Case report

First-line treatment with modified FOLFOXIRI plus bevacizumab in patients with locally advanced colorectal cancer

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Abstract
Introduction: The combination regimen of fluorouracil, folinate, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab (Bmab) is recommended as the first-line treatment for patients with mutant RAS/BRAF or patients with wild RAS/BRAF right-side located, according to the 2019 colorectal cancer guidelines of the Japanese Society of Cancer for Colon and Rectum. However, little is known the practical results for Japanese patients.

Patients: Five cases with FOLFOXIRI + Bmab therapy as first-line for locally advanced colorectal cancer (CRC) with or without metastasis in our department from August 2018 were analyzed.

Results: A median age was 71 years old including 4 male and 1 female. The location of cancer was as right-side colon in 1 case, left-side colon in 3 cases, and rectum in 1 case. Three cases had KRAS mutation. One case of BRAF mutation was found. Bypass or colostomy was performed in all patients prior to chemotherapy. A median number of 10 (3–16) chemotherapy courses were administered, and the best response was partial response (PR) in four cases and stable disease (SD) in one case. Considering primary tumor, four cases achieved primary site resection and one case was radically resected as Cur B resection. Three patients experienced grade 3 toxicity and then the treatment dose was reduced.

Conclusion: Our experienced 5 cases of locally advanced CRC treated with modified FOLFOXIRI + Bmab as first-line therapy demonstrated that quite good tumor shrinkage was obtained in a quite short period of therapy even with quite high incidence of severe toxicities.

Keywords: modified FOLFOXIRI, bevacizumab, locally advanced colorectal cancer

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intravenously, consisted of Bmab 5 mg/kg on day 1 plus modified FOLFOXIRI (irinotecan 150 mg/m² over the course of 1 hour on day 1, immediately followed by oxaliplatin 85 mg/m² and l-leucovorin 200 mg/m² of infused concomitantly over the course of 2 hours, and then followed by a continuous 46-hour infusion of fluorouracil at a dose of 2400 mg/m² on day 1).

Clinical course and adverse events were assessed. The response evaluation criteria for solid tumors (RESIST) and the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) ver. 4.0 were used to evaluate.

**Results**

**Patients’ characteristics**

The characteristics of each patient before the initiation of chemotherapy were summarized in Table 1. All patients had T4b tumor and 3 out of 5 patients were recognized as having metastasis, then they were initiated for the purpose of early shrinkage. Three out of 5 patients have RAS mutation. One patient was not evaluated gene status not to obtain sufficient materials. All patients were received surgical treatment to prevent bowel obstruction including intestinal bypass or stoma creation.

**Treatment outcomes**

The median cycles of treatment were 10 (3–16) cycles. Three out of 5 cases was received 20–40% dose reduction because of toxicities (Table 2). The best overall response was assessed as partial response in 4 cases and as stable disease in 1 case. The RR was 80% and the DCR was 100% respectively. Four patients underwent resection of primary lesion. Two cases of Stage 3 were obtained Cur A⁶ resection (Fig. 1: Case 1). One out of 3 Stage 4 patients was obtained Cur B⁶ resection (Fig. 2: Case 4). One patient continued the treatment without surgery until the recognition of disease progression. In Case 2, the primary lesion was surgically resected due to the perforation of large bowel around stoma after 6 cycles of treatment because of obtaining PR in primary site and

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**Table 1 Patients’ characteristics before initiation of chemotherapy**

| Case | Age | Gender | Location | T*            | N* | M*            | cStage* | RAS/BRAF status | Pretreatment surgery |
|------|-----|--------|----------|---------------|----|---------------|---------|-----------------|----------------------|
| 1    | 74  | M      | A        | T4b (retroperitoneum) | N3 | M0            | cStage IIIb | BRAF V600D | Ileo-colectomy       |
| 2    | 73  | M      | RS       | T4b (urinary bladder) | N0 | M1b | liver, lung | cStage IV | KRAS G12D | Stoma creation       |
| 3    | 44  | F      | S        | T4b (retroperitoneum) | N3 | M1b | liver, peritoneum | cStage IV | NE³⁹ | Ileo-colectomy       |
| 4    | 71  | M      | S        | T4b (urinary bladder, rectum) | N2 | M1a | liver | cStage IV | KRAS G12D | Stoma creation       |
| 5    | 50  | M      | S        | T4b (urinary bladder) | N1 | M0            | cStage IIIa | KRAS G12V | Stoma creation       |

*: according to Japanese Classification of Colorectal Carcinoma, **: not evaluated

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**Table 2 Treatment summary**

| Case | Cycles | Dose reduction | Best response | Outcome |
|------|--------|----------------|---------------|---------|
| 1    | 3      | Yes 20%        | PR            | Cur A resection |
| 2    | 16*    | Yes 40%        | PR            | Primary lesion resection |
| 3    | 12     | Yes 20%        | PR            | Disease progression |
| 4    | 6      | No             | PR            | Cur B resection |
| 5    | 8      | No             | SD            | Cur A resection |

*: After 6 cycles, the primary lesion was resected. The more 10 cycles were administered.
metastasis (Fig. 3).

