Efficacy and Safety of Modified FOLFOXIRI+α in the Treatment of Advanced and Recurrent Colorectal Cancer: A Single-center Experience

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Abstract:
Objective In the treatment of advanced and recurrent colorectal cancer (ARCC), FOLFOXIRI regimens have been proven to be significantly superior to FOLFIRI in terms of the progression-free survival (PFS), response rate (RR), and overall survival (OS). Furthermore, the Tribe trial showed that the RR and PFS rates in patients who received bevacizumab (Bmab)+FOLFOXIRI were superior to those in patients treated with Bmab+FOLFIRI. A phase III trial of panitumumab (Pmab)+FOLFOXIRI is currently ongoing. A modified FOLFOXIRI regimen is also widely used to reduce adverse events. In our department, we introduced modified FOLFOXIRI+α (mFOLFOXIRI+α) in 2015. The present study reviewed the efficacy and safety of mFOLFOXIRI+α.

Methods Eligible patients were retrospectively reviewed, and their results were compared to those of patients treated with other regimens (OTHERS) (n=134) to demonstrate the efficacy of this treatment.

Patients: Between February 2015 and November 2018, 12 patients with ARCC (male/female=6/6; average age, 60.7 years old) received mFOLFOXIRI+α (Bmab: 10, Pmab: 1, alone: 1).

Results The median PFS in the mFOLFOXIRI+α and OTHERS groups was 565 and 322 days, respectively (p=0.0544). The RR in the mFOLFOXIRI+α and OTHERS groups was 66.7% and 31.3%, respectively (p=0.0135). The conversion rate (Conv R) in the mFOLFOXIRI+α and OTHERS groups was 50.0% and 12.7%, respectively (p=0.0007). While 58% of patients treated with FOLFOXIRI+α developed grade ≥3 leukopenia, the incidence of febrile neutropenia (FN) was only 17%. In all patients with symptoms due to the tumor burden, the symptoms subsided with mFOLFOXIRI+α treatment.

Conclusion Based on the RR, Conv R, and symptom palliation ability, mFOLFOXIRI+α was suggested to be a viable candidate for first-line treatment for patients with ARCC, especially those with a high tumor burden.

Key words: mFOLFOXIRI+α, colorectal cancer, tumor burden

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Introduction

The Gruppo Oncologico Nord Ovest (GONO) demonstrated that FOLFOXIRI is significantly superior to FOLFIRI with respect to the response rate (RR; 60% vs. 34%), progression-free survival (PFS; 9.8 vs. 6.9 months) and overall survival (OS; 22.6 vs. 16.7 months) for the treatment advanced and recurrent colorectal cancer (ARCC) (1). Furthermore, the Tribe trial showed that bevacizumab...
Table 1. Patient Characteristics in the Modified FOLFOXIRI+α Group.

| Sex | Age | PS | Primary site | RAS Status | UGT1A1 | Metastatic site | Tumor burden | Symptoms | Combined agent | Res |
|-----|-----|----|--------------|------------|--------|----------------|--------------|----------|---------------|-----|
| F   | 57  | 0  | A            | mutant     | *6 hetero | liver         | moderate     | -        | Bmab         | PR  |
| F   | 62  | 1  | S            | mutant     | *28 hetero | liver, lung   | bulky        | pain     | Bmab         | PR  |
| M   | 63  | 0  | A            | mutant     | *28 hetero | liver, lung   | bulky        | pain     | Bmab         | SD  |
| M   | 37  | 0  | D            | wild       | all wild  | liver, pd     | bulky        | anemia   | Pmab         | PR  |
| F   | 66  | 1  | R            | mutant     | all wild  | liver, lung   | bulky        | pain, constipation | Bmab | PR  |
| F   | 71  | 1  | R            | mutant     | all wild  | liver, lung   | bulky        | pain     | Bmab         | PR  |
| M   | 57  | 0  | R            | mutant     | all wild  | liver         | bulky        | pain, constipation | Bmab | PR  |
| F   | 68  | 1  | R            | wild       | all wild  | ir            | bulky        | -        | Bmab         | PR  |
| F   | 69  | 2  | R            | wild       | all wild  | liver         | bulky        | pain, constipation | Bmab | SD  |
| M   | 65  | 0  | R            | mutant     | *28 hetero | liver, lung   | bulky        | -        | -             | SD  |
| F   | 76  | 2  | R            | mutant     | *28 hetero | liver, lung   | bulky        | abdominal distension | constipation | Bmab | PR  |

