

# Complete remission of peritoneal dissemination of colon cancer by alternate-day S-1 and oxaliplatin plus bevacizumab treatment and maintenance chemotherapy comprising alternate-day S-1 plus bevacizumab: A case report

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Received August 20, 2018; Accepted December 7, 2018

DOI: 10.3892/mco.2018.1791

**Abstract.** A 56-year-old man diagnosed with sigmoid colon cancer underwent sigmoid colectomy. Nine months later, his serum carcinoembryonic antigen (CEA) level had increased, and the diagnosis of recurrent peritoneal dissemination was made based on positron emission tomography/computed tomography (PET/CT) findings. Although systemic chemotherapy comprising S-1 and oxaliplatin (SOX) plus bevacizumab was initiated, severe diarrhea occurred on day 4 of the second cycle despite reduction in S-1 dose. By changing the daily oral intake schedule for S-1 to an alternate-day intake from the third cycle (modified SOX plus bevacizumab), the patient was able to continue undergoing chemotherapy without any adverse gastrointestinal effects. All tumors disappeared after four cycles, and the patients received eight cycles of modified SOX plus bevacizumab followed by maintenance chemotherapy comprising alternate-day S-1 plus bevacizumab. Maintenance chemotherapy was discontinued after 17 cycles owing to adverse events, including thrombocytopenia, corneal and lacrimal duct disorders, and hyperbilirubinemia. The patient has been radiographically confirmed to be in remission for 5 years without any recurrence, and his serum CEA

level has been within normal range for >3 years. To conclude, compared with the conventional consecutive treatment, alternate-day SOX plus bevacizumab treatment may reduce the adverse effects of these chemotherapeutic drugs.

## Introduction

Peritoneal dissemination is one of the leading causes of death associated with colon cancer recurrence and is often challenging to treat. Population-based data revealed that the median survival period after diagnosis of peritoneal dissemination is 6 months (1). A pooled analysis of two large prospective randomized phase III trials revealed that peritoneal carcinomatosis is associated with a significantly shorter overall survival and progression-free survival compared with other metastatic sites, despite delivering intense systemic chemotherapy (2). However, another nationwide population-based study has demonstrated that the use of bevacizumab as a supplement improved the overall median survival of patients with peritoneal carcinomatosis (3).

S-1 is an oral anticancer agent containing two biochemical modulators for 5-FU and tegafur (FT), which is a metabolically activated prodrug of 5-FU. A recent randomized phase III study (SOFT trial) demonstrated that the effect of S-1 and oxaliplatin (SOX) plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab as first-line treatment for metastatic colorectal cancer among Asian populations (4). Although leucopenia and neutropenia of grade 3 or higher were more common in patients given mFOLFOX6 plus bevacizumab than in those given SOX plus bevacizumab, anorexia and diarrhea of grade 3 or higher were significantly more common in patients given SOX plus bevacizumab than in those given mFOLFOX6 plus bevacizumab. In contrast, Shirasaka *et al* (5) reported lower gastrointestinal toxicity of alternate-day S-1 intake than that of conventional consecutive S-1 intake (6,7), and a recent randomized controlled trial supported their results (8).

We herein report a case of successful management of severe diarrhea and achievement of long-term complete remission

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*Abbreviations:* CEA, carcinoembryonic antigen; PET/CT, positron emission tomography/computed tomography; SOX, S-1 and oxaliplatin; 5-FU, 5-fluorouracil; FT, tegafur; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; CapeOX, capecitabine and oxaliplatin

*Key words:* recurrent colon cancer, peritoneal dissemination, peritoneal metastases, chemotherapy, alternate-day pattern, S-1, oxaliplatin, complete remission

