Impact of UGT1A1 genotype on the efficacy and safety of irinotecan-based chemotherapy in metastatic colorectal cancer

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Abbreviations: AE, adverse event; AXEPT, Asian XELIRI Project; CI, confidence interval; DHH, double heterozygous or homozygous; FOLFIRI, fluorouracil plus leucovorin with irinotecan; HR, hazard ratio; mCRC, metastatic colorectal cancer; mXELIRI, modified capecitabine plus irinotecan; OS, overall survival; PFS, progression-free survival; SH, single heterozygous.

Satoru Iwasa and Kei Muro contributed equally to this work. Trial registration: ClinicalTrials.gov Identifier: NCT01996306, and UMIN Clinical Trials Registry Identifier: UMIN000012263.

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1 | INTRODUCTION

The combination of fluorouracil with irinotecan (FOLFIRI) is widely accepted as a standard cytotoxic chemotherapy regimen for mCRC, either as a first- or second-line treatment. Additionally, FOLFIRI combined with a molecular targeted agent (ie, bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab) is commonly selected as a second-line therapeutic option. Irinotecan is converted to its active metabolite (SN-38) by carboxylesterase and glucuronidated to SN-38G by UDP-glucuronosyltransferase encoded by the UGT1A1 gene. As such, patients who are heterozygous or homozygous for UGT1A1*28 and UGT1A1*6 polymorphisms have reduced ability to form SN-38G and delayed SN-38 metabolism compared with those who do not carry these polymorphisms. The use of irinotecan in patients with such polymorphisms has been associated with the occurrence of more serious AEs such as neutropenia or diarrhea. However, the appropriate dose and efficacy of irinotecan for patients homozygous for UGT1A1*28 or *6, or heterozygous for both UGT1A1*28 and *6 is yet to be determined. The prescription information for irinotecan as approved by the US FDA states that “when administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of irinotecan should be considered for patients known to be homozygous for the UGT1A1*28 allele.” Importantly, Toffoli et al suggested an association between UGT1A1*28 homozygosity and greater efficacy, despite more severe toxicity; however, other studies failed to find any significant impact of UGT1A1 genotypes on survival. As such, an individualized dose for irinotecan in this patient population has yet to be established by large-scale prospective clinical studies. Recently, the phase III AXEPT study found the noninferiority of modified capecitabine plus irinotecan (mXELIRI) with or without bevacizumab relative to fluorouracil, leucovorin, and irinotecan (FOLFIRI) with or without bevacizumab as a second-line treatment for metastatic colorectal cancer. We evaluated the associations between the UGT1A1 genotype linked to adverse events—caused by irinotecan—and the efficacy and safety of mXELIRI and FOLFIRI. The UGT1A1 genotype was prospectively determined and patients were categorized into three groups according to WT (*1/*1), single heterozygous (SH; *28/*1 or *6/*1), and double heterozygous or homozygous (DHH; *28/*28, *6/*6, or *28/*6). Overall survival (OS), progression-free survival, response rate, and safety were assessed. The UGT1A1 genotype was available in all 650 randomized patients (WT, 309 [47.5%]; SH, 291 [44.8%]; DHH, 50 [7.7%]). The median OS was 15.9, 17.7, and 10.6 months in the WT, SH, and DHH groups, respectively, with an adjusted hazard ratio (HR) of 1.53 (95% confidence interval [CI], 1.12-2.09; P = .008) for DHH vs WT or SH. The median OS in the mXELIRI and FOLFIRI arms was 18.1 vs 14.3 months (HR 0.80; 95% CI, 0.62-1.03) in the WT group, 16.3 vs 18.3 months (HR 1.04; 95% CI, 0.79-1.36) in the SH group, and 13.0 vs 9.1 months (HR 0.71; 95% CI, 0.39-1.31) in the DHH group, respectively. Modified capecitabine plus irinotecan with or without bevacizumab could be a standard second-line chemotherapy in terms of efficacy and safety regardless of the UGT1A1 genotype.

2 | MATERIALS AND METHODS

2.1 | Patients

The detailed eligibility criteria for this study have been previously reported. In brief, patients aged 20 years or older with histologically confirmed mCRC, ECOG performance status of 0-2, adequate organ function, and disease progression or intolerance to
first-line chemotherapy were eligible for enrollment. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was reviewed and approved by the institutional review board of each study site prior to the initiation of the study. All patients provided written informed consent.

