Usefulness of Monthly Chemotherapy for Patients with Unresectable Metastatic Colorectal Cancer

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Abstract. *Background/Aim: Unresectable metastatic colorectal cancer with very slow tumour growth rate does not necessarily require for strong short-interval chemotherapy. In the present study, we administered monthly chemotherapy and aimed to evaluate the usefulness of the specific treatment schedule in patients with unresectable metastatic colorectal cancer with slow tumour growth rate. Patients and Methods: Since 2009, at our Institution, patients' whose serum carcinoembryogenic antigen (CEA) values on the treatment day were not higher than those before initial chemotherapy, and patients who did not wish to undergo intensive chemotherapy, were prospectively scheduled for specific chemotherapy. Between January 2009 and December 2011, 10 patients with unresectable metastatic colorectal cancer who received monthly chemotherapy were enrolled in the current study. During the same period, 14 patients with unresectable metastatic colorectal cancer were administered conventional-interval chemotherapy, oxaliplatin with oral S-1 (SOX) or capecitabine (XELOX), and comprised the control group. Results: Three patients received first-line, four patients received second-line, and three patients received third-line treatment. All patients were able to receive a single-regimen of chemotherapy for more than a year. The survival of patients who received monthly chemotherapy was significantly better than survival of those who received SOX or XELOX within 30 months after starting chemotherapy ($p<0.05$). Conclusion: For patients with very slow tumour growth rates, our monthly chemotherapy may be beneficial.*

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In ESMO consensus guidelines for the management of patients with colon and rectal cancer, first-line treatment of advanced disease has been divided into four groups, Group 0: liver or lung metastases, R0 resectable; group 1: liver or lung metastases, not R0 (R1) resectable; group 2: intermediate intensive treatment; group 3: not intensive/sequential treatment. In group 3, maximal shrinkeage of metastases is not the primary treatment aim (1). Without imminent symptoms or risk of rapid deterioration, the aim is rather prevention of tumour progression with symptom control and prolongation of life, with minimal treatment burden. Therefore, an escalