A case of clinical complete response of colorectal liver metastasis following chemotherapy with S-1 and oxaliplatin (SOX) in combination with bevacizumab

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Abstract
Although the survival of patients with liver metastases was previously extremely poor, the introduction of novel chemotherapeutic agents, such as oxaliplatin, has increased the median survival of these patients. S-1 has been reported to show strong antitumor activity in various types of cancer, such as colorectal cancer (CRC), and its feasibility in combination with oxaliplatin (SOX) has been reported to have a promising efficacy with fair tolerability in patients with metastatic CRC. We here present a case of synchronous liver metastasis of CRC in which a complete clinical response was successfully achieved by SOX plus bevacizumab (BV). CT scan results confirmed a clinical complete response after eight cycles, and monotherapy with S-1 was ongoing for 6 months. Currently, there was no evidence of any recurrent or metastatic lesions. We found that a regimen of SOX plus BV is a safe and effective treatment for metastatic CRC that does not require central venous access.

Keywords: Complete response, colorectal cancer, liver metastases, SOX, bevacizumab

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Introduction
The five-year survival rate of patients with resectable colorectal cancer (CRC) has improved in recent years, reaching more than 80%¹. However, the survival of patients with CRC with unresectable metastasis remains low. About half of CRC patients develop liver metastases, which is an important factor for their survival².

The FOLFOX regimen, which includes bolus/infusional 5-fluorouracil (5-FU) with folinic acid modulation and oxaliplatin, has become an effective first-line treatment for patients with metastatic CRC. However, treatment with infusional 5-FU has increased inconvenience, cost and morbidity related to the use of portable infusion pumps and a central venous catheter port. The use of oral fluoropyrimidines has been evaluated as an alternative to infusional 5-FU. S-1 is an orally active prodrug of 5-FU that contains tegafur, which is constantly metabolized to 5-FU combined with modulators, including gimeracil and potassium oxonate³. S-1 has shown strong antitumor activity in various types of cancer, including CRC, and its feasibility and a combination with oxaliplatin (SOX) have shown promising efficacy with fair tolerability in patients with metastatic CRC⁴. Moreover, no increases in toxicities were observed when BV and oxaliplatin were used in combination⁵. Yamada et al. reported that SOX plus BV was not only inferior to mFOLFOX6 plus BV with respect to progression free survival, but it also led to equivalent responses for metastatic CRC⁶. They also concluded that SOX plus BV could be a first-line option for patients who require tumor shrinkage or are expected to subsequently receive treatments similar to mFOLF-OX6 plus BV.

We herein report a case of liver metastasis that had a marked clinical response to SOX plus BV and achieved a clinical complete response (CR).

Case report
A 70-year-old female visited Seitokai Azuhata Hospital at Naka-city, Ibaraki, Japan with a chief com-
plait of bloody stool. Colonoscopic examination revealed a stenotic cancerous lesion in the rectosigmoid area, and the pathologic finding of the biopsied specimen was tubular adenocarcinoma. Subsequent abdominal computed tomography showed a solitary liver tumor in segment 4. Therefore, low anterior resection of the rectum with lymphadenectomy was performed. Resection of the liver tumor was planned preoperatively. However, since there were multiple peritoneal nodules, which were thought to be a symptom of peritoneal dissemination of rectal cancer in the pelvic cavity, resection of the liver tumor was not performed at surgery. Pathological examination of the surgical specimens revealed the presence of moderately differentiated tubular adenocarcinoma with involvement of the regional lymph nodes. Systemic chemotherapy with SOX plus BV was administered at five weeks postoperatively. Oxaliplatin (130 mg/m²) and BV (75 mg/kg) were given intravenously on Day 1, and S-1 (80 mg/m²/day) was administered orally twice a day for 14 days followed by seven days of no treatment. The treatment cycle was repeated every three weeks. Since grade 3 neutropenia appeared in the first cycle, the oxaliplatin and S-1 doses were both reduced after cycle 2. The patient was monitored continuously with CT from the chest to pelvis. Serum concentrations of carcinoembryonic antigen (CEA) and CA19-9 were checked monthly, and these levels did not increase above the normal range.