F: female, M: male, PS: ECOG-PS (Eastern Cooperative Oncology Group Performance Status), A: ascending colon, D: descending colon, R: rectum, ln: lymph node, pd: peritoneal dissemination, ir: local recurrence, bulky: total diameter of single or multiple tumors>15 cm, moderate: total diameter of single or multiple tumors ≤15 cm and no symptoms due to tumors, Bmab: bevacizumab, Pmab: panitumumab, Res: response, PR: partial response, SD: stable disease

The FOLFOXIRI regimen comprises irinotecan (165 mg/m² on day 1), oxaliplatin (85 mg/m², day 1), leucovorin (L-LV) (200 mg/m² on day 1), and fluorouracil (5-FU) (3,200 mg/m² 48-h continuous infusion, starting on day 1) every 2 weeks. Reduced-dose FOLFOXIRI (modified FOLFOXIRI), which comprises irinotecan (150 mg/m² on day 1), oxaliplatin (85 mg/m² on day 1), L-LV (200 mg/m² on day 1), and 5-FU (2,400 mg/m² 46-h continuous infusion, starting on day 1) every 2 weeks is also frequently used (7). In our department, we started using a modified FOLFOXIRI regimen (FOLFOXIRI+α) to treat ARCC as part of the JACCC-CC-11 trial (7) and have treated 12 patients with this regimen so far.

We herein report the efficacy and feasibility of the FOLFOXIRI+α regimen.

Materials and Methods

Chemotherapy-naïve ARCC patients (between May 2013 and November 2018) who were treated with at least one course of mFOLFOXIRI+α and in whom the response was measured at least one time were eligible for the present study. mFOLFOXIRI comprised irinotecan (150 mg/m², day 1), oxaliplatin (85 mg/m², day 1), L-LV (200 mg/m², day 1), and 5-FU (2,400 mg/m² 46-h continuous infusion, starting on day 1) every 2 weeks. If α is Bmab, we administer Bmab (5 mg/kg) before mFOLFOXIRI on day 1 every 2 weeks. When α is Pmab, Pmab (6 mg/kg) is infused on day 1 every 2 weeks. The efficacy was compared to that in ARCC patients who received chemotherapy with regimens other than FOLFOXIRI+α (OTHERS). The patients’ medical records were retrospectively reviewed to compare the results of chemotherapy with FOLFOXIRI+α and OTHERS.

The response evaluation criteria for solid tumors (REST) and the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) ver. 4.0 were used to evaluate the chemotherapy regimens. The median survival time (MST) and median PFS (mPFS) were calculated by the Kaplan-Meier method. Other factors were evaluated by the chi-squared test with Yate’s adjustment. The Stat View J 5.0 software package (Abacus Concepts, Stat View. Abacus Concepts, Inc., Berkeley, CA, USA) was used to perform the statistical analyses. P values of <0.05 were considered to indicate a statistically significant difference.

Results

Patient characteristics

Twelve patients (male, n=6; female, n=6) receiving treatment with FOLFOXIRI+α satisfied the eligibility criteria; 134 patients received treatment with other regimens (OTHERS). The characteristics of the patients who received FOLFOXIRI+α are shown in Table 1. Only one patient received FOLFOXIRI alone, partly because the patient had 3+ proteinuria, which is a contraindication for Bmab. The characteristics of the patients in the OTHERS group are shown in
The real anti-tumor effect is shown in Fig. 1. Mor burden had their symptoms subside during treatment. Furthermore, in the FOLFOX-FOXIRI+ (CR, n=0; PR, n=42; SD, n=76; PD, n=16). The RR of disease, n=0), while that in the OTHERS group was 31.3%. The DCRs of the two groups did not differ to a statistically significant extent; however, it is worth noting that the RR was 66.7% in the FOLFIRI+α group and 5 (range: 1-12). The median number of treatment courses in the FOLFOXIRI+α group was perfect. The rate of conversion to surgery (Conv R) in the FOLFOXIRI+α group was 50.0% (6/12), while that in the OTHERS group was 100%, while that in the OTHERS group was 50.0% (6/12), while that in the OTHERS group was 88.1%. The DCRs of the two groups did not differ to a statistically significant extent; however, it is worth noting that the DCR of the FOLFOXIRI+α group was 31.3% (CR, n=0; PR, n=42; SD, n=76; PD, n=16). The RR of FOLFOXIRI+α was significantly higher than that of the OTHERS group (p=0.0171). Furthermore, in the FOLFOXIRI+α group, all patients with symptoms caused by the tumor burden had their symptoms subside during treatment. The real anti-tumor effect is shown in Fig. 1.