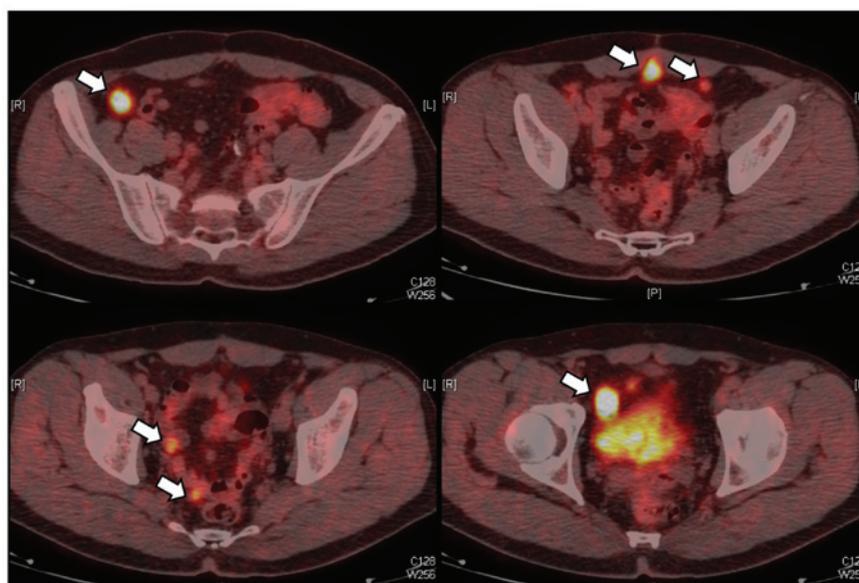


Figure 1. Positron emission tomography-computed tomography revealed high tracer accumulation in multiple tumors spread across the abdominal cavity (arrows).

of peritoneal dissemination of colon cancer by changing the conventional schedule for S-1 administration to an alternate-day S-1 administration pattern along with oxaliplatin (modified SOX) plus bevacizumab, which was combined with maintenance chemotherapy comprising alternate-day S-1 plus bevacizumab.

### Case report

A 56-year-old man diagnosed with sigmoid colon cancer was referred to our hospital for surgery. There was no evidence of peritoneal dissemination at the operation, and open sigmoid colectomy involved colonic mobilization with high ligation of the inferior mesenteric vessels and complete mesocolic excision. Anastomosis was completed using a circular stapler. The operation time was 169 min with 175 g blood loss. The postoperative course was uneventful, with no complications. Pathological examination revealed a well-differentiated adenocarcinoma with wild-type KRAS: 30x33 mm, pT3 (SS), int, INFb, ly1, v1, pN0 (0/15), pPM0 (115 mm), pDM0 (140 mm), pRM0, M0, and pStage IIA. Histopathology of the primary sigmoid colon cancer indicated an ordinary well-differentiated tubular adenocarcinoma with nothing to be noted pathologically (figure not shown).

Nine months after the surgery, his serum carcinoembryonic antigen (CEA) level increased to 9.2 ng/ml. Positron emission tomography/computed tomography (PET/CT) revealed high levels of tracer accumulation in multiple tumors that were present across the abdominal cavity (Fig. 1). As there were no other suspicious primary lesions, the sigmoid colon cancer was advanced, and the CEA level was high, it was considered appropriate to diagnose the patient with peritoneal dissemination of sigmoid colon cancer. We did not perform either staging laparoscopy or pathological tissue examination.

After obtaining informed consent from the patient, systemic chemotherapy comprising SOX plus bevacizumab was initiated. The patient received an intravenous infusion of

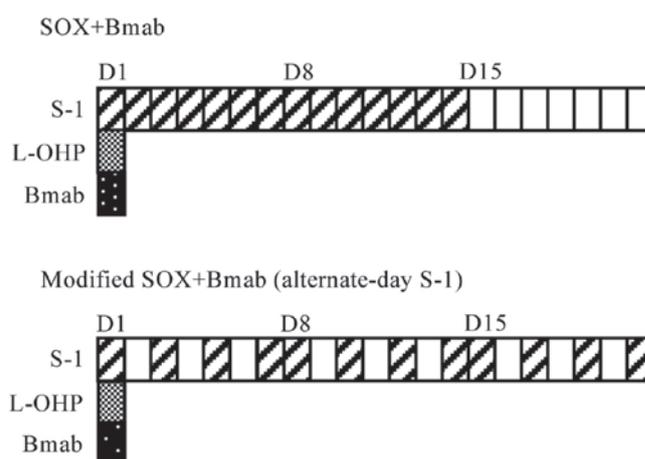


Figure 2. Schedules of chemotherapy. SOX, S-1 and oxaliplatin; L-OHP, oxaliplatin; Bmab, bevacizumab.

7.5 mg/kg bevacizumab followed by an intravenous infusion of 130 mg/m<sup>2</sup> oxaliplatin on day 1 of a 3-week cycle. A dose of 120 mg/day for S-1 was prescribed according to the body surface area and was taken orally twice daily starting after dinner from day 1 for 2 weeks. However, anorexia and severe diarrhea occurred to an extent that infusion treatment was necessary during the first cycle. Although the second cycle involving a reduced dose of S-1 was resumed 2 weeks later than the usual schedule, anorexia and severe diarrhea recurred on day 4 of this cycle. Oral S-1 intake was stopped and the patient was hospitalized for 2 weeks to manage the adverse effects.

