Feasibility Study of Oxaliplatin with Oral S-1 or Capecitabine as First-line Therapy for Patients with Metastases from Colorectal Cancer

KAZUHIRO WATANABE[1], HIDEJIRO KAWAHARA[1], HIROYA ENOMOTO[1], YOICHI TOYAMA[1], TADASHI AKIBA[1] and KATSUHIKO YANAGA[2]

[1]*Department of Surgery, Kashiwa Hospital, the Jikei University School of Medicine, Chiba, Japan;*
[2]*Department of Surgery, Jikei University School of Medicine, Tokyo, Japan*

Abstract. *Background/Aim: The aim of this study was to determine the feasibility of S-1 plus oxaliplatin (SOX) or capecitabine plus oxaliplatin (XELOX) as first-line therapy for patients with initially unresectable metastases from colorectal cancer. Patients and Methods: Fourteen patients with colorectal cancer who underwent elective colorectal resection between January 2009 and December 2010 at the Department of Surgery, Kashiwa Hospital, the Jikei University School of Medicine, with initially unresectable metastatic lesions were enrolled in this study. After curative resection for the primary colorectal cancer, they underwent adjuvant chemotherapy with SOX or XELOX, starting at one month after surgery. Results: Seven patients (50%) received SOX, and the others received XELOX as first-line therapy for initially unresectable metastases from colorectal cancer. Four (29%) patients had complete response for liver metastases over six months after chemotherapy, and liver metastases were subsequently judged to be completely resected by surgery. For the other ten patients, the median progression-free survival was 9.1 months and median overall survival was 24.1 months. There were no patients with grade 3 or 4 adverse reactions throughout the entire chemotherapy. Conclusion: Oxaliplatin with oral S-1 or capecitabine as first-line therapy for patients with initially unresectable metastases from colorectal cancer is safe and feasible.*

5-Fluorouracil/folinic acid (5FU/FA) plus oxaliplatin (FOLFOX4 or FOLFOX6) has been the standard systemic regimen in the first-line treatment for patients with metastatic colorectal cancer (1-3). However, infusion of 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 of 5-FU metabolism and capecitabine (Xeloda; Hoffmann-La Roche, Basel, Switzerland) are effective derivatives used in Japan. This study was undertaken to determine the feasibility of S-1 plus oxaliplatin (SOX) or capecitabine plus oxaliplatin (XELOX) as first-line therapy for patients with initially unresectable metastases from colorectal cancer.

Correspondence to: Hidejiro Kawahara, MD, Ph.D., Department of Surgery, Kashiwa Hospital, Jikei University School of Medicine, 163-1 Kashiwashita, Kashiwashi, Chiba 277-8567, Japan. Tel: +81 471641111 Ext. 3421, Fax: +81 471633488, e-mail: kawahide@jikei.ac.jp

Key Words: Colorectal cancer, oxaliplatin, S-1, SOX, XELOX, metastasis.

Patients and Methods

Patients. Fourteen patients with colorectal cancer who underwent elective colorectal resection between January 2009 and December 2010 at the Department of Surgery, Kashiwa Hospital, Jikei University School of Medicine, with initially unresectable metastatic lesions were enrolled in this study. They had sufficient oral intake, no prior treatment except surgery, and were aged between 20 and 80 years. The patients also had to have adequate organ function ($4{,}000 \leq$ leukocytes $< 12{,}000/mm^3$; thrombocytes $\geq 100{,}000/mm^3$, total bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <100 IU/l, creatinine ≤ 1.5 mg/dl). After curative resection for the primary colorectal cancer, they underwent chemotherapy with SOX or XELOX, starting at one month after the surgery.

Treatment schedule. Oxaliplatin at 130 mg/m^2 was administered as a 2-h infusion on the first day every three weeks. S-1 was available in capsule form containing 20 or 25 mg of tegafur, while capecitabine was available in capsule form containing 300 mg. 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 for those with the body surface area (BSA) <1.5 m^2 or at 100 mg for those with BSA $\geq$1.5 m^2, followed by a 6-day rest period in the 3-weekly schedule. Patients received capecitabine orally twice daily from the morning of day 2 to the evening of day 15 at a dose of 2,400 mg for those with BSA <1.5

