Comparison of UGT1A1 Polymorphism as Guidance of Irinotecan Dose Escalation in RAS Wild-Type Metastatic Colorectal Cancer Patients Treated With Cetuximab or Bevacizumab Plus FOLFIRI as the First-Line Therapy

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Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) polymorphism plays a crucial role in the increased susceptibility and toxicity of patients to irinotecan. This retrospective, observational study compared the clinical outcomes and adverse events (AEs) in RAS wild-type metastatic colorectal cancer (mCRC) patients treated with cetuximab or bevacizumab plus FOLFIRI with UGT1A1 genotyping and irinotecan dose escalation as the first-line therapy. In total, 173 patients with mCRC with RAS wild-type were enrolled. Among them, 98 patients were treated with cetuximab, whereas 75 patients were treated with bevacizumab. All patients received irinotecan dose escalation based on UGT1A1 genotyping. We compared the progression-free survival (PFS), overall survival (OS), objective response rates (ORRs), disease control rates (DCRs), metastatectomy, and severe adverse events (SAEs) between the two groups. Over a median follow-up of 23.0 months [interquartile range (IQR), 15.0–32.5 months], no significant differences were observed between the cetuximab and bevacizumab groups in PFS [18.0 months vs. 14.0 months; 95% confidence interval (CI), 0.517–1.027; hazard ratio (HR), 0.729; p = 0.071], OS (40.0 months vs. 30.0 months; 95% CI, 0.410–1.008; HR, 0.643; p = 0.054), ORR (65.3% vs. 62.7%; p = 0.720), DCR (92.8% vs. 86.7%; p = 0.175), metastatectomy (36.7% vs. 29.3%; p = 0.307), and SAEs (p = 0.685). Regardless of primary tumor sidedness and target therapy crossover, no significant differences were noted in efficacy and safety between the two groups (all p > 0.05). Our results revealed that patients with wild-type RAS mCRC, regardless of biologics, with UGT1A1 genotyping can tolerate escalated doses of irinotecan and potentially achieve a more favorable clinical outcome without significantly increased toxicity.

Key words: UGT1A1 polymorphism; Metastatic colorectal cancer (mCRC); Irinotecan dose escalation; Biologics; Efficacy; Safety

INTRODUCTION

Despite recent advances in medicine, the management of patients with metastatic colorectal cancer (mCRC) remains challenging because of considerable interindividual differences in therapeutic responses. In recent years, pharmacogenomics has been adopted for the personalization of mCRC treatment. Typically, majority of patients with mCRC receiving first-line treatment might require later lines of therapy. Therefore, first-line
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treatment is the most critical phase of therapy, and its
effects on patient outcomes might be more prominent
than those of any subsequent line. For example, absolute
improvements in median overall survival (OS) even with
intensive second-line regimens tend to be relatively min-
imal. However, the incremental OS gain provided by
the addition of biological agents to chemotherapy and the
mainstay treatment for patients with mCRC is still repre-
sented by doublet or triplet chemotherapy of compounds
with fluoropyridine backbones combined with oxalipla-
tin, irinotecan, or both.

Irinotecan-based chemotherapy is a standard first-line
or second-line regimen for mCRC. However, irinote-
can has dose-limiting toxicity, mainly neutropenia and
delayed-onset diarrhea. *UGT1A1* gene polymorphism is
differently distributed among different ethnicities, which
may lead to various toxicity and efficacies of irinotecan.
Even with the same ethnicity, the gene frequency dif-
fers in varying geographical regions. The recommended
irinotecan dose in FOLFIRI (leucovorin + fluorouracil + irinotecan) is 180 mg/m^2 based on a dose-finding
study. The recommended dose is considerably lower
than that tolerated in patients with *UGT1A1*/*1/*1 and
*/1/*28 genotypes. Our retrospective studies have also
demonstrated that patients with mCRC who underwent
*UGT1A1* genotyping may receive escalated irinotecan
doses to obtain a better clinical response with compara-
ble toxicity. The recommendations of the Pan-Asian
European Society for Medical Oncology (ESMO) consen-
sus guidelines showed that it depends on the prevale-
ce of *UGT1A1* polymorphisms per country whether a
lower irinotecan threshold dose for *UGT* genotyping may
be used.

