 mg/m² infusion for 46 h; bevacizumab 5 mg/kg, day 1. Repeat every 2 weeks | DLT was defined as hematologic grade 4 toxicity or nonhematologic grade 3–4 toxicity. MTD was defined as the highest dose at which less than 4 of 10 patients had a DLT. | The MTD was 310 mg/m² for *1/*1 patients and 260 mg/m² for *1/*28 patients |

mCRC, metastatic colorectal cancer; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; DA, defective allele.

A prospective study was about high dose FOLFIRI (260 mg/m²) combined with local surgery and radiofrequency ablation for the unresectable liver metastases from CRC patients with UGT1A1 *1/*1 or *1/*28 (23). Due to insufficient recruitment, the trial was terminated early. The evaluable results showed good objective response rate (ORR), disease control rate (DCR), high complete clearance rate, promising survival and excellent safety.

Three studies focused on high dose FOLFIRI in combination with biologics for mCRC. One of these, direct high dose FOLFIRI plus bevacizumab, was prematurely terminated due to the high incidence of overly strict toxicity events specified in the trial protocol, leading to a possible outcome bias (25). The other two studies were dose-escalating FOLFIRI combined with bevacizumab (24) and direct high dose FOLFIRI combined with cetuximab (26) based on UGT1A1 genotypes, including, UGT1A1 homozygous variant (*28/*28). The results suggested that high dose FOLFIRI combined with biological agents can have good chemotherapy response rate, survival and tolerable toxicity in mCRC with UGT1A1 wild-type and heterozygous variant.

Another trial of dose-escalating FOLFIRI in combination with regorafenib based on UGT1A1 genotypes, as a non-first-line treatment for mCRC, also demonstrated a tolerable toxicity associated with irinotecan and an effective clinical outcome that can improve survival (27).

Double-Arm Trials Results
In the double-arm trials, both retrospective and prospective studies demonstrated similar safety and no significant difference in toxicity between high dose and routine dose FOLFIRI based on UGT1A1 genotypes in mCRC.

In the two retrospective studies, the treatment was FOLFIRI combined with bevacizumab. In the high dose group of mCRC with UGT1A1 *1/*1 or *1/*28, the dose of irinotecan was gradually increased to or close to 260 mg/m², while the dose of irinotecan in the routine dose group remained at 180 mg/m². One of the studies showed statistically significant improvements in chemotherapy response (p = 0.028) and progression-free survival (PFS) (p = 0.025) in the high dose group over the routine dose group (28). In another small sample study of mCRC with BRAF mutation, although the high dose group showed an advantage in survival, there was not statistically significant difference (31).

A multicenter, open-label randomized trial from Europe (29) showed that in mCRC with UGT1A1 *1/*1 or *1/*28, high dose FOLFIRI group (irinotecan doses was 300 mg/m² for *1/*1 and 260 mg/m² for *1/*28) had a significant advantage in chemotherapy response (p = 0.001). The survival was also better than that in the routine dose group, but was not statistically significant.

In a multicenter, open-label randomized controlled trial from Asia (30), the high dose group was treated with dose-escalating FOLFIRI combined with bevacizumab for mCRC and the maximal dose of irinotecan was 260, 240, and 180 mg/m² for UGT1A1 *1/*1, *1/*28.
**DISCUSSION**

Previous systematic review suggested that for low dose irinotecan, the absolute risk of toxicity in patients with **U****G**T1A1 *+28/*+28 genotype is similar to the overall risk of all patients. However, moderate and high dose irinotecan increased the absolute risk of toxicity (32, 33), suggesting the tolerance of patients with **U****G**T1A1 wild-type or heterozygous variant to high dose of irinotecan. With conventional dose of irinotecan, the chemotherapy response rate and survival of patients with **U****G**T1A1 *+1/*1 was worse than that of patients with **U****G**T1A1 *+28/*+28 (34–36), which was associated with the higher glucuronidation rate of SN38 (34). Therefore, in order to improve the response rate and even survival of chemotherapy based on irinotecan in patients with **U****G**T1A1 wild-type or heterozygous variant, it is necessary to reasonably increase the **TABLE 2 | Single-arm Trials of High dose Irinotecan based Regimen in mCRC.**