Table I. *Clinicopathological features of the patients.*

Variable	Value
Gender, n (%)	
Male	10 (71)
Female	4 (29)
Age, median years (range)	66 (61-79)
Location of the tumor, n (%)	
Colon	7 (50)
Rectum	7 (50)
Metastatic site, n (%)	
Liver-only	13 (93)
Peritoneal dissemination	1 (7)
Regimen of chemotherapy	
Oxaliplatin with oral S-1	7 (50)
Oxaliplatin with oral capecitabine	7 (50)
Number of chemotherapy cycles, median (range)	11 (9-20)
Conversion therapy, n (%)	
No	10 (71)
Yes	4 (9)

m^2 or 3000 mg for those with BSA ≥1.5 m^2 followed by a 6-day rest period in the 3-weekly schedule. Before chemotherapy, all patients received pre-medication with a 5-hydroxytryptamine-3-receptor antagonist with or without dexamethasone, given as a 30-min drip infusion. 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 bilirubin (T.Bil) less than 1.5-times the upper limit of normal, creatinine less than the upper limit of normal, and when diarrhea, stomatitis, or hand-food syndrome had resolved to grade 0 or 1. Treatment was repeated until the onset of disease progression or severe toxicity. When the administration of oxaliplatin was discontinued due to oxaliplatin-induced neuropathy, S-1 or capecitabine was also discontinued.

Toxicity evaluation and response criteria. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE v3.0) (4). 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) (5). Tumour dimensions were assessed by computed tomography (CT) scanning every month to confirm response, and after efficacy by RECIST was confirmed, every two months.

Statistical analysis. Progression-free survival (PFS) and overall survival (OS) were analyzed by the Kaplan–Meier method (6). The clinical cutoff date for the study analysis was May 1st 2013.

Table II. *Adverse reactions at six months after starting chemotherapy.*

	Grade				
Variable	1	2	3	4	Total, n (%)
Laboratory findings					
Leukopenia	4	0	0	0	4 (29)
Thrombocytopenia	0	0	0	0	0 (0)
Anemia	0	0	0	0	0 (0)
AST	0	0	0	0	0 (0)
ALT	0	0	0	0	0 (0)
Total bilirubin	0	0	0	0	0 (0)
Creatinine	0	0	0	0	0 (0)
Clinical findings					
Anorexia	10	0	0	0	10 (71)
Nausea	10	0	0	0	10 (71)
Vomiting	0	0	0	0	0 (0)
Diarrhea	0	0	0	0	0 (0)
Stomatitis	0	0	0	0	0 (0)
Fatigue	0	0	0	0	0 (0)
Pigmentation changes	7	0	0	0	7 (50)
Rash	0	0	0	0	0 (0)
Peripheral neuropathy	8	2	0	0	10 (71)
Hand-foot syndrome	0	0	0	0	0 (0)
Weight loss	0	0	0	0	0 (0)

AST: Aspartate aminotransferase, ALT: alanine aminotransferase.

Results

Clinicopathological features of the patients (Table I). The median patient age was 66 years (range=61-79 years), and four of them were female. The tumor was located in the colon in seven and in the rectum in the other seven patients. The site of metastasis was the liver only in thirteen patients; the other patient had both liver metastasis and peritoneal dissemination. The regimen of chemotherapy was SOX in seven and XELOX in seven patients. The median number of chemotherapy cycles was 11 (range=9-20). Four patients had complete response of the liver metastases over six months after chemotherapy, and liver metastases were judged to be completely resectable by surgery, resection in so-called conversion therapy.

Adverse reactions at 6 months after starting chemotherapy (Tables II and III). No patient in this study had treatment discontinuation due to adverse reactions. The frequent hematological toxicities were only leukopenia, and all of them were grade 1. The frequent non-hematological toxicities were anorexia, nausea, pigmentation change, and sensory neuropathy. Sensory neuropathy occurred in 10/14 patients, but no functional impairment was observed. Therefore, oxaliplatin, S-1, and capecitabine were administered without dose reduction. Pigmentation changes occurred in all patients treated with SOX, in contrast to none treated with XELOX. Hand-food syndrome did not occur.

Table III. *Adverse reactions under therapy with XELOX, SOX at six months after starting chemotherapy.*

Variable	No. of patients (%)	
	XELOX (n=7)	SOX (n=7)
Laboratory findings		
Leukopenia	2 (29)	2 (29)
Thrombocytopenia	0 (0)	0 (0)
Anemia	0 (0)	0 (0)
AST	0 (0)	0 (0)
ALT	0 (0)	0 (0)
Total bilirubin	0 (0)	0 (0)
Creatinine	0 (0)	0 (0)
Clinical findings		
Anorexia	5 (71)	5 (71)
Nausea	5 (71)	5 (71)
Vomiting	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)
Stomatitis	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)
Pigmentation changes	0 (0)	7 (100)
Rash	0 (0)	0 (0)
Peripheral neuropathy	5 (71)	5 (71)
Hand-foot syndrome	0 (0)	0 (0)
Weight loss	0 (0)	0 (0)

AST: Aspartate aminotransferase, ALT: alanine aminotransferase.

Response to therapy. Excluding four patients who underwent resection of liver metastases, the median PFS for the other 10 patients was 254 days (9.1 months) (Figure 1), and the median OS was 675 days (24.1 months) (Figure 2) by the Kaplan-Meier method.