In this retrospective, observational study, we com-
pared the efficacy and safety following different doses
of irinotecan in 173 RAS wild-type patients with mCRC
treated with first-line FOLFIRI plus cetuximab or bevacizumab.

**MATERIALS AND METHODS**

**Patients and Study Design**

In this retrospective, observational study, patients
with mCRC with histologically proven synchronous or

![Flowchart of patient disposition. AEs, adverse events; Gr., grade; Iri, irinotecan.](image-url)
metachronous adenocarcinoma were enrolled. All participants received routine KRAS (codons 12, 13, 59, 61, 117, and 146), NRAS (codons 12, 13, 59, 61, 117, and 146), BRAF (codon 600), and UGT1A1 genotyping tests. The patients with RAS wild-type received irinotecan dose escalation according to their UGT1A1 genotyping. Irinotecan dose escalation was based on UGT1A1 polymorphisms and adverse events (AEs) observed after two cycles of dose adjustment, and escalation was terminated if grade III/IV AEs occurred (Fig. 1). We included data on patients’ demographic (age and gender), clinical [Eastern Cooperative Oncology Group (ECOG) performance status], and tumor (primary tumor site, UGT1A1 status, RAS status, BRAF status, and number and sites of metastases) characteristics.

In this study, we retrospectively analyzed 173 patients with mCRC receiving cetuximab or bevacizumab combined with FOLFIRI as the first-line treatment. Each group was divided into three subgroups on the basis of their UGT1A1 genotype.

Subgroup 1: UGT1A1 6TA/6TA

The treatment regimen comprised cetuximab (500 mg/m²) or bevacizumab (5 mg/kg) as a 120-min intravenous (IV) infusion on day 1, followed by irinotecan (180 mg/m²) plus normal saline 500 ml as a 4-h IV infusion, and leucovorin (200 mg/m²) plus 5-FU (2,800 mg/m²) plus 500 ml of IV normal saline for 42 to 48 h; this regimen was repeated once every 2 weeks. The AEs, hematological or nonhematological, were observed during the treatment course. If the AEs were below grade II, the dose was gradually escalated in increments of 30 mg/m². The estimated maximal dose of irinotecan was 260 mg/m².

Subgroup 2: UGT1A1 6TA/7TA

The procedure was the same as that for subgroup 1, but irinotecan was initiated at 180 mg/m² once every 2 weeks, and the estimated maximal dose was 240 mg/m².

Subgroup 3: UGT1A1 7TA/7TA

The procedure is the same as that for subgroup 1, but irinotecan was initiated at 120 mg/m² once every 2 weeks, and the estimated maximal dose was 180 mg/m².

Written informed consent was obtained from each participant. The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-E(I)-20200036].

Genomic DNA Extraction and UGT1A1, RAS, and BRAF Genotyping

To analyze constitutional gene polymorphisms, DNA was first extracted from 4 ml of peripheral blood using a PUREGENE DNA isolation kit (Gentra Systems, Minneapolis, MN, USA). The patients’ genomic DNA was then analyzed using direct sequencing to determine the UGT1A1 promoter region genotype. Detailed genotyping procedures were previously reported.

For RAS genotyping, macrodissected paraffin-embedded samples were then placed in sterile tubes. After deparaffinization and rehydration, DNA was isolated using a PUREGENE DNA isolation kit. The primers used in this study were designed using primer3 free software (https://primer3.org/). The sequences of the forward and reverse primers were 5’-TCATTATTTTTATATAGGCCTGCT GAA-3’ and 5’-CAAAAGACTGTCCCTGCACCAGTA-3’, respectively. The polymerase chain reaction (PCR) volume was 40 μl, and the PCR conditions for KRAS were as follows: 94.0°C for 10 min; 35 cycles of denaturation for 30 s at 94.0 °C, annealing for 60 s at 56.0°C, and primer extension for 30 s at 72.0°C; and final hold for 7 min at 72.0°C. Fragment analysis of the PCR products was conducted to verify the genotypes using automated capillary electrophoresis on an ABI PRISM 310 Genetic Analyzer system and Genotyper software (Applied Biosystems, Foster City, CA, USA).

For BRAF mutation analysis, we extracted DNA from formalin-fixed, paraffin-embedded (FFPE) CRC tissue samples for clinical BRAF mutation analysis by direct sequencing. Detailed genotyping procedures were previously reported.