2.2 Study design and administration of drugs

Patients were centrally randomly assigned at a 1:1 ratio to receive either FOLFIRI with or without bevacizumab or mXELIRI with or without bevacizumab. The FOLFIRI regimen consisted of irinotecan 180 mg/m² plus leucovorin 400 mg/m² plus fluorouracil 400 mg/m² bolus, all on day 1, followed by fluorouracil 2400 mg/m² given as a 46-hour continuous infusion with or without bevacizumab 5 mg/kg on day 1, repeated every 2 weeks. The mXELIRI regimen consisted of irinotecan 200 mg/m² on day 1, plus capecitabine 800 mg/m² twice daily on days 1-14 with or without bevacizumab 7.5 mg/kg on day 1, repeated every 3 weeks. A reduced starting dose of irinotecan of 150 mg/m² was given in patients identified as homozygous for UGT1A1*6 or UGT1A1*28 or double heterozygous for both UGT1A1*6 and UGT1A1*28, regardless of the treatment arm. Detailed treatment modifications were as previously described.14

2.3 UGT1A1 genotyping

The UGT1A1 genotype was determined using the Invader assay (Sekisui Medical Co. Ltd.), the TaqMan assay and PCR direct sequencing (DNA Link, Inc), and the UGT1A1 Genotype Detection Kit (Shanghai Yuanqi Bio-Pharmaceutical Co. Ltd.). The UGT1A1*28 polymorphism has seven TA repeats in the promoter region (TATA) instead of the six repeats in WT UGT1A1; thus, the genotypes were designated as WT (UGT1A1*28 6/6), heterozygous (UGT1A1*28 6/7), and homozygous (UGT1A1*28 7/7). Similarly, the UGT1A1*6 polymorphism involves an amino acid substitution in exon 1 (211G>A); as such, the genotypes were designated as WT (UGT1A1*6 G/G), heterozygous (UGT1A1*6 G/A), and homozygous (UGT1A1*6 A/A). Accordingly, we stratified patients into three groups: WT (UGT1A1*6 G/G or *28 6/6), SH (UGT1A1*6 G/G and *28 6/7, or UGT1A1*6 G/A and *28 6/6), and DHH (UGT1A1*6 G/A and *28 6/7, UGT1A1*6 A/A, or *28 7/7).

2.4 End-points and assessments

The end-points of this study were OS, PFS, objective response rate, and safety. Tumor responses were assessed according to the RECIST guideline version 1.1. Overall survival was defined as the time from the date of randomization to death from any cause. Progression-free survival was defined as the time from the date of randomization to disease progression or death from any cause. Adverse events were assessed according to the NCI’s Common Terminology Criteria for Adverse Events version 4.0. Relative dose intensity was calculated as the total dose of each drug actually administered divided by the planned dose during the protocol treatment.

2.5 Statistical analysis

Survival end-points were estimated using the Kaplan-Meier method and compared with log-rank test. The HRs and associated 95% CIs for the comparison of OS and PFS between different UGT1A1 genotypes were calculated using the Cox proportional hazards models adjusted by country (Japan vs South Korea vs China), ECOG performance status (0-1 vs 2), number of metastatic sites (1 vs >1), previous use of oxaliplatin treatment (yes vs no), and concurrent bevacizumab treatment (with vs without). The objective response rate and incidences of AEs were assessed with the \( \chi^2 \) test and Fisher’s exact test, respectively. The significance level was set to .05. All statistical analyses were carried out using SAS versions 9.3 and 9.4.

3 RESULTS

3.1 Patients

In total, 650 patients were enrolled between December 2, 2013 and August 13, 2015, and the cut-off for data accrual was July 28, 2017. Nine patients were identified as ineligible after enrolment (five for recurrence more than 6 months after last dose of adjuvant chemotherapy, and one each for use of aspirin for more than 325 mg/d, baseline hemoglobin less than 9.0 g/dL, baseline total bilirubin more than 1.5 mg/dL, and active gastrointestinal bleeding) and 21 patients did not receive any study treatment. The dataset for full analysis used for the efficacy end-point included all 650 patients, of whom 620 received at least one dose on protocol and were included in the safety analysis. The UGT1A1 genotypes of the patients were as follows: WT (n = 309; 47.5%), SH (n = 291; 44.8%), and DHH (n = 50; 7.7%) (Figure 1); the proportions of patients carrying the different genetic polymorphisms were similar among different countries (Table S1). The baseline demographics and disease characteristics were generally well-balanced among the three groups, with the exception of the higher percentages of patients with right-sided tumors and those without liver metastasis in the DHH group (Tables 1 and S2).