From the third cycle, we adopted an alternate-day S-1 and oxaliplatin (modified SOX) administration pattern, i.e., for 4 days in a week (Monday, Wednesday, Friday, and Sunday), along with bevacizumab (Fig. 2); thus, the patient was able to continue chemotherapy without adverse gastrointestinal effects. PET-CT revealed that all tumors disappeared after

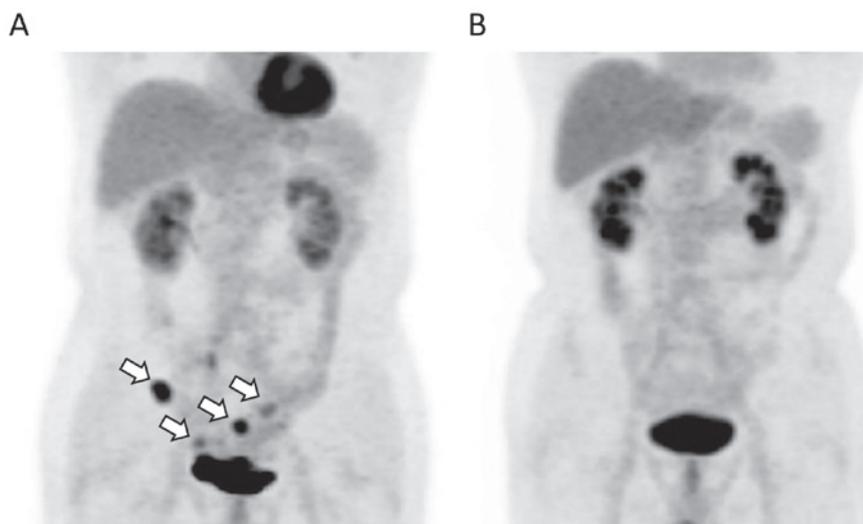


Figure 3. (A) Positron emission tomography revealed an accumulation of a large amount of tracer in the peritoneal metastases prior to chemotherapy (arrows). (B) Disappearance of all tumors following four cycles of chemotherapy.

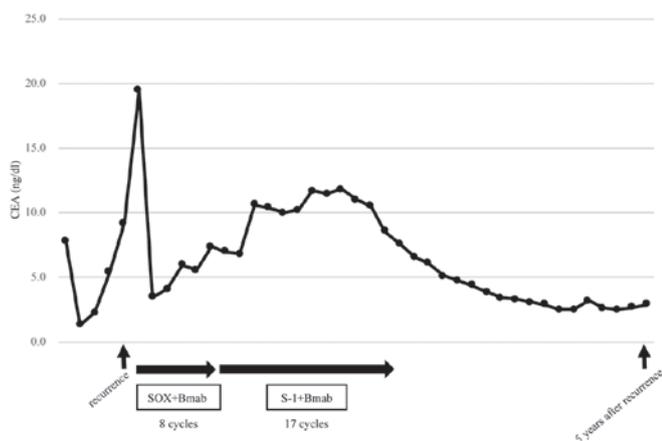


Figure 4. Serum CEA transition graph. Serum CEA level normalized soon after the initiation of chemotherapy and gradually began to increase. As maintenance chemotherapy continued, serum CEA level gradually decreased and normalized again. SOX, S-1 and oxaliplatin; Bmab, bevacizumab; CEA, carcinoembryonic antigen.

four cycles (Fig. 3). Due to the manifestation of grade 3 peripheral neuropathy after eight cycles, we switched to maintenance chemotherapy comprising alternate-day S-1 plus bevacizumab. Although maintenance chemotherapy was discontinued after 17 cycles owing to adverse events, including thrombocytopenia, corneal and lacrimal duct disorders, and hyperbilirubinemia, serum CEA level gradually began to decrease and normalized around the same time as chemotherapy discontinuation (Fig. 4). He has been in remission for 5 years without recurrence and his serum CEA level has been within normal range for >3 years.

## Discussion

In the present case, SOX plus bevacizumab and maintenance chemotherapy without oxaliplatin was highly effective against peritoneal carcinomatosis of recurrent colon cancer. We successfully managed severe gastrointestinal adverse effects

by changing the conventional oral S-1 intake schedule to an alternate-day pattern.