Efficacy and Safety Outcome Measures

Assessment of the tumor responses was typically performed after every six cycles of the interventional regimen. Response measurements are based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The AEs were monitored and graded in each cycle according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCT-CTCAE) Version 4.3 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Progression-free survival (PFS) was defined as the time from the date of enrollment until the first documentation of progression, regardless of the patient’s treatment status. OS was defined as the time from the date of enrollment until the date of death or the last date of follow-up. The complete responses and partial responses were defined as objective response rate (ORR), and disease control rate (DCR) was defined as confirmed complete responses, partial responses, and stable disease cases.

Target Agent Crossover Therapy

In this retrospective, observational study, we observed the effects of target therapy crossover. If the first-line regimen failed, the patients received other biologics under stable ECOG status. According to the reimbursement of...
the National Health Insurance Administration of Taiwan, the second-line regimen would be FOLFOX after first-line treatment failure of FOLFIRI plus target agents. The third-line regimen could be FOLFIRI plus cetuximab in wild-type RAS mCRC patients, but self-paid bevacizumab in mutant RAS mCRC patients. The OS was used as an endpoint of target agent crossover therapy.

Statistical Analysis

The analyses included patients who completed the sixth cycle of treatment and were not lost to follow-up. Continuous variables are presented as the mean ± standard deviation, and dichotomous variables as numbers and percentages. All statistical analyses were performed using SPSS v21.0 (SPSS, Chicago, IL, USA). The clinicopathological characteristics of the two groups were compared using Pearson’s chi-square test. Cox regression analysis was used to estimate the hazard ratios (HRs) for all independent variables in the model. PFS and OS were evaluated using the Kaplan-Meier method, and the log-rank test was used to compare time-to-event distributions. Statistical significance was set to a value of $p < 0.05$.

RESULTS

Patients’ Population and Disposition

Between August 2014 and February 2020, 245 patients were initially enrolled, and 173 patients were finally analyzed. The patient flowchart is presented in Figure 2. Except for age, primary lesion site, and BRAF status, the baseline demographics and characteristics were similar between the two groups (Table 1). Most patients (70.7%) were less than 65 years old. In the bevacizumab group, 12.0% had mutant BRAF status, and in the cetuximab group, most patients had left-sided mCRC (88.7%). The database for the final analysis was locked on March 31, 2021. At the cutoff time for analysis, the median follow-up time was 23.0 months [interquartile range (IQR), 15.0–32.5 months].

![Figure 2. Patient selection flowchart. FOLFIRI, leucovorin + fluorouracil + irinotecan; Tx, treatment. Escalated dose of irinotecan according to UGT1A1 polymorphisms.](image-url)
Table 1. Baseline Characteristics of the 173 Enrolled Wild-Type RAS Patients With Metastatic Colorectal Cancer Under Chi-Square Analysis Between the Cetuximab Group and the Bevacizumab Group