Table 2. Patient Characteristics in the OTHERS Group (n=134).

| Regimen | Sex (male/female) | Age (median) (range) | ECOG-PS (0/1/2/3) | Primary site (app C/T/D/S/R) | Metastatic/recurrent site (local/lung/liver/LN/spleen/bone/brain) | Metastatic organ (solitary/multiple) | Recurrence/metastatic style (synchronous/metachronous) |
|---|---|---|---|---|---|---|---|
| Oxaliplatin base doublet | 75/59 | 70 (34-85) | 70/56/80 | 2/10/19/48/37/8/4 | 18/35/66/26/29/2/1 | 91/63 | 71/63 |
| Oxaliplatin base doublet+Anti-VEGF mAb | 9 | 1 | 1 | 1 | 1 | 1 | 1 |
| Oxaliplatin base doublet+Anti-EGFR mAb | 49 | 24 | 3 | 14 | 3 | 32 |
| Irinotecan base doublet | 3 | 1 | 1 | 1 | 1 | 1 |
| Irinotecan base doublet+Anti-VEGF mAb | 14 |
| Irinotecan base doublet+Anti-EGFR mAb | 3 |
| Oral 5-FU+zBmab (for frail or elderly) | 5-FUs include UZEL/UFT, capecitabine, and S-1. Anti-VEGF mAbs include Bmab and ramucirumab. Anti-EGFR mAbs include cetuximab and Pmab. Oral 5-FUs include UZEL/UFT, capecitabine, and S-1. Response and time-to-event measures

The median follow-up periods of the FOLFOXIRI+α group were 390 days (range: 152-1,530 days) and 322 days in the OTHERS group. The RR was 66.7% in the FOLFIRI+α group and 322 days in the OTHERS group. The PFS of the FOLFOXIRI+α group tended to be longer than that of the OTHERS group (p=0.0544). The MST of the FOLFOXIRI+α group was 1,161 days, while that of the OTHERS group was 1,036 days. The OS did not differ to a statistically significant extent.

Adverse events

The adverse events of the FOLFOXIRI+α group are shown in Table 5. The incidence of grade ≥3 leukopenia, which occurred in 7 cases (58%), was remarkably high. However, febrile neutropenia only occurred in 2 cases (17%). The mean incidence of grade ≥3 adverse events was 13%. Among all-grade non-hematological toxicities, the incidence rates of general fatigue (83.3%), diarrhea (58.3%), and peripheral nerve injury (50.0%) were remarkably high. No treatment-related deaths occurred, and there were no uncontrollable adverse events.

Discussion

In the present study, we achieved an RR of 66.7%, a DCR of 100%, and a Conv R of 50.0%. The Conv R in our study (50.0%) was higher than that reported in the Tribe and JACCRO-CC-11 trials (2, 7), as shown in Table 6. However, as our study was retrospective in nature and the study population was small, it is impossible to simply compare our results to these clinical trials.

Patients are transferred to surgery based on a consensus decision in a team conference including colorectal surgeons and hepatology surgeons. One reason for the high conversion rate to surgery is that our department is certified as a liver transplant facility. We can perform difficult liver resec-
after 6 courses treatment

Conv R of FOLFOXIRI+

and JACCRO-CC-11 studies. Furthermore, given that the static sites (7).

FOXIRI were able to undergo surgical resection at metastatic sites (7).

In the JACCRO-CC-11 trial for RAS mutant patients, the overall and complete resection rates were 33% and 31%, respectively (9).

4. In patients with liver-limited disease, the overall and complete resection rates were 33% and 31%, respectively (9).

In the OTHERS group, 75.4% of the patients received oxaliplatin or irinotecan-doublet+α, resulting in an MST of 1,036 days (34.5 months) and a Conv R of 12.7% (almost equivalent to that in the Bmab+FOLFIRI arm of the Tribe trial) (2). The use of other regimens in daily clinical practice in real-world settings is therefore considered valid. As the

Figure 1. Anti-tumor activity. Enhanced computed tomography (CT). Huge multiple liver metastases with an unclear border and heterogeneous intensity (before treatment (a). After treatment, remarkable shrinkage of the liver metastases was observed, the border became clear, morphologic changes were observed, and a homogeneous low intensity was observed inside the tumor (b). A huge primary lesion with remarkable lymph node swelling before treatment (c). Remarkable shrinkage of both the primary tumor and lymph nodes was observed after treatment (d).