SOFT trial had previously demonstrated that SOX plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab as first-line treatment for metastatic colorectal cancer (4), and it was noted that unlike patients receiving mFOLFOX6, patients receiving SOX and those receiving CapeOX (capecitabine and oxaliplatin) did not need an intravenous port or an ambulatory infusion pump. Phase 3 trials have demonstrated that SOX is similar to CapeOX with respect to overall survival associated with its role as the first-line treatment agent for patients with metastatic colorectal cancer (9,10). However, the median time to failure was significantly longer and the rate of objective response was significantly higher in the SOX group than those in the CapeOX group, despite the former having lower dose intensity of oxaliplatin and more frequent delays in chemotherapeutic cycles caused by the occurrence of adverse events, especially thrombocytopenia and diarrhea. Therefore, reduction of these SOX-related adverse effects by achieving an adequate dose intensity of oxaliplatin might facilitate better results without any delays in chemotherapy cycles. Our patient experienced severe diarrhea despite undergoing a reduction in S-1 dose during the second cycle. Changing chemotherapy to capecitabine-based therapy at this point would have been one possible method; however, the authors selected an alternate-day drug administration pattern developed by Shirasaka *et al* (11) to reduce gastrointestinal toxicity. Consequently, severe diarrhea became manageable, and modified SOX plus bevacizumab proved to be highly effective and brought about the disappearance of peritoneal dissemination after four cycles. Moreover, the patient was able to undergo eight cycles of modified SOX administration followed by maintenance chemotherapy. A randomized phase II study to verify the clinical effects of alternate-day S-1 administration pattern on colorectal cancer is currently ongoing (12), and its results might help elucidate whether such a modified chemotherapeutic regimen will be useful for reducing the adverse effects associated with conventional chemotherapy.

Another clinical problem that was targeted in the present case is whether chemotherapy should be discontinued after complete remission is achieved. OPTIMOX2 study compared chemotherapy discontinuation with maintenance therapy after six cycles of FOLFOX chemotherapy as the first-line treatment for metastatic colorectal cancer and revealed that a complete discontinuation of chemotherapy had a negative impact on the duration of disease control and progression-free survival (13). CAIRO3 study revealed that performing maintenance treatment with capecitabine and bevacizumab after the administration of CapeOX plus bevacizumab for metastatic colorectal cancer was advantageous, and the benefit of such a maintenance therapy was most pronounced in patients with RAS/BRAF wild-type (14). Contrastingly, Dy *et al* (15) reported survival outcomes among patients with metastatic colorectal cancer who achieved a complete response to systemic treatment, and no difference was observed in survival between patients who received maintenance treatment beyond two cycles after documentation of complete response and those who did not; however, this was not a randomized study. In the present case, maintenance therapy comprising alternate-day S-1 plus bevacizumab was continued owing to the persistence of a high serum CEA level even after achieving complete remission. In case of peritoneal dissemination, we believe that maintenance therapy is imperative, as radiologically evident lesions might result in bowel transit obstruction due to intestinal narrowing and peristaltic failure, as opposed to other metastatic lesions, including those in the liver. Wang *et al* (16) reported that measurement of CEA levels might be useful for monitoring chemotherapeutic response in patients with metastatic colorectal cancer when imaging studies are unsuitable. Approximately 3 years after chemotherapy initiation, after radiographically confirming absence of recurrence, the authors discontinued maintenance chemotherapy after obtaining the patient's consent, owing to the occurrence of adverse events. Because the patient's serum CEA level had normalized for >3 years after chemotherapy discontinuation and no recurrence was radiologically detected for >5 years, indicating complete remission, continuing maintenance therapy was appropriate in the present case.

Finally, a limitation of the present case report is the absence of staging laparoscopy to diagnose and confirm peritoneal dissemination pathologically. Because PET/CT is reported to be the most reliable modality with the highest positive predictive value for pathologic staging in the care of patients with malignant diseases unless the cancer has a predominantly mucinous histology (17,18), the authors used a PET/CT scan to diagnose and confirm the peritoneal dissemination in the present case, and the cancer could be eradicated by intense chemotherapy combined with maintenance therapy since the patient was in long-term complete remission. However, close follow-up is warranted, as peritoneal dissemination is known to be a late (2 years or later) recurrence risk factor (19).

#### Acknowledgements

Not applicable.

#### Funding

No funding was received.

#### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

#### Authors' contributions

NN prepared the manuscript draft and participated in revising the manuscript. NN, AyK, TD, JN, AT and YI treated the patient. MT, RU, NM, MK, TK, HH, HE, AtK, TH and MM also assisted in patient treatment. HH is a medical oncologist and gave NN scientific advice on manuscript preparation. All authors read and approved the final version of this manuscript.

#### Ethics approval and consent to participate

All protocols in the present case report were followed in accordance with the ethical principles of the Declaration of Helsinki. Written and verbal informed consent was obtained from the patient. This case report was approved by the Ethics Committee of International University of Health and Welfare, Mita Hospital.

#### Patient consent for publication

Written and verbal informed consent was obtained from the patient.

#### Competing interests

The authors declare that they have no competing interests.

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