| Baseline Data                      | Cetu Group (N = 98) | Beva Group (N = 75) | p Value |
|-----------------------------------|---------------------|---------------------|---------|
| **Gender**                        |                     |                     | 0.176   |
| Male                              | 109                 | 66 (67.3%)          | 43 (57.3%) |
| Female                            | 64                  | 32 (32.7%)          | 32 (42.7%) |
| **Age (years)**                   |                     |                     | 0.304   |
| Median (range)                    | 63.0 (34.0–88.0%)   | 57.0 (25.0–81.0%)   |         |
| **Age (years)**                   |                     |                     | 0.013   |
| <65                               | 104                 | 51 (52.0%)          | 53 (70.7%) |
| ≥65                               | 69                  | 47 (48.0%)          | 22 (29.3%) |
| **ECOG PS**                       |                     |                     | 0.126   |
| 0 + 1                             | 170                 | 95 (96.9%)          | 75 (100.0%) |
| 2                                 | 3                   | 3 (3.1%)            | 0 (0%)   |
| **Primary lesion site**           |                     |                     | 0.009   |
| Left-sided                        | 142                 | 87 (88.7%)          | 55 (73.3%) |
| Right-sided                       | 31                  | 11 (11.3%)          | 20 (26.7%) |
| **Synchronous/metachronous**      |                     |                     | 0.124   |
| Synchronous                       | 104                 | 54 (55.1%)          | 50 (66.7%) |
| Metachronous                      | 69                  | 44 (44.9%)          | 25 (33.3%) |
| **BRAF genotyping**               |                     |                     | 0.008   |
| Wild type                         | 162                 | 96 (97.9%)          | 66 (88.0%) |
| Mutant type                       | 11                  | 2 (2.1%)            | 9 (12.0%) |
| **UGT1A1 genotyping**             |                     |                     | 0.245   |
| (6,6)                             | 137                 | 82 (63.7%)          | 55 (73.3%) |
| (6,7)                             | 32                  | 14 (14.3%)          | 18 (24.0%) |
| (7,7)                             | 4                   | 2 (2.0%)            | 2 (2.7%)  |
| **Metastatic sites**              |                     |                     | 0.642   |
| Liver                             | 69                  | 41 (41.8%)          | 28 (37.3%) |
| Lungs                             | 23                  | 15 (15.3%)          | 8 (10.7%)  |
| Liver + lungs                     | 15                  | 8 (8.2%)            | 7 (9.3%)   |
| Others                            | 66                  | 34 (34.7%)          | 32 (42.7%) |
| **No. of metastatic sites**       |                     |                     | 0.546   |
| 1                                 | 133                 | 77 (78.6%)          | 56 (74.7%) |
| ≥2                                | 40                  | 21 (21.4%)          | 19 (25.3%) |
| **Subsequent target therapy**     |                     |                     | 0.590   |
| Yes                               | 63                  | 34 (34.7%)          | 29 (38.7%) |
| No                                | 110                 | 64 (65.3%)          | 46 (61.3%) |
| **MSI status**                    |                     |                     | <0.001  |
| MSI-H                             | 6                   | 1 (1.0%)            | 5 (6.7%)  |
| MSI-L                             | 66                  | 49 (50.0%)          | 17 (22.7%) |
| No tested                         | 62                  | 34 (34.7%)          | 28 (37.3%) |
| No surgery                        | 39                  | 14 (14.3%)          | 25 (33.3%) |

Values are number (N) with percentage in parentheses. Cetu group, cetuximab group; Beva group, bevacizumab group; ECOG PS, the Eastern Cooperative Oncology Group performance status; Left-sided, descending colon + sigmoid colon + rectosigmoid colon + rectum; Right-sided, cecum + ascending colon + transverse colon; Synchronous, metastatic lesions occurred initially; Metachronous, metastatic lesions occurred at least 6 months after resection of the primary lesion; Subsequent target therapy, cetuximab changes to anti-VEGF drug or bevacizumab changes to anti-EGFR drug after progression; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; No tested, means that the MSI status test has not been performed on the resected specimen; No surgery, means that patients have not received surgery.
Efficacy Outcomes

No significant differences were observed between the cetuximab and bevacizumab groups in ORR (65.3% vs. 62.7%, \(p = 0.720\)), DCR (92.8% vs. 86.7%, \(p = 0.175\)), and metastatectomy (36.7% vs. 29.3%, \(p = 0.307\)) (Table 2). In the cetuximab group, the median PFS was 18.0 months and 29 (29.6%) of 98 patients were progression-free at the final follow-up, whereas in the bevacizumab group, the median PFS was 14.0 months and 11 (14.7%) of 75 patients were progression-free at the final follow-up [HR, 0.729; 95% confidence interval (CI), 0.157–1.027; \(p = 0.071\)] (Fig. 3A). The median OS was 40.0 and 30.0 months in the cetuximab and bevacizumab groups, respectively, and 64 (65.3%) and 31 (41.3%) patients, respectively, were still alive at the final follow-up of the OS data cutoff (HR, 0.643; 95% CI, 0.410–1.008; \(p = 0.054\)) (Fig. 3B). Although the cetuximab group was not superior to the bevacizumab group in terms of PFS and OS, it seemed to have nonsignificantly higher survival.