| Source                  | Region  | Study type  | Tumor stage                | No. of person | Treatment | Chemotherapy response | Survival time | Toxicity |
|-------------------------|---------|-------------|-----------------------------|---------------|-----------|-----------------------|--------------|----------|
| Hebbar et al. (23)      | Europe  | Prospective | mCRC with metastases       | *1/*1 and *1/*28, 18 | HD-FOLFIRI (irinotecan, 260 mg/m²), every 2 weeks. Every local chemotherapy was assessed every 4 cycles of chemotherapy | PR, 6 (44%); SD, 6 (33.3%); DCR, 14 (77.3%); PD, 4 (22%). Local treatment was performed in 6 patients and all were complete clearance | PFS, 15.3 m; OS, 33.7 m | No grade 4 toxicity, and grade 3, 3 times |
| Lu et al. (24)          | Asia    | Retrospective | mCRC                        | *1/*1, *1/*28, 26, 5 | Bevacizumab plus FOLFIRI, every 2 weeks. Starting dose of irinotecan, 180 mg/m² for Group 1 and 120 mg/m² for Group 2. If toxicity ≥ grade 3, the dose was escalated to 20 to 30 mg/m² every 2 cycles. The maximal dose was 260, 240, and 210 mg/m² for *1/*1, *1/*28 and *28/*28, respectively | Group 1: CR + PR, 50 (76.9%); SD, 11 (16.9%); DCR, 61 (93.8%); PD, 4 (6.2%); Group 2: CR + PR, 1 (20%); SD, 1 (20%); DCR, 2 (40%); PD, 3 (60%) | PFS was significantly different for the different U**G**T1A1 genotypes (P = 0.002), and the first Group 1 was longer | Group 1, 4 patients; Group 2, 3 patients |
| Manfredi et al. (25)    | Europe  | Prospective | mCRC that had not previously been treated | *1/*1, 40; *1/*28, 46 | Bevacizumab plus FOLFIRI, and the dose of irinotecan was 260 mg/m². The treatment was stopped in the event of patient withdrawal, disease progression, or unacceptable toxic effects | ORR: *1/*1, 18 (45%); *1/*28, 26 (56.5%) | PFS: *1/*1, 10.7 m; *1/*28, 10.4 m; OS: *1/*1, 25.5 m; *1/*28, 23.9 m | *1/*1, 30 and *1/*28, 37 exhibited at least one grade 3–4 toxicity |
| Phelps et al. (26)      | Europe  | Prospective | mCRC with initially borderline-resectable liver metastases, no more than 2 potentially resectable extrahepatic metastases, and KRAS status is wild-type | *1/*1, 9; *1/*28, 14; *1/*28, 3 | High dose FOLFIRI (irinotecan 220 mg/m² for *28/*28, and 260 mg/m² for *1/*1 and *1/*28 plus cetuximab. Treatment was carried out for 6 cycles in the absence of disease progression or unacceptable toxicity. In cases of objective response and disease that remained unresectable, 2 more cycles were permitted. 23 patients received at least 6 cycles, of which 4 received 8 cycles | The overall cumulative ORR at 8 cycles was 76.9% (20/26), no PD. Among the 23 patients who received at least 6 cycles, the ORR was 82.6%, metastasectomy, 21 (80.7%) | PFS, 15.8 m, 3-year OS was 23.3%; OS was not reached and 3-year OS was 66.1%. Among 21 resected patients, 18 (85.7%) had a relapse, with a median relapse-free survival of 15.3 m | Grade 3–4 toxicity: neutropenia (31%), diarrea (20.8%), anorexia (16.4%). No deaths due to toxicity |
| Ma et al. (27)          | Asia    | Prospective | mCRC who were previously treated with FOLFIRI, anti-VEGFR, or anti-EGFR if KRAS was wild-type | *1/*1, 12; *1/*28, 0; FOLFIRI, anti-VEGFR, or anti-EGFR if KRAS | Regorafenib plus FOLFIRI with irinotecan dose escalation (starting dose was 180 mg/m² for *28/*28 and 120 mg/m² for *1/*28 and *1/*28 plus cetuximab. The dose was increased by 30 mg/m² every 2 cycles until grade ≥3 AEs. The highest prescribed irinotecan dose was 290 mg/m² for *28/*28 | PR, 2 (15.4%); SD, 7 (53.8%); DCR, 69.2% (30.8%); PD, 4 (30.8%) | PFS, 9.5 m (95% CI: 3.0–16.0); OS, 13.0 m (95% CI: 7.2–18.8) | Grade ≥3: AE: hand–foot syndrome, 8; mucositis, 5; neutropenia, 4; diarrhea, 4; fatigue, 3 |