Table 3. Anti-tumor Effects of Modified FOLFOXIRI+α and OTHERS.

|                        | mFOLFOXIRI+α (n=12) | OTHERS (n=134) | p value |
|------------------------|---------------------|----------------|---------|
| Response rate (RR)     | 66.7%               | 31.3%          | p=0.0135|
| CR/PR/SD/PD            | 0/8/40              | 0/42/76/16     |         |
| Disease control rate (DCR) | 100%                | 88.1%          | p=0.2046|
| CR/PR/SD/PD            | 0/8/40              | 0/42/76/16     |         |
| Conversion rate (Conv R) | 50.0%              | 12.7%          | p=0.0007|
|                        | (6/12)              | (17/134)       |         |

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

tion, which is impossible in ordinary hospitals.

Regarding the RAS status-specific conversion rates, the Prime trial, which only included RAS wild-type patients, reported the rates of any resection (14%) and complete resection (10%) in patients treated with panitumumab+FOLFIRI 4. In patients with liver-limited disease, the overall and complete resection rates were 33% and 31%, respectively (9).

In the JACCRO-CC-11 trial for RAS mutant patients, only 18% of the patients treated with bevacizumab+FOLFOXIRI were able to undergo surgical resection at metastatic sites (7).

The Conv R of our study was higher than in the Prime and JACCRO-CC-11 studies. Furthermore, given that the Conv R of FOLFOXIRI+α in patients with RAS wild-type is the same as in patients with RAS mutations, FOLFOXIRI +α is the treatment choice when immediate treatment is needed for patients with severe symptoms caused by a high tumor burden but in whom the RAS status is unknown. Indeed, in the present study, three patients with a high tumor burden and whose RAS status was unknown were treated by FOLFOXIRI+α. The RAS status was determined in these cases after surgery.

In the OTHERS group, 75.4% of the patients received oxaliplatin or irinotecan-doublet+α, resulting in an MST of 1,036 days (34.5 months) and a Conv R of 12.7% (almost equivalent to that in the Bmab+FOLFIRI arm of the Tribe trial) (2). The use of other regimens in daily clinical practice in real-world settings is therefore considered valid. As the
outcomes of FOLFOXIRI+α were better than those of OTHERS, at least over the short term, mFOLFOXIRI+α is considered a powerful treatment of choice for ARCC.

We compared the findings of our study to those of two other clinical trials, shown in Table 6. The QUATTRO study evaluated the original FOLFOXIRI+Bmab regimen in Japanese patients with ARCC (8). As the feasibility and efficacy were high in the Japanese patients, the original FOLFOXIRI+Bmab regimen may be used to treat Japanese patients in the clinical setting. However, the incidence of grade ≥3 leukopenia (n=125; 50.0%) in patients who received FOLFOXIRI+Bmab was markedly higher than in the Tribe (original) and JACCRO-CC-11 (modified) trials (2, 7, 8). Given the efficacy and based on the fact that the incidence of grade ≥3 leukopenia in the JACCRO-CC-11 (Japanese patients) trial was similar to the rate reported in the Tribe (world) trial, mFOLFOXIRI+α may be considered appropriate for Japanese patients with ARCC.

In the present study, the symptoms in all symptomatic patients subsided as a result of treatment with FOLFOXIRI+α, which improved their quality of life. The greatest positive effect of mFOLFOXIRI+α in this study was that even if conversion was not attained, the treatment had the ability to improve symptoms that occurred due to a heavy tumor burden. Furthermore, in two cases, the PFS was more than 1,000 days, potentially indicating a cure.

Of note, FOLFOXIRI+Bmab is the first colorectal cancer regimen to adopt a continuous maintenance concept, similar to chemotherapy for non-small-cell lung cancer (10). After the patient’s symptoms are alleviated by a deep response to chemotherapy for non-small-cell lung cancer (10), the patient’s symptoms are alleviated by a deep response to chemotherapy for non-small-cell lung cancer (10) after the patient’s symptoms are alleviated by a deep response to chemotherapy for non-small-cell lung cancer (10).

