Abstract. Aim: The aim of this study was to evaluate the impact of chemotherapy with molecular-targeting agents on liver metastases from colorectal cancer. Patients and Methods: Six patients with synchronous colorectal liver metastases who underwent hepatectomy after chemotherapy with S-1 and oxaliplatin (SOX) between January 2010 and December 2011 at the Department of Surgery, Kashiwa Hospital, the Jikei University School of Medicine were enrolled. Two patients received only SOX as chemotherapy, while the others received SOX in combination with one of the three molecular-targeting agents, bevacizumab, cetuximab, and panitumumab.

Results: In the two patients who received SOX alone, liver metastases completely disappeared at more than six months after starting chemotherapy as shown by computed tomographic (CT) scan. However, malignant cells were diffusely detected by pathological examination at the site of liver metastases, as detected by CT scan before chemotherapy. In the other four patients who received SOX in combination with molecular targets, the size of liver metastases appeared unchanged at three months after limited chemotherapy by CT scan. Pathologically, few malignant cells were detected, only at the borderline of the tumor, while most tumor cells inside the tumor were necrotized and been replaced by fibroconnective tissue.

Conclusion: Molecular-targeting agents may induce tumor necrosis rapidly from inside the tumor, which might not be detected by CT scan before surgery.

Recently, more efficient chemotherapy regimens and molecular targets have opened new perspectives in the treatment of both resectable and non-resectable colorectal liver metastases. 5-Fluorouracil/folinic acid (5-FU/FA) plus oxaliplatin (FOLFOX4 or FOLFOX6) has been the standard systemic regimen in the first-line treatment of patients with metastatic colorectal cancer (1-3). However, infusional 5-FU with FA has the disadvantages of increased inconvenience, cost, and morbidity related to the use of a portable infusion pump and a central venous catheter. Oral fluoropyrimidine derivatives have been developed to circumvent the problems associated with continuous infusion of 5-FU. S-1 (Taiho Pharmaceuticals Co. Ltd., Tokyo, Japan) combines tegafur with two modulators, gineracil and oteracil potassium, of 5-FU metabolism is effective derivatives in Japan. In Japan, a phase I/II study of oxaliplatin plus oral S-1 (SOX) showed promising efficacy with good tolerability in patients with colorectal metastases (4). However, the impact of SOX plus molecular targets on colorectal liver metastases remains unknown.

This study was undertaken to evaluate the impact of chemotherapy with molecular-targeting agents on liver metastases from colorectal cancer.

Patients and Methods

Patients. Six patients with synchronous colorectal liver metastases who underwent hepatectomy after SOX chemotherapy between January 2010 and December 2011 at the Department of Surgery, Kashiwa Hospital, the Jikei University School of Medicine were enrolled. As shown in Table I, two patients received only SOX as chemotherapy, while the others received SOX in combination with one of the three molecular targets, one with bevacizumab, one with cetuximab, and two with panitumumab; these patients had Kirsten rat sarcoma viral oncogene homolog (K-RAS) wild-type colorectal adenocarcinoma. Patients had sufficient oral intake, no prior treatment except for surgery, and were aged between 20 and 80 years. Patients also had to have adequate organ function (4,000 ≤ leukocytes <12,000/mm3; thrombocytes ≥100,000/mm3; total...
bilirubin ≤1.5 mg/dl; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <100 IU/l; creatinine ≤1.5 mg/dl). After curative resection of the primary lesion, so-called R0 operation, as defined in the Japanese Classification of Colorectal Carcinoma (5), chemotherapy was initiated one month after the surgery. 

**Treatment schedule 1 (SOX alone).** Oxaliplatin at 130 mg/m² was administered as a 2-h infusion on the first day in every three weeks. S-1 was available in capsule form containing 20 or 25 mg of tegafur. Patients received S-1 orally twice daily from the morning of day 2 to the evening of day 15 at a dose of 80 mg the body surface area (BSA) <1.5 m² or 100 mg (BSA ≥1.5 m²) followed by a 6-day rest period in the 3-weekly schedule. We have reported that this dose of S-1 was safe and feasible as monotherapy (6). All patients received pre-medication with a 5-hydroxytryptamine-3-receptor antagonist with or without dexamethasone, given as a 30 min drip infusion before chemotherapy. Treatment was routinely given on an outpatient basis. Subsequent treatment was withheld until the neutrophil and platelet counts were greater than 3,000 and 75,000/ml, respectively, AST or ALT less than 150 IU/l, total 

Figure 1. In two patients (case 1 and 2) who received chemotherapy with S-1 and oxaliplatin (SOX) alone, liver metastases completely disappeared after over six months chemotherapy as seen by computed tomographic (CT) scan.

Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Regimen</th>
<th>Response</th>
<th>Duration (months)</th>
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<tr>
<td>1</td>
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<td>CR</td>
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<td>SOX</td>
<td>CR</td>
<td>8</td>
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<td>3</td>
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<td>Male</td>
<td>SOX+Bmab</td>
<td>NC</td>
<td>3</td>
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<tr>
<td>4</td>
<td>56</td>
<td>Male</td>
<td>SOX+Cmab</td>
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<tr>
<td>5</td>
<td>74</td>
<td>Male</td>
<td>SOX+Pmab</td>
<td>NC</td>
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<tr>
<td>6</td>
<td>56</td>
<td>Male</td>
<td>SOX+Pmab</td>
<td>NC</td>
<td>3</td>
</tr>
</tbody>
</table>

bilirubin (T.Bil) less than 1.5-times the upper limit of normal, creatinine less than the upper limit of normal, and diarrhea, stomatitis, and hand-foot syndrome had resolved to grade 0 or 1. Treatment was repeated until the onset of disease progression or the appearance of severe toxicity. When the administration of oxaliplatin was discontinued due to oxaliplatin-induced neuropathy, S-1 was also discontinued.