mCRC, metastatic colorectal cancer; CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease; DCR, disease control rate; PD, progressive disease; PFS, progression-free survival; OS, overall survival; AE, adverse event; FOLFIRI, Oxaliplatin combined with 5-FU and leucovorin; FOLFIRI, irinotecan combined with 5-FU and leucovorin; VEGFR, vascular epithelial growth factor receptor; EGFR, epidermal growth factor receptor; CI, confidence interval.

*1/*28, and *28/*28, respectively. The dose of irinotecan in the routine dose group remained at 180 mg/m² without **U****G**T1A1 test. Compared with the routine dose group, the high dose group showed significant advantages in chemotherapy response (ORR, P < 0.001; DCR, p = 0.007; metastasectomy, p = 0.007) and survival (PFS, P < 0.001; OS, P = 0.02).
dose of irinotecan on the premise of tolerable toxicity. The results of this systematic review basically confirm this hypothesis.

The studies finally included in this systematic review have been carried out in the past decade, from the exploration of the MTD of irinotecan in CRC patients with UGTA1A wild-type and heterozygous variant in the early stage, to the single-arm study of the therapeutic effect of high dose irinotecan on target patient heterozygous variant in the early stage, to the single-arm study been re-

**TABLE 3 | Double-arm Trials of High dose Irinotecan based Regimen in mCRC.**

| Source          | Region | Study type          | Tumor stage | No. of person | Treatment                                                                 | Chemotherapy response | Survival time | Toxicity |
|-----------------|--------|---------------------|-------------|---------------|---------------------------------------------------------------------------|------------------------|--------------|----------|
| Lu et al. (29)  | Asia   | Retrospective       | mCRC, 79;   | HDG, RDG, 28  | Bevacizumab plus FOLFIRI. Starting dose of irinotecan, 180 mg/m² for 1/1/1 and 1/1/28, 120 mg/m² for 28/28 in HDG. If toxicity grade 3, the dose was escalated by 30 mg/m². The maximal dose was 260, 240, 210 mg/m² for 1/1, 1/1/28, and 28/28, respectively. The dose of RDG was 180 mg/m² | ORR, 55 (69.6%) and 13 (46.4%); SD + PD, 24 (30.4%) and 15 (53.6%) in HDG and RDG, respectively (p = 0.028) | PFS, 12.2 m and 9.4 m in HDG and RDG, respectively (p = 0.025); OS, NA | Grade 3/4 AEs were not significantly different between the 2 groups (P = 0.199) |
| Paez et al. (29) | Europe | Randomized, multicenter, open-label, non-blinded | mCRC with UGTA1A *1/1 or *1/28, no prior treatment for metastatic disease | mCRC, HDG, 40; RDG, 39 | FOLFIRI. Irinotecan doses for 1/1 and 1/28 in HDG were 300 and 260 mg/m², respectively; and 180 mg/m² was administered in RDG | ORR, 27 (67.5%) and 17 (43.6%) (p = 0.001); SD, 3 (7.5%) and 17 (43.6%); PD, 10 (25%) and 5 (12.8%); metastasectomy, 9 (22.5%) and 6 (15.4%) in HDG and RDG, respectively | PFS, 8.6 m and 8.2 m (P = 0.48); OS, 26 m and 17.6 m (P = 0.74) in HDG and RDG, respectively | No significant differences in grade 3-4 toxicities between the two groups. No differences in serious AEs, dose reduction, or use of G-CSF |
| Tsai et al. (30) | Asia   | Multicenter, randomized, controlled, open-label | mCRC | HDG: 1/1; 1/28; 23/28; 28/28; 2; RDG, 106 | Bevacizumab plus FOLFIRI. Starting dose of irinotecan, 180 mg/m² for 1/1 and 1/28, 120 mg/m² for 28/28 in HDG. If toxicity grade 3, the dose was escalated by 30 mg/m². The maximal dose was 260, 240, 180 mg/m² for 1/1, 1/28, and 28/28, respectively. The dose of RDG was 180 mg/m² | ORR, 77 (71.9%) and 44 (41.5%) (p <0.001); DCR, 98 (91.6%) and 83 (78.2%) (p = 0.007); PD, 9 (8.4%) and 23 (21.7%); metastasectomy, 34 (31.8%) and 17 (16.1%) (p = 0.007) in HDG and RDG, respectively | PFS, 14.0 m and 10.0 m (P <0.001); OS, 30 m and 22 m (P = 0.02) in HDG and RDG, respectively | Irinotecan-related grade 3/4 AEs, 25 (23.6%) and 25 (23.6%) in HDG and RDG, respectively (P = 0.520) |
| Hsieh et al. (31) | Asia   | Retrospective       | mCRC with Braf mutation, and UGTA1A *1/1 or *1/28 | mCRC, HDG, 8; RDG, 9 | Bevacizumab plus FOLFIRI. Starting dose of irinotecan was 180 mg/m² and the dose was escalated 20–30 mg/m² until grade 3/4 AEs in HDG. The maximum dose reached 260, 240, 210 mg/m² in 4, 2 and 2 patients, respectively. The dose of RDG was 180 mg/m² | PR, 1 (12.5%) and 1 (11.1%); SD, 5 (62.5%) and 4 (44.4%); DCR, 75% and 55.6%; PD, 2 (25%) and 4 (44.4%) in HDG and RDG, respectively (p = 0.697) | PFS, 11.5 m and 5.7 m (P = 0.552); OS, 15.8 m and 14.5 m (P = 0.40) in HDG and RDG, respectively | In total, grade 3 toxicity, 2 (11.8%) patients, and no grade 4/5 toxicity |