**Toxicities**

All toxicities of any grade in each case were summarized in Table 3. ALL 5 cases have several kinds of toxicities. Three patients experienced grade 3 toxicity and then the treatment dose was reduced (Table 2).

**Discussion**

JACCRO CC-11 was conducted to prospectively evaluate early tumor shrinkage (ETS) and depth of response (DpR) in all of the subjects. ETS was confirmed in 74% of the 61 assessable patients in whom response was evaluated by a board independent of attending doctor\(^3\). It was relative high compared with ETS of 63% in TRIBE trial, and the ETS ranged from 62% to 69% in the CRYSTAL, OPUS, and FIRE-3 trials\(^7,8\). They have reported that patients who had an early response had better survival than without ETS\(^3\). The results of CC-11 showed that treatment with FOLFOXIRI + Bmab positively correlated with ETS or DpR and survival\(^9\). It indicates that FOLFOXIRI + Bmab therapy is an active first-line treatment for patients with metastatic CRC who harbor RAS mutant tumors. And it also suggests that modified FOLFOXIRI + Bmab might become an alternative regimen of triplet chemotherapy for Japanese patients\(^9\).

According to these results, we inducted modified FOLFOXIRI + Bmab for locally advanced CRC with or without metastasis to expect tumor shrinkage. 80% of RR was obtained and 80% of cases were performed the resection of primary lesion after 3–8 cycles of treatment including even in assessment with SD. Additionally, 1 case achieved Cur B resection. This indicated that this regimen really could show ETS and DpR even in locally advanced CRC.

On the other hand, adverse events were occurred in all 5 patients with G2 and in 3 patients with G3. The dose reduction was needed in 60% patients, however, no patients discontinued due to toxicities. In QUATTRO study, 5 patients out of 69 patients could not continue the induction therapy scheduled 12 cycles due to toxicities including 1 patient with treatment related death\(^4\). If the purpose of use this regimen is to achieve tumor shrinkage in a short period, we should perform standard supportive treatments for chemotherapy including prophylactic use of anti-emetic drugs such as corticosteroids, 5-hydroxytryptamine 3 (5-HT3) receptor antagonists,

Fig. 2 CT scan of Case 4. A large tumor of sigmoid colon (white arrow) invaded to urinary bladder (white arrow head) (A, C). After 6 course of treatment, the shrinked tumor (white arrow) was released from urinary bladder (white arrow head) (B, D).
and neurokinin 1 (NK-1) receptor antagonists, granulocyte colony stimulating factor for fibril neutropenia and drip infusions for anorexia to maintain chemotherapy.

In conclusion, we experienced 5 cases treated with modified FOLFOXIRI + Bmab for locally advanced unresectable CRC with or without metastasis as fist-line therapy. Quite good tumor shrinkage was obtained in a quite short period of therapy even with quite high incidence of severe toxicities.

Conflict of interest:
The authors declare that they have no conflict of interest.

Ethical approval:
All procedures performed in studies involving human participants

Table 3 Toxicities

| Adverse event               | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|-----------------------------|--------|--------|--------|--------|--------|
| Leukopenia                  | G3     | G3     |        |        |        |
| Neutropenia                 | G4     |        |        |        |        |
| Thrombocytopenia            | G2     |        |        |        |        |
| Anemia                      |        |        | G2     |        |        |
| Febrile neutropenia         | G3     |        |        |        |        |
| Anorexia                    | G3     | G2     | G1     |        |        |
| Nausea                      |        | G3     | G1     |        |        |
| Vomiting                    |        |        | G1     |        |        |
| Stomatitis                  |        |        |        | G1     |        |
| Diarrhea                    | G1     |        |        | G1     |        |
| Liver dysfunction           |        |        |        |        | G2     |
| Bowel perforation           |        |        |        |        | G3     |
| Ascites                     |        |        |        |        |        |
| Fatigue                     |        |        |        | G1     | G1     |
| Urinary tract infection     |        |        |        | G2     | G2     |
| Pollakuria                  |        |        |        |        | G1     |
| Peripheral neuropathy       |        |        | G1     | G1     | G1     |
| Edema                       |        |        |        |        | G2     |

Fig. 3 CT scan of Case 2. CT scan (A, C) before chemotherapy presented sigmoid colon cancer (white arrow) invaded to urinary bladder (white arrow head) with multiple liver metastasis. After 6 course of treatment, the shrinked tumor (white arrow) was released from urinary bladder (white arrow head) and liver metastasis were markedly reduced tumor size (B, D).
were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:**
Informed consent was obtained from all individual participants included in the study.

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