We further analyzed the efficacy of subgroups from the viewpoint of sidedness. In the subgroup of left-sided mCRC, no significant difference was noted between the two groups in the ORR (63.3% vs. 70.9%, \(p = 0.345\)), DCR (91.8% vs. 89.1%, \(p = 0.564\)), and metastatectomy (37.9% vs. 30.9%, \(p = 0.393\)) in Table 3. Among the left-sided patients with mCRC, the median PFS was 16.0 months in the cetuximab group and 14.0 months in the bevacizumab group (HR, 0.759; 95% CI, 0.522–1.104; \(p = 0.149\)) (Fig. 4A), and the median OS was 40.0 months versus 31.0 months (HR, 0.666; 95% CI, 0.403–1.102; \(p = 0.114\)) (Fig. 4B). Among the right-sided patients with mCRC, no significant difference was noted between the two groups in DCR (100.0% vs. 80.0%; \(p = 0.112\)) and metastatectomy (27.3% vs. 25.0%; \(p = 0.890\), but ORR was significantly different (81.8% vs. 40.0%; \(p = 0.025\)) (Table 4). The median PFS was 25.0 and 14.0 months in the cetuximab and bevacizumab groups, respectively (HR, 0.545; 95% CI, 0.221–1.348; \(p = 0.189\)) (Fig. 5A), and the median OS was 29.0 and 24.0 months, respectively (HR, 0.538; 95% CI, 0.185–1.563; \(p = 0.254\)) (Fig. 5B). We compared the PFS and OS between the 6TA/6TA group and the 7TA/7TA group after irinotecan dose escalation based on UGT1A1 genotyping. There were no significant differences in PFS and OS (\(p = 0.091\) and \(p = 0.799\), respectively).

Efficacy of Target Agent Crossover Therapy

Among the 173 analyzed patients with mCRC, 63 patients (34 from the cetuximab group and 29 from the bevacizumab group) received target therapy crossover. The OS of the cetuximab group was not superior to that of the bevacizumab group (40.0 vs. 35.0 months; HR, 0.734; 95% CI, 0.345–1.560; \(p = 0.421\)) (Fig. 6). Notably, 25 (73.5%) of 34 patients from the cetuximab group received bevacizumab as the third-line therapy, but 25 (86.2%) of 29 patients from the bevacizumab group received cetuximab as the third-line therapy because of reimbursement.

Safety Measures

For the 173 patients with mCRC, irinotecan-related grade III/IV AEs occurred in 25.5% and 26.7% of patients

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### Table 2. The Comparison of Efficacy Between the Cetuximab Group and the Bevacizumab Group Under Chi-Square Analysis

| Efficacy                  | N   | Cetu Group \((N = 98)\) | Beva Group \((N = 75)\) | \(p\) Value |
|---------------------------|-----|-------------------------|-------------------------|------------|
| **Response**              |     |                         |                         | 0.570      |
| Complete response (CR)   | 3   | 2 (2.2%)                | 1 (1.4%)                |            |
| Partial response (PR)    | 108 | 62 (63.2%)              | 46 (61.3%)              |            |
| Stable disease (SD)      | 45  | 27 (27.5%)              | 18 (24.0%)              |            |
| Progressive disease (PD) | 17  | 7 (7.1%)                | 10 (13.3%)              |            |
| **ORR**                  |     |                         |                         | 0.720      |
| CR + PR                  | 111 | 64 (65.3%)              | 47 (62.7%)              |            |
| SD + PD                  | 62  | 34 (54.7%)              | 28 (37.3%)              |            |
| **DCR**                  |     |                         |                         | 0.175      |
| CR + PR + SD             | 156 | 91 (92.8%)              | 65 (86.7%)              |            |
| PD                        | 17  | 7 (7.2%)                | 10 (13.3%)              |            |
| **Metastatectomy**       |     |                         |                         | 0.307      |
| Yes                      | 58  | 36 (36.7%)              | 22 (29.3%)              |            |
| No                       | 115 | 62 (63.3%)              | 53 (70.75)              |            |

Values are number (N) with percentage in parentheses. Cetu group, cetuximab group; Beva group, bevacizumab group; ORR, objective response rates; DCR, disease control rates. All mCRC patients with wild-type RAS gene.
Figure 3. The 173 RAS wild-type patients with mCRC including 98 patients with cetuximab plus FOLFIRI (blue line) and 75 patients with bevacizumab plus FOLFIRI (green line). (A) Progression-free survival (18.0 months vs. 14.0 months; hazard ratio (HR), 0.729; 95% confidence interval (CI), 0.517–1.027; p = 0.071). (B) Overall survival (40.0 months vs. 30.0 months; HR, 0.643; 95% CI, 0.410–1.008; p = 0.054).
in the cetuximab and bevacizumab groups, respectively ($p = 0.658$) (Table 5). The most common severe AEs were neutropenia in both groups (7.1% and 8.0%, respectively). No significant differences were noted in the left-sided patients with mCRC (25.3% vs. 25.5%; $p = 0.871$) and right-sided patients with mCRC (27.3% vs. 30.0%; $p = 0.434$) (Table 6). Neutropenia was still the most common severe AE regardless of sidedness (6.8% vs. 7.3% in left-sided mCRC, and 9.1% vs. 10.0% in right-sided mCRC). No gastrointestinal tract bleeding or perforation related to bevacizumab was found in the bevacizumab group.