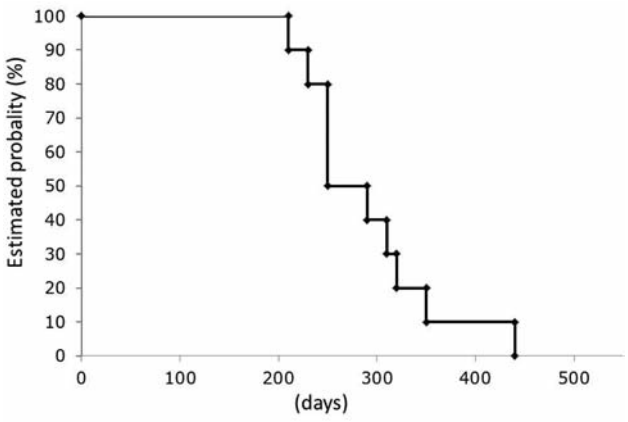

Figure 1. *Excluding four patients who underwent resection of liver metastases, the median progression-free survival was 254 days (9.1 months) by the Kaplan-Meier method.*

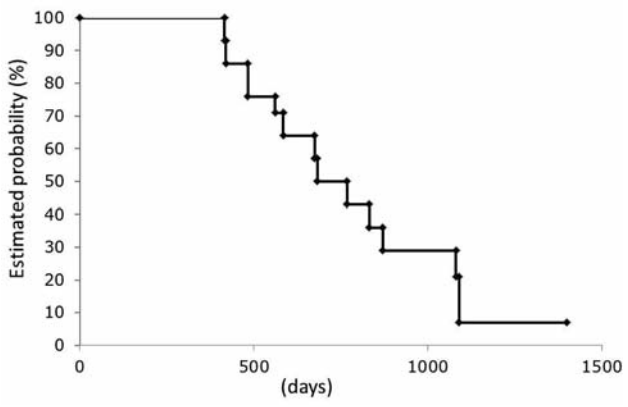

Figure 2. *In ten patients excluding four patients who underwent resection of liver metastasis, the median overall survival was 675 days (24.1 months) by the Kaplan-Meier method.*

Discussion

FOLFOX4 or FOLFOX6 have been the standard systemic regimens in the first- and second-line treatment of patients with metastatic colorectal cancer (1-3). Since the efficacy of XELOX is not inferior to that of FOLFOX4 or FOLFOX6 in the first- and second-line treatment of patients with metastatic colorectal cancer (7, 8), in 2009, the Japanese Ministry of Health, Labor and Welfare approved the use of XELOX or SOX as chemotherapy for patients with metastatic colorectal cancer instead of FOLFOX4 or FOLFOX6, with the cost covered by the National Health Insurance System of Japan.

We have tried to use SOX or XELOX as the first-line chemotherapy for patients with metastatic colorectal cancer since then. Fourteen patients received SOX or XELOX between 2009 and 2010 for initially unresectable metastatic lesions to evaluate the feasibility of SOX or XELOX as first-line treatment. Our results suggest that SOX and XELOX are safe and effective as first-line treatment for metastases from colorectal cancer. These regimens have demonstrated promising efficacy with a response rate of 4/14 at six months after starting chemotherapy, with a median PFS of 254 days (9.1 months). The four patients who demonstrated response of liver metastases to SOX/XELOX subsequently underwent conversion therapy. The efficacy of this study is the same as these reported by others for SOX or XELOX (9-12), with the median PFS ranging from 7.1 to 9.5 months. In those reports, the administered dose of oxaliplatin was the same, 130 mg/m^2, as in our study, while the administered dose of S-1 or capecitabine was higher than that of our study.

Because of the lack of treatment discontinuation under adverse reactions and of dose reduction of oxaliplatin, S-1, and capecitabine in this study, the toxicity profile seems acceptable.

In our present study, the median OS was over 24 months, which was superior to that of other reports for SOX or XELOX (9-12), with a median OS of 16.8 to 20.8 months. In excluding the four patients who underwent resection of liver metastases, second- and third-line chemotherapy were given with bevacizumab or panitumumab. Potential differences between our treatment and other previous reports can be masked by second-line and later chemotherapy when OS is used as the end point.

As for the difference between SOX and XELOX, Hong *et al*. conducted a phase III randomized trial, and demonstrated that the efficacy of SOX is not inferior to that of XELOX in the first-line treatment of patients with metastatic colorectal cancer (13).

Conclusion

SOX and XELOX are safe and effective as first-line treatments for metastases from colorectal cancer, and could replace FOLFOX.

Conflicts of Interest

We declare that we have no conflicts of interest.

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