3.2 Treatment efficacies according to UGT1A1 genotypes

During a median follow-up of 15.8 months (interquartile range, 8.7-24.9 months), the median PFS was 7.1 (95% CI, 6.5-8.3), 8.6 (95% CI, 7.3-9.9), and 5.3 (95% CI, 3.9-9.9) months in the WT, SH, and DHH
groups, respectively (Figure 2A). During the same period, the median OS was 15.9 (95% CI, 14.5-18.1), 17.7 (95% CI, 15.5-19.7), and 10.6 (95% CI, 8.0-14.1) months in the WT, SH, and DHH groups, respectively (Figure 2B). The adjusted HR for OS in the DHH group vs WT or SH groups was 1.53 (95% CI, 1.12-2.09; \( P = .008 \)).

3.3 | Treatment efficacies in FOLFIRI and mXELIRI arms according to UGT1A1 genotypes

The median PFS of patients in the mXELIRI and FOLFIRI arms was 8.3 vs 6.8 months (HR 0.88; 95% CI, 0.70-1.12; \( P = .299 \)) in the WT group, 8.7 vs 8.8 months (HR 1.06; 95% CI, 0.83-1.35; \( P = .626 \)) in the SH group, and 6.5 vs 4.8 months (HR 0.73; 95% CI, 0.41-1.32; \( P = .295 \)) in the DHH group (Figure 3A). The median OS in the mXELIRI and FOLFIRI arms was 18.1 vs 14.3 months (HR 0.80; 95% CI, 0.62-1.03; \( P = .077 \)) in the WT group, 16.3 vs 18.3 months (HR 1.04; 95% CI, 0.79-1.36; \( P = .805 \)) in the SH group, and 13.0 vs 9.1 months (HR 0.71; 95% CI, 0.39-1.31; \( P = .271 \)) in the DHH group (Figure 3B). No differences were observed in PFS and OS for each treatment among UGT1A1*6 and UGT1A1*28 (Figure S1). Among the 620 evaluable patients, the proportion of patients achieving an objective response was lower in the FOLFIRI arm than in the mXELIRI arm of the DHH group (response rate 0% vs 17.4%, \( P = .033 \)) (Tables 2 and S3).

3.4 | Safety and treatment intensity in FOLFIRI and mXELIRI arms

The safety profiles of FOLFIRI and mXELIRI have been previously reported. The most common grade 3-4 AEs of special interest in the FOLFIRI and mXELIRI arms were neutropenia (42.9% and 16.8%, respectively) and diarrhea (3.2% and 7.1%, respectively). Adverse events tended to be similar regardless of the UGT1A1 genotype. Overall, grade 3-4 neutropenia was more common in the FOLFIRI arm than in the mXELIRI arm (35.9%, 50.4%, and 45.8% vs 17.0%, 15.7%, and 21.7%, respectively, in the WT, SH, and DHH groups) (Table S3). Grade 3-4 neutropenia was more likely to occur during the earlier cycles (up to #4) than during later cycles in both treatment groups. Especially with the FOLFIRI regimen, grade 3-4 neutropenia developed more frequently during the earlier cycles in the DHH group than in the WT and SH groups (Table S4). Grade 3-4 diarrhea was more common in the mXELIRI arm than the FOLFIRI arm (Table 3). Grade 3-4 neutropenia and diarrhea tended to be more common in patients with the UGT1A1*6 genotype than those with the UGT1A1*28 genotype (Table S5).