The AEs less than grade III between the 6TA/6TA and 7TA/7TA groups were compared. In the 6TA/6TA group, the incidences of grade I and grade II AEs were 32.4% and 24.9%, respectively. Simultaneously, the incidences of grade I and grade II AEs were 50.0% and 50.0% in the 7TA/7TA group, respectively. It showed that it was not significant ($p = 0.853$).

**DISCUSSION**

Despite the advances in medicine, classical chemotherapy remains the first-line treatment of cancer, especially metastatic tumors. Tumor drug resistance and potential side effects are the main limiting factors in cancer treatment. The novel findings of $UGT1A1$ genotyping-guided irinotecan dose escalation in the present study were as follows: (1) anti-VEGF inhibitors or anti-EGFR inhibitors plus irinotecan dose escalation as the first-line treatment in mCRC patients seemed to have favorable PFS and OS. (2) OS seemed not significantly different in the crossover therapy of biologics used in this study under irinotecan dose escalation. (3) Irinotecan dose escalation combined with biologics does not significantly increase the incidence of severe AEs, regardless of vascular endothelial growth factor (VEGF) inhibitor or epidermal growth factor receptor (EGFR) inhibitor.

CRC is a heterogeneous group of tumors at the intertumoral and intratumoral levels. With advances in mCRC treatment over the past 20 years, the median OS has surpassed 40 months in a select patient group with the incorporation of targeted agents into cytotoxic chemotherapy regimens\cite{18,19}. Currently, two promising classes of molecularly targeted compounds have been introduced for the clinical management of mCRC: EGFR antagonists and angiogenesis inhibitors\cite{20}. One large trial, CALGB/SWOG 80405, which compared the cetuximab or bevacizumab plus chemotherapy as first-line therapy in mCRC, revealed that the median OS was 30.0 and 29.0 months and the median PFS was 10.5 and 10.6 months in the cetuximab and bevacizumab groups, respectively\cite{21}. In our study, the median OS and PFS of the two groups significantly improved, and the severe adverse events (SAEs)

| Efficacy                  | N   | Cetu Group ($N = 87$) | Beva Group ($N = 55$) | $p$ Value |
|---------------------------|-----|----------------------|----------------------|-----------|
| Response                  |     |                      |                      |           |
| Complete response (CR)    | 2   | 2 (2.4%)             | 0 (0.0%)             |           |
| Partial response (PR)     | 92  | 53 (60.9%)           | 39 (70.9%)           |           |
| Stable disease (SD)       | 35  | 25 (28.7%)           | 10 (18.2%)           |           |
| Progressive disease (PD)  | 13  | 7 (8.0%)             | 6 (10.9%)            |           |
| **ORR**                   |     |                      |                      |           |
| CR + PR                   | 94  | 55 (63.3%)           | 39 (70.9%)           |           |
| SD + PD                   | 48  | 32 (36.7%)           | 16 (29.1%)           |           |
| **DCR**                   |     |                      |                      |           |
| CR + PR + SD              | 129 | 80 (91.8%)           | 49 (89.1%)           |           |
| PD                        | 13  | 7 (8.2%)             | 6 (10.9%)            |           |
| **Metastatectomy**        |     |                      |                      |           |
| Yes                       | 50  | 33 (37.9%)           | 17 (30.9%)           |           |
| No                        | 92  | 54 (62.1%)           | 38 (69.1%)           |           |