Table 4. Anti-tumor Effects of MFOLOXXI1+α and OTHERS (RAS Status-specific).

| Regimen                        | n   | RR (%) | DCR (%) | Conversion rate |
|--------------------------------|-----|--------|---------|-----------------|
| FOLFOXIRI+α (alone: 1, bmab: 12, pmab: 1) | 14  | 66.7   | 100.0   | OVERALL         |
| OTHERS                         |     |        |         | RAS WILD        |
| Oxaliplatin base doublet       | 9   | 22.2   | 88.9    | 0.0 (0/9)       |
| Oxaliplatin base doublet + Anti-VEGF mAb | 49  | 32.7   | 91.8    | 20.4 (10/49)    |
| OTHERS                         |     |        |         | RAS mutant      |
| Oxaliplatin base doublet + Anti-EGFR mAb | 24  | 45.8   | 83.3    | 25.0 (6/24)     |
| Irinotecan base doublet        | 3   | 33.3   | 33.3    | 0 (0/3)         |
| Irinotecan base doublet + Anti-VEGF mAb | 14  | 28.6   | 71.4    | 0 (0/14)       |
| OTHERS                         |     |        |         | RAS unknown     |
| Oxaliplatin base doublet + Anti-EGFR mAb | 3   | 33.3   | 100.0   | 33.3 (1/3)     |
| Oral 5-FU+Bmab (for frail or elderly) | 32  | 21.9   | 90.6    | 0.0 (0/32)     |

Figure 2. Survival analyses. Kaplan-Meier curves for the progression-free survival (a) and overall survival (b) in the mFOLFOXIRI+α and OTHERS group.
Table 5. Adverse Events of Modified FOLFOXIRI+α.

| Grade | 1 (0%) | 2 (8%) | 3 (58%) | 4 (0%) |
|-------|--------|--------|---------|--------|
| leukopenia | 0 (0%) | 1 (8%) | 7 (58%) | 0 (0%) |
| febrile neutropenia (FN) | 0 (0%) | 0 (0%) | 2 (17%) | 0 (0%) |
| anemia | 0 (0%) | 0 (0%) | 2 (17%) | 0 (0%) |
| thrombocytopenia | 0 (0%) | 1 (8%) | 0 (0%) | 0 (0%) |
| fever (non-FN) | 0 (0%) | 1 (8%) | 0 (0%) | 0 (0%) |
| general fatigue | 2 (17%) | 7 (58%) | 1 (8%) | 0 (0%) |
| nausea/vomiting | 0 (0%) | 2 (17%) | 0 (0%) | 0 (0%) |
| appetite loss | 0 (0%) | 3 (25%) | 1 (8%) | 0 (0%) |
| diarrhea | 0 (0%) | 4 (33%) | 3 (25%) | 0 (0%) |
| alopecia | 4 (33%) | 5 (42%) | - | - |
| peripheral nerve injury | 1 (8%) | 4 (33%) | 1 (9%) | 0 (0%) |
| renal dysfunction | 0 (0%) | 0 (0%) | 1 (9%) | 0 (0%) |
| dehydration | 0 (0%) | 0 (0%) | 0 (0%) | 1 (8%) |
| electrolyte abnormality | 0 (0%) | 0 (0%) | 0 (0%) | 1 (8%) |
| skin erosion | 0 (0%) | 0 (0%) | 1 (8%) | 0 (0%) |

Table 6. Comparison of Original FOLFOXIRI to Modified FOLFOXIRI.

|                  | Tribe (original) | JACCRO-CC11 (modified) | Our study (modified) |
|------------------|------------------|------------------------|----------------------|
| RR (%)           | 65.1             | 75.8                   | 66.7                 |
| Conv R (%)       | 15               | 15                     | 50.0                 |
| median PFS (month) | 12.1            | 11.5                   | 18.8                 |
| MST (month)      | 29.8             | not reached            | 38.7                 |
| leukopenia Grade ≥3 (%) | 50.0          | 54.0                   | 58.3                 |
| FN (%)           | 8.8              | 5.0                    | 16.6                 |

+leucovorin+α, which maintains their quality of life, even if conversion is not achieved. FOLFOXIRI+α is therefore also considered appropriate for palliative purposes.

Further studies with the accumulation of more cases and a longer study period are needed to validate the findings of the present study.

Conclusion

Given the high response rate and conversion rate, symptom palliation ability, and good tolerability, mFOLFOXIRI+α was suggested to be a suitable candidate for first-line treatment for Japanese patients with ARCC, especially those with a high tumor burden, both as a conversion treatment and as a palliative treatment.

The authors state that they have no Conflict of Interest (COI).

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