In the FOLFIRI arm, the relative dose intensity of irinotecan was lower in the DHH group (62.1%) than in the WT (74.6%) and SH (73.1%) groups. In the mXELIRI arm, the relative dose intensities of irinotecan were 85.7%, 84.6%, and 86.1% in the WT, SH, and DHH groups, respectively (Table 4). Discontinuation of study treatment for unacceptable toxicity was more common among DHH patients treated with FOLFIRI (16.7%)
**TABLE 1** Baseline characteristics of patients with metastatic colorectal cancer, grouped according to UGT1A1 genotype (WT, single heterozygous [SH], or double heterozygous or homozygous [DHH]).

|                          | Patients, n (%) |       |       |       | P    |
|--------------------------|----------------|-------|-------|-------|------|
|                          | WT (n = 309)   | SH (n = 291) | DHH (n = 50) |       |
| Age, median (range), y   | 60.0 (24-85)   | 61.0 (27-84) | 62.0 (25-78) | .5303 |
| Treatment arm            |                |       |       |       |      |
| FOLFIRI with or without BV | 158 (51.1)   | 140 (48.1) | 26 (52.0) | .7232 |
| XELIRI with or without BV | 151 (48.9)   | 151 (51.9) | 24 (48.0) |        |
| Sex                      |                |       |       |       |      |
| Male                     | 183 (59.2)     | 174 (59.8) | 28 (56.0) | .8806 |
| Female                   | 126 (40.8)     | 117 (40.2) | 22 (44.0) |        |
| Country                  |                |       |       |       |      |
| Korea                    | 107 (34.6)     | 103 (35.4) | 18 (36.0) | .9784 |
| China                    | 77 (24.9)      | 66 (22.7)  | 12 (24.0) |        |
| Japan                    | 125 (40.5)     | 122 (41.9) | 20 (40.0) |        |
| ECOG PS                  |                |       |       |       |      |
| 0-1                      | 307 (99.4)     | 288 (99.0) | 49 (98.0) | .6287 |
| 2                        | 2 (0.6)        | 3 (1.0)   | 1 (2.0)   |        |
| Primary tumor location   |                |       |       |       |      |
| Right side               | 78 (25.2)c     | 69 (24.2)c | 17 (34.0) |        |
| Left side                | 237 (76.7)d    | 221 (77.5)e | 33 (66.0) |        |
| No. of metastatic sites  |                |       |       |       |      |
| 1                        | 107 (34.6)     | 112 (38.5) | 16 (32.0) | .5035 |
| >1                       | 202 (65.4)     | 179 (61.5) | 34 (68.0) |        |
| Adjuvant chemotherapy    |                |       |       |       |      |
| Yes                      | 75 (24.3)      | 73 (25.1)  | 11 (22.0) | .8908 |
| No                       | 234 (75.7)     | 218 (74.9) | 39 (78.0) |        |
| Prior oxaliplatin        |                |       |       |       |      |
| Yes                      | 300 (97.1)     | 285 (97.9) | 49 (98.0) | .7789 |
| No                       | 9 (2.9)        | 6 (2.1)   | 1 (2.0)    |        |
| Prior anti-EGFR Ab therapy| 48 (15.5)  | 49 (16.8)  | 8 (16.0)   | .9097 |
| No                       | 261 (84.5)     | 242 (83.2) | 42 (84.0)  |        |
| Prior BV                 |                |       |       |       |      |
| Yes                      | 89 (28.8)      | 85 (29.2)  | 16 (32.0)  | .8767 |
| No                       | 220 (71.2)     | 206 (70.8) | 34 (68.0)  |        |
| Concomitant BV in this study| 256 (82.8)  | 243 (83.5) | 42 (84.0)  | .9659 |
| No                       | 53 (17.2)      | 48 (16.5)  | 8 (16.0)   |        |
| KRAS status              |                |       |       |       |      |
| WT                       | 121 (39.2)     | 125 (43.0) | 17 (34.0)  | .4395 |
| Mutant                   | 101 (32.7)     | 77 (26.5)  | 16 (32.0)  |        |
| Unknown                  | 87 (28.2)      | 89 (30.6)  | 17 (34.0)  |        |

Abbreviations: BV, bevacizumab; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, plus irinotecan; PS, performance status; XELIRI, capecitabine plus irinotecan.