Treatment schedule 2 (SOX plus molecular targets). All four patients had KRAS wild-type colorectal adenocarcinoma with synchronous liver metastases. The chemotherapy regimen consisted of four courses (for three months) of oxaliplatin with oral S-1 plus one of the three molecular targets, either of the three molecular targets, bevacizumab at 7.5 mg/kg, cetuximab at 400 mg/m² or panitumumab at 6 mg/kg, were administered as a 1-h infusion following administration of oxaliplatin at 130 mg/m² as a 2-h infusion on the first day in every three weeks. Patients received S-1 orally twice daily from the morning of day 2 to the evening of day 15 at a dose of 80 mg (BSA <1.5 m²) or 100 mg (BSA ≥1.5 m²), followed by a 6-day rest period in the 3-weekly schedule. All patients received pre-medication with a 5-hydroxytryptamine-3-receptor antagonist with or without dexamethasone, given as a 30 min drip infusion before chemotherapy. Treatment was routinely given on an outpatient basis.

Toxicity and response criteria. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE v3.0) (7). Neurotoxicity was assessed according to the following specific neurotoxicity grading scale: grade 1, dysesthesia or paresthesia that completely regressed within six days; grade 2, dysesthesia or paresthesia persisting for seven days or longer; and grade 3, dysesthesia or paresthesia causing functional impairment. During the study, all patients were evaluated every three weeks for signs and symptoms of toxicity. Complete blood cell counts, including differential count, liver function tests, measurement of serum urea nitrogen, creatinine, and electrolyte levels, and urinalysis were performed every three weeks. The response of measurable and assessable disease sites was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) (8). Tumor dimensions were assessed by computed tomographic (CT) scanning every month to confirm response, and every two months after RECIST efficacy was confirmed.

Results

Characteristics of the patients (Table I). The median patient age was 64 years (range=56-74 years), and patients were male. Two (case 1 and 2) of the patients received only SOX as chemotherapy while the other four patients (cases 3-6)
received SOX in combination with one of the three molecular targets, one with bevacizumab (case 3), one with cetuximab (case 4), and two with panitumumab (case 5 and 6).

Treatment discontinuation under adverse reactions did not occur in this study.

**Response to therapy with SOX alone.** In the two patients (case 1 and 2) who received SOX alone, liver metastases completely disappeared more than six months after chemotherapy, as shown by CT scan (Figure 1). All such lesions were detected macroscopically in the resected specimens. Furthermore, malignant cells were diffusely detected by pathological examination at the sites of the liver, as detected by CT scan before chemotherapy (Figure 2).

**Response to therapy with SOX in combination with molecular-targeting agents.** In the other four patients (cases 3-6) who received SOX in combination with one of the three molecular targets, the size of the liver metastases appeared unchanged by CT scan after three months of limited chemotherapy (Figure 3). The metastatic lesions demonstrated a mosaic pattern, and peripheral rim enhancement was shown at the margin of the tumors before chemotherapy (Figure 3). After chemotherapy, the metastatic lesions changed from a mosaic pattern to a cystic pattern, and peripheral rim enhancement at the border of the tumors disappeared on imaging (Figure 3). In the resected specimens, a few malignant cells were detected only at the margin of the tumor, and the central tumor cells had undergone almost total necrosis and replacement by fibroconnective tissue (Figure 4).

**Discussion**

The efficacy of SOX was superior to that reported for each drug as monotherapy (9, 10), with a response rate of 14/28 (50%), median progression-free survival of 193 days, and a 1-year survival rate of 22/28 (78.6%) (4). The results suggest that tri-weekly treatment with the SOX regimen is an adequate substitute for FOLFOX and can be administered more readily since it does not require central vein access. Recently, more
efficient chemotherapy regimens, SOX with molecular targeting agents, have opened new perspectives in the treatment of both resectable and non-resectable colorectal liver metastases (11-15). However, the impact of these regimens on liver metastases from colorectal cancer remains unknown.

In our present study, diffuse liver metastasis in the patients who received SOX alone required a long time for reduction or complete disappearance on imaging, usually over six months. Although the lesions had achieved complete response on imaging, the metastatic lesions had not achieved complete response pathologically. On the other hand, in patients who received SOX in combination with one of the three molecular-targeting agents, a few malignant cells remained only at the border of the tumor, after only three months of limited chemotherapy. Molecular-targeting agents may induce tumor necrosis rapidly from the inside of the tumor. However, this effect could not be evaluated accurately by CT scan before surgery.

CT scan is used to monitor chemotherapy according to the RECIST criteria (7). Complete response is usually defined as the disappearance of target lesions on imaging and is considered as a good indicator of the efficacy of chemotherapy. However, the correlation between imaging and pathological status is not well-defined (16). Optimal morphological response was defined as a change in metastases from lesions with heterogeneous attenuation and thick irregular borders into bland homogeneous and hypodense masses with sharp interface between the tumor and adjacent normal liver parenchyma, which mimic a cyst (17).

In our study, after chemotherapy with molecular-targeting agents, the metastatic lesions changed from a mosaic pattern to a cystic pattern inside the tumor and peripheral rim enhancement at border of the tumors disappeared on imaging. The lack of malignant cells, tumor necrosis and replacement with fibroconnective tissue may be defined as a nearly complete response although there was no change in the size of metastatic lesions between pre- and post-chemotherapy on imaging. However, such concepts need to be verified by large-scale studies and long-term observation.
Conclusion

Molecular-targeting agents may induce tumor necrosis rapidly from inside the tumor. Such an effect cannot be evaluated accurately by CT scan before surgery.

Conflicts of Interest

We declare that we have no conflicts of interest.

References


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