mCRC, metastatic colorectal cancer; HDG, High dose group; RDG, routine dose group; FOLFIRI, irinotecan combined with 5-FU and leucovorin; ORR, objective response rate; SD, stable disease; DCR, disease control rate; PD, progressive disease; PFS, progression-free survival; OS, overall survival; AE, adverse event.

In the first-line treatment, high dose FOLFIRI alone has shown a satisfactory chemotherapy response rate (23, 29), with an ORR of 67.5% in the randomized controlled study, although there was no statistical advantage in survival (29). Chemotherapy combined with biologics has shown a survival advantage over chemotherapy alone in first-line treatment of mCRC (37–40). High dose FOLFIRI in combination with bevacizumab or cetuximab in patients with wild-type or heterozygous variant of UGTA1A*28 have yielded good clinical outcomes (24–26, 28, 30). Survival in the randomized controlled trial (30) is equivalent to that of FOLFIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) combined with bevacizumab (41, 42). This makes us look forward to the study of high dose FOLFIRI combined with anti-vascular endothelial growth factor receptor or anti-epidermal growth factor receptor or immunotherapy in selected target mCRC patients according to UGTA1A genotypes.

**BRAF** mutation exists in approximately 10% of CRC (43). The **BRAF** mutation is related to reduced overall survival and poor treatment response compared with tumors with wild-type **BRAF** (44, 45). High dose FOLFIRI in mCRC patients with **BRAF** wild-type or heterozygous variant and **BRAF** mutant showed a survival advantage (31) and represented statistical difference from the routine dose in the subgroup analysis of a randomized controlled trial (29). In addition, in the small sample trial of non-first-line treatment, the exploration of adjusting the dose of irinotecan in mCRC patients based on
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**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

HZ and BH designed the project. YL, XZ, YX, and LW searched pieces of literature and wrote the manuscript. YL, YZ and MC revised the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: [https://www.frontiersin.org/articles/10.3389/fonc.2022.854478/full#supplementary-material](https://www.frontiersin.org/articles/10.3389/fonc.2022.854478/full#supplementary-material)

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