*χ² test (except for one-way ANOVA); comparing proportion of each characteristic.

|       |       |       |       |      |

No comparison made because of duplicate aggregation.

|       |       |       |       |      |

Total numbers do not match as six patients had duplicates for WT.

|       |       |       |       |      |

Total numbers do not match as five patients had with duplicates for SH.
FIGURE 2 Kaplan-Meier analysis of (A) progression-free survival and (B) overall survival in patients with metastatic colorectal cancer according to UGT1A1 genotypes. CI, confidence interval; DHH, double heterozygous or homozygous; SH, single heterozygous.
FIGURE 3  Kaplan-Meier analysis of (A) progression-free survival and (B) overall survival in patients with metastatic colorectal cancer according to UGT1A1 genotypes and treatment groups. CI, confidence interval; DHH, double heterozygous or homozygous; FOLFIRI, fluorouracil, leucovorin, plus irinotecan; SH, single heterozygous; mXELIRI, modified capecitabine plus irinotecan.
when compared with mXELIRI (8.7%). After discontinuation of protocol treatment, third-line chemotherapy was given to 60.1% of WT patients in the FOLFIRI arm and 58.3% of WT patients in the mXELIRI arm. These values were 55.0% and 62.3% in the SH group, and 65.4% and 54.2% in the DHH group, for the FOLFIRI and mXELIRI arms, respectively.

### DISCUSSION

Here, we showed that mXELIRI with or without bevacizumab is non-inferior to FOLFIRI with or without bevacizumab in terms of OS, regardless of the UGT1A1 genotype. No significant differences were found in the PFS and objective response between the treatment groups regardless of UGT1A1 genotypes. Adverse events such as neutropenia were less common in the mXELIRI arm than in the FOLFIRI arm across all UGT1A1 genotypes. Our results suggest that mXELIRI with bevacizumab could become one of the standard treatments for colorectal cancer as a second-line treatment regardless of the UGT1A1 genotype.

Another interesting finding from the current study is that patients with the DHH genotype had significantly worse OS than patients with WT or SH genotypes, especially in the FOLFIRI arm. The same trends were observed for objective response rate and PFS. This is in contrast to the results of the study by Toffoli et al., which reported that FOLFIRI consisting of irinotecan 180 mg/m² as the first-line chemotherapy achieved a higher response rate (67%) in patients homozygous

### TABLE 2  Response rates in patients with metastatic colorectal cancer, grouped according to UGT1A1 genotype (WT, single heterozygous [SH], or double heterozygous or homozygous [DHH]) and treatment (fluorouracil, leucovorin, plus irinotecan [FOLFIRI] or capecitabine plus irinotecan [XELIRI])

|                  | Patients |                |                |                |                |
|------------------|----------|----------------|----------------|----------------|----------------|
|                  |          | FOLFIRI (n = 153) | mXELIRI (n = 147) | FOLFIRI (n = 133) | mXELIRI (n = 140) | FOLFIRI (n = 24) | mXELIRI (n = 23) |
|                  |          | Complete response |                |                |                |                |                |
|                  |          | 2 (1.3) | 8 (5.4) | 0 (0.0) | 5 (3.6) | 0 (0.0) | 0 (0.0) |
|                  |          | Partial response |                |                |                |                |                |
|                  |          | 28 (18.3) | 28 (19.0) | 27 (20.3) | 30 (21.4) | 0 (0.0) | 4 (17.4) |
|                  |          | Stable disease |                |                |                |                |                |
|                  |          | 88 (57.5) | 76 (51.7) | 63 (47.4) | 77 (55.0) | 15 (62.5) | 12 (52.2) |
|                  |          | Progressive disease |            |                |                |                |                |
|                  |          | 29 (19.0) | 26 (17.7) | 32 (24.1) | 18 (12.9) | 6 (25.0) | 6 (26.1) |
|                  |          | Not evaluable |                |                |                |                |                |
|                  |          | 6 (3.9) | 9 (6.1) | 11 (8.3) | 10 (7.1) | 3 (12.5) | 1 (4.3) |
|                  |          | Objective response |            |                |                |                |                |
|                  |          | 30 (19.6) | 36 (24.5) | 27 (20.3) | 35 (25.0) | 0 (0.0) | 4 (17.4) |
|                  |          | \(P = .308\) | \(P = .354\) | \(P = .033\) | \(P = .033\) | \(P = .033\) | \(P = .033\) |

Note: Data are shown as n (%).