Values are number ($N$) with percentage in parentheses. Left-sided, descending colon + sigmoid colon + rectosigmoid colon + rectum; Right-sided, cecum + ascending colon + transverse colon; N, number; Cetu group, cetuximab group; Beva group, bevacizumab group; ORR, objective response rates; DCR, disease control rates. All mCRC patients with wild-type $RAS$ gene.
Figure 4. The 142 RAS wild-type and left-sided patients with mCRC including 87 patients with cetuximab plus FOLFIRI (blue line) and 55 patients with bevacizumab plus FOLFIRI (green line). (A) Progression-free survival (16.0 months vs 14.0 months; HR, 0.759; 95% CI, 0.522–1.104; \(p = 0.149\)). (B) Overall survival (40.0 months vs 31.0 months; HR, 0.666; 95% CI, 0.403–1.102; \(p = 0.114\)).
were acceptable and did not increase with irinotecan dose escalation. In the FIRE-3 study, the association with longer OS suggests that FOLFIRI plus cetuximab might be the preferred first-line regimen for patients with mCRC with the KRAS exon 2 wild-type. Furthermore, a per-protocol analysis of FIRE-3 in 2021 showed that FOLFIRI plus cetuximab resulted in a significantly higher ORR and longer OS compared with FOLFIRI plus bevacizumab among patients with left-sided tumors22. In our study, we demonstrated that the cetuximab group has nonsignificantly better PFS and OS than the bevacizumab group. However, ORR was also not significantly different between the groups, so we escalated the dose of irinotecan in the patients with left-sided mCRC.

The sidedness of the colon is an independent prognostic factor for survival in metastatic disease23. Two recent meta-analyses have concluded that right-sided colon cancer carries poorer prognosis than left-sided tumors, irrespective of race, adjuvant chemotherapy, number, and quality of studies included24,25. A retrospective study suggested that the addition of anti-EGFR antibodies to chemotherapy has no benefit for right-sided metastatic colon cancer26. Our study revealed no significant difference in the prognosis regardless of mCRC sidedness that irinotecan dose escalated based on the clinical response28. Furthermore, two phase II trials demonstrated a higher ORR and resectability rate in the high-dose irinotecan group29,30. In our previous prospective study, we demonstrated that irinotecan dose escalation with bevacizumab can improve the ORR and metastasectomy31. Similarly, the current study indicated that the escalated-dose group had a better ORR (65.3% vs. 62.7%) and metastasectomy rates (36.7% vs. 29.3%) in the cetuximab and bevacizumab groups, respectively. The potential emergence of cancer cell resistance in EGFR-expressing cancers treated with EGFR inhibitors may explain the refractoriness to these drugs in some cancer patients. VEGF is secreted by cancer cells and regulates tumor-induced endothelial cell proliferation and permeability32. Its upregulation in association with resistance to cetuximab has been reported in experimental models32,33. In the clinical setting, such phenotypic changes could favor the use of anti-VEGFs as a second-line therapy after the first-line cetuximab therapy. Similarly, our study indicated that 73.5% of patients received bevacizumab as the second-line therapy after failure of first-line cetuximab. Nevertheless, OS was not significantly different in either crossover arm.

Studies have demonstrated dose-dependent associations between the UGT1A1 7TA genotype and irinotecan-induced toxicity34,35, and UGT1A1 7TA genotyping is used to reduce dose-limiting neutropenia without affecting its efficacy36. Shulman et al. also indicated that the UGT1A1 7TA genotype is strongly associated with severe hematological toxicity and poorer survival in irinotecan-treated patients37. By contrast, our study emphasizes that

| Efficacy                      | N | Cetu Group (N = 11) | Beva Group (N = 20) | p Value |
|-------------------------------|---|---------------------|---------------------|---------|
| **Response**                  |   |                     |                     |         |
| Complete response (CR)        | 1 | 0 (0.0%)            | 1 (5.0%)            | 0.078   |
| Partial response (PR)         | 16| 9 (81.8%)           | 7 (35.0%)           |         |
| Stable disease (SD)           | 10| 2 (18.2%)           | 8 (40.0%)           |         |
| Progressive disease (PD)      | 4 | 0 (0.0%)            | 4 (20.0%)           |         |
| **ORR**                       |   |                     |                     | 0.025   |
| CR + PR                       | 17| 9 (81.8%)           | 8 (40.0%)           |         |
| SD + PD                       | 14| 2 (18.2%)           | 12 (60.0%)          |         |
| **DCR**                       |   |                     |                     | 0.112   |
| CR + PR + SD                  | 27| 11 (100.0%)         | 16 (80.0%)          |         |
| PD                            | 4 | 0 (0.0%)            | 4 (20.0%)           |         |
| **Metastatectomy**            |   |                     |                     | 0.890   |

Values are number (N) with percentage in parentheses. Cetu group, cetuximab group; Beva group, bevacizumab group; ORR, objective response rates; DCR, disease control rates. All mCRC patients with wild-type RAS gene.