The liver metastasis was markedly decreased in size on CT scans after completion of two cycles of SOX plus BV (Fig. 1A and B), which was considered to reflect a partial response to the chemotherapy. The liver metastasis then became completely undetectable after five cycles of SOX plus BV (Fig. 1C). There was no evidence of peritoneal dissemination and no other detectable metastatic lesions. After achievement of marked response from the metastatic liver tumor, additional three cycles of SOX plus BV were administered. CT images confirmed a complete response after eight cycles of SOX plus BV (Fig. 1D). Monotherapy with S-1 has been ongoing for 6 months and to date there has been no evidence of any recurrent or metastatic lesions (Fig. 1E).

Discussion

We presented a case of synchronous liver metastasis of CRC in which a clinical complete response (CR) was successfully achieved by SOX plus BV. CRC patients with synchronous liver metastases are known to have a poorer prognosis than patients with metachronous liver metastases. The potential occult liver metastasis is pointed out in patients with synchronous liver metastases and it was reported that new metastatic lesions may appear in these patients during three months after the resection of primary colonic tumor. In the present case, a solitary liver metastasis was found preoperatively, and postoperative treatment with SOX plus BV was successfully performed. The solitary liver mass successfully decreased in size within five cycles of SOX plus BV without an appearance of any other metastases, and additional three cycles were performed. S-1 was administered alone for a further six months.

Although the survival of patients with liver metastases was previously extremely poor, the introduction of novel chemotherapeutic agents such as oxaliplatin has increased the median survival of these patients. It is reported that SOX plus BV is as effective as FOLFOX6 plus BV in terms of progression free survival in patients with metastatic CRC in SOFT trial. However it has also been reported that only four cases of 256 who were treated with SOX plus BV achieved CR in SOFT trial.

It has been noted that a complete disappearance of liver lesions on radiological imaging does not always reflect a complete disappearance of viable tumor cells on pathological examination. Adam et al. reported that pathological CR (pCR) was observed in 4% of patients with CRC liver metastases who received preoperative chemotherapy. Blazer et al reported that the CEA levels less than 5 ng/mL and the presence of metastases of 3 cm or less at diagnosis is independent predictive markers for pCR. Therefore, since the level of CEA was not more than 5 ng/mL, and the size of the metastatic liver tumor was less than 3 cm in the present case, her clinical CR is expected to be a pCR. Kiishi Y et al reported that prolonged and extended preoperative chemotherapy (more than 9 cycles) with FOLFOX plus bevacizumab was not associated with an improved pathologic response in patients with colorectal liver metastasis. In the present case, clinical CR was achieved within 8 cycles of SOX plus BV and S-1 monotherapy was additionally administered with tight inspection and CT examination.

We conclude that the present case is a rare case of colorectal liver metastases that achieved a CR following SOX plus BV combination chemotherapy. This SOX plus BV regimen is a safe and effective treatment of metastatic CRC that does not require central venous access.

Conflict of interest

The authors do not have conflict of interests to declare.

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Fig. 1 Follow-up images (1: coronary section, 2: frontal section) of abdominal computed tomography (CT) scan. Solitary liver metastatic tumor is shown in liver S4.

A: before chemotherapy,
B: after two cycles of SOX plus BV,
C: after five cycles of SOX plus BV,
D: after eight cycles of SOC plus BV,
E: after two additional cycles of S-1 monotherapy

The metastatic liver tumor was decreased in size after two cycles (partial response), became faint after five cycles, and disappeared (complete response) after eight cycles. There have been no metastatic lesions after CR with S-1 monotherapy.

SOX: S-1 and oxaliplatin regimen, BV: bevacizumab
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