### TABLE 3  Grade 3 or 4 toxicities in the safety population of study patients with metastatic colorectal cancer, grouped according to UGT1A1 genotype (WT, single heterozygous [SH], or double heterozygous or homozygous [DHH]) and treatment (fluorouracil, leucovorin, plus irinotecan [FOLFIRI] or modified capecitabine plus irinotecan [mXELIRI])

|                  | FOLFIRI |                | mXELIRI |                |                |                |                |
|------------------|---------|----------------|---------|----------------|----------------|----------------|----------------|
|                  | WT (n = 153) | SH (n = 133) | DHH (n = 24) | WT (n = 147) | SH (n = 140) | DHH (n = 23) |
|                  |          | Any |                |          | Any |                |          | Any |
|                  |          | 73 (47.7) | 78 (58.6) | 15 (62.5) | 49 (33.3) | 47 (33.6) | 9 (39.1) |
|                  |          | Leucopenia |                |          | Neutropenia |                |          | Anemia |
|                  |          | 13 (8.5) | 16 (12.0) | 6 (25.0) | 7 (4.8) | 7 (5.0) | 2 (8.7) |
|                  |          | Neutropenia |                |          | 55 (35.9) | 67 (50.4) | 11 (45.8) | 25 (17.0) | 22 (15.7) | 5 (21.7) |
|                  |          | 7 (4.6) | 5 (3.8) | 1 (4.2) | 3 (2.0) | 4 (2.9) | 3 (13.0) |
|                  |          | Thrombocytopenia |            |          | 1 (0.7) | 0 (0.0) | 0 (0.0) | 2 (1.4) | 1 (0.7) | 1 (4.3) |
|                  |          | Febrile neutropenia |            |          | 9 (5.9) | 3 (2.3) | 1 (4.2) | 2 (1.4) | 6 (4.3) | 2 (8.7) |
|                  |          | Nausea |                |          | 4 (2.6) | 3 (2.3) | 2 (8.3) | 4 (2.7) | 6 (4.3) | 3 (13.0) |
|                  |          | Diarrhea |            |          | 2 (1.3) | 8 (6.0) | 0 (0.0) | 7 (4.8) | 15 (10.7) | 0 (0.0) |
|                  |          | Mucositis |            |          | 5 (3.3) | 4 (3.0) | 0 (0.0) | 2 (1.4) | 2 (1.4) | 1 (4.3) |
|                  |          | Fatigue |            |          | 4 (2.6) | 2 (1.5) | 2 (8.3) | 5 (3.4) | 5 (3.6) | 0 (0.0) |
|                  |          | Hand-foot syndrome |            |          | 1 (0.7) | 0 (0.0) | 0 (0.0) | 3 (2.0) | 2 (1.4) | 1 (4.3) |

Note: Data are shown as n (%).
for UGT1A1*28 than WT (40%) or SH (42%) patients. Such a difference in the efficacy is likely due to different ethnicity, as homozygosity for UGT1A1*6 was observed exclusively in Asian populations and the frequency of UGT1A1*6 is higher than UGT1A1*28 in Asian populations.\textsuperscript{15,16} Regarding the UGT1A1*6 and *28 alleles, our findings revealed that more patients with the UGT1A1*6 genotype developed grade 3-4 neutropenia and diarrhea compared with patients carrying the UGT1A1*28 genotype. A dose-finding study of irinotecan monotherapy with 150 mg/m\textsuperscript{2} in Japanese patients with UGT1A1 SH and/or DHH genotype showed dose reductions or delayed treatment in subsequent cycles because of grade 3 or 4 neutropenia.\textsuperscript{17} In fact, compared with patients with other genotypes, DHH patients were more likely to develop grade 3-4 neutropenia during the early treatment cycles, more so especially in the FOLFIRI group than in the mXELIRI group. We considered the possibility that the inferior PFS for FOLFIRI compared with mXELIRI might reflect the higher rate of treatment discontinuation as a result of unacceptable toxicity associated with FOLFIRI. Therefore, FOLFIRI with irinotecan 150 mg/m\textsuperscript{2} might have been overdosed in some cases in the DHH group.

Higher irinotecan dose intensity (86.1\% vs 62.1\%) and improved safety (grade 3 or higher toxicities, 39.1\% vs 62.5\%) were evident in the mXELIRI arm compared with the FOLFIRI arm in the DHH group. Efficacy as assessed by PFS and OS was better with the mXELIRI regimen than the FOLFIRI regimen in the DHH group (6.5 vs 4.8 months, and 13.0 vs 9.1 months, respectively); however, these differences were not statistically significant, which is probably due to the limited sample size. Although the superiority of mXELIRI could not be proven, the median PFS and OS were both longer in the mXELIRI group than in the FOLFIRI group by 1.7 months (HR 0.73; 95\% CI, 0.41-1.32) and 3.9 months (HR 0.71; 95\% CI, 0.39-1.31), respectively. These data suggest that mXELIRI can be given safely to patients with the DHH genotype while maintaining efficacy.