Table 4. The Comparison of Efficacy for 31 Right-Sided mCRC Patients Between the Cetuximab Group and the Bevacizumab Group Under Chi-Square Analysis
Figure 5. The 31 RAS wild-type and right-sided patients with mCRC including 11 patients with cetuximab plus FOLFIRI (blue line) and 20 patients with bevacizumab plus FOLFIRI (green line). (A) Progression-free survival (25.0 months vs. 14.0 months; HR, 0.545; 95% CI, 0.221–1.348; p = 0.189). (B) Overall survival (29.0 months vs. 24.0 months; HR, 0.538; 95% CI, 0.183–1.563; p = 0.254).
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UGT1A1 6TA genotyping for irinotecan dose escalation is relevant to its maximal therapeutic effect. Furthermore, the implication of dose escalation is essential for Asian populations because they inherit the UGT1A1 6TA allele more frequently than Caucasian populations.

Genotyping-guided, patient-specific dose optimization represents an approach to individualize therapy. In the Pan-Asian adapted ESMO consensus guidelines, recommendation 7b showed that UGT1A1 genotyping remains an option and is recommended to be conducted in patients.

**Figure 6.** The 63 patients with crossover therapy of target agents including 34 patients from the cetuximab group (red line) and 29 patients from the bevacizumab group (green line). The overall survival was not significantly different between the two groups (40.0 months vs. 35.0 months; HR, 0.734, 95% CI, 0.345–1.560; \( p = 0.421 \)).

**Table 5.** The Comparison of Severe Adverse Events (≥Grade III) of 173 mCRC Patients Between the Cetuximab Group and Bevacizumab Group

| Events                      | Cetuximab (\( N = 98 \)) | Bevacizumab (\( N = 75 \)) | \( p \) Value |
|-----------------------------|---------------------------|-----------------------------|--------------|
| Events                      | 25 (25.5%)                | 20 (26.7%)                  | 0.658        |
| Neutropenia                 | 7 (7.1%)                  | 6 (8.0%)                    |              |
| Anemia                      | 4 (4.1%)                  | 6 (8.0%)                    |              |
| Oral mucositis              | 2 (2.0%)                  | 1 (1.3%)                    |              |
| Diarrhea                    | 0 (0.0%)                  | 2 (2.6%)                    |              |
| Paresthesia                 | 3 (3.1%)                  | 0 (0.0%)                    |              |
| Nausea/vomiting             | 4 (4.1%)                  | 3 (4.0%)                    |              |
| Liver function impairment   | 1 (1.0%)                  | 2 (2.6%)                    |              |
| Renal function impairment   | 3 (3.1%)                  | 0 (0.0%)                    |              |
| Alopecia                    | 1 (1.0%)                  | 0 (0.0%)                    |              |

All mCRC patients with wild-type RAS gene.
with a suspicion of UGT1A1 deficiency reflected by low conjugated bilirubin or in patients where an irinotecan dose >180 mg/m² per administration is planned. Patients with a favorable UGT1A1 genotype (homozygous wild 6TA/6TA and heterozygous 6TA/7TA) can be treated with high-dose irinotecan without significant toxicity15.

The limitations of this study were as follows: (1) it was a retrospective, observational study; (2) some patients were excluded because of noncompletion of six cycles (17 patients) and loss to follow-up over 6 months (10 patients); (3) the UGT1A1*6 polymorphism may be a potential predictor of severe irinotecan-related neutropenia, but pretherapeutic UGT1A1*6 genotyping was not performed in this study according to Pan-Asian adapted ESMO consensus guidelines; and (4) because of certain circumstances of the patient, not all of the patients can receive escalated irinotecan dose based on the UGT1A1 genotyping.

In summary, our study provides evidence that higher-than-recommended doses of irinotecan might be safely implemented in the FOLFIRI regimen plus anti-EGFR inhibitor or anti-VEGF inhibitor for patients with mCRC receiving a regular dose of irinotecan may be feasible to improve efficacy without increasing toxicity, regardless of sidedness and crossover therapy. However, a further prospective, randomized study is warranted to validate our observational results.

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