Our study has several limitations. First, because the concentration of drug in the blood was not quantified, we do not know whether the concentration of the active form of a poor metabolizer was increased in the blood, thereby leading to a higher efficacy due to greater SN-38 levels. Second, biases could have been present because the distribution of right-sided colon cancer, which is a prognostic factor in patients with colorectal cancer, was not adjusted in this study in order to investigate the usefulness of UGT1A1 genotyping. Third, the sample size might have been too small to rigorously compare the efficacy of mXELIRI- and FOLFIRI-based treatments in the DHH group. Finally, it is difficult to conclusively suggest an appropriate dose of irinotecan for FOLFIRI in the DHH group, although it might have been necessary to further reduce the starting dose to 120 mg/m\textsuperscript{2} irinotecan, or to eliminate the bolus infusion of fluorouracil.

Although UGT1A1 genotyping was mandatory in this study, it is not recommended in routine practice. Real-world data showed that the proportion of patients with DHH genotypes for UGT1A1 was 7%-10% and that they did not tolerate the standard FOLFIRI regimen containing 180 mg/m\textsuperscript{2} irinotecan.\textsuperscript{8} Therefore, UGT1A1 genotyping would be considered prior to treatment with FOLFIRI containing irinotecan 180 mg/m\textsuperscript{2} when extra caution is required due to comorbidities or older age. Despite the establishment of some recommendations, routine upfront UGT1A1 genotyping is not currently carried out. This could be because there have been few prospective studies that evaluated the clinical effects of genotype-directed dosing.\textsuperscript{18,19} Other challenges for routine UGT1A1 testing to avoid severe neutropenia include added costs and long turnaround time.

Precision medicine based on next-generation sequencing of tumor tissues is becoming a standard-of-care in mCRC and other cancers, and the costs thereof are covered by insurance in several countries such as the United States, Germany, Korea, and Japan. Recently, the MI-ONCOSQ study produced reliable germline pharmacogenetics information on several clinically relevant pharmacogenes (eg, TPMT, DYPD, and CYP2C19).\textsuperscript{20} Further updates on UGT1A1 through prospective studies are needed. Integration of germline pharmacogenetics into tumor sequencing programs and the bioinformatics workflow will provide a unique opportunity to streamline and maximize the clinical benefit of genome testing without additional genotyping costs.

In conclusion, mXELIRI with or without bevacizumab as second-line chemotherapy for mCRC was efficacious and had an acceptable AE profile regardless of the UGT1A1 genotype.

**ACKNOWLEDGMENTS**

We thank the Scientific Publications Team and Joon Seo Lim at Asan Medical Center for their editorial assistance. This trial was sponsored by the Epidemiological and Clinical Research...
DISCUSSION

Satoru Iwasa reported receiving honoraria from Chugai and Taiho and research funding from Daiichi Sankyo and Pfizer. Kei Muro reported receiving honoraria from Chugai and Taiho and research funding from Daiichi Sankyo, Pfizer, and Taiho. Satoshi Morita reported receiving honoraria from Chugai, Pfizer, and Taiho. Masato Nakamura reported receiving honoraria from Chugai, Yakult Honsha, and Taiho. Masahito Kotaka reported receiving honoraria from Chugai and Yakult Honsha. Tomohiro Nishina reported receiving honoraria from Chugai and Taiho and research funding from Chugai, Daiichi Sankyo, and Taiho. Keun-Wook Lee reported receiving honoraria from Genexine, MedPacto, and ISU abxis. Yasuhide Yamada reported receiving honoraria from Chugai, Nipponkayaku, and Taiho and grants from Daiichi Sankyo. Junichi Sakamoto reported receiving an honorarium from Chugai. The other authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Iwasa S, Muro K, Morita S, et al. Impact of UGT1A1 genotype on the efficacy and safety of irinotecan-based chemotherapy in metastatic colorectal cancer. Cancer Sci. 2021;112:4669-4678. https://doi.org/10.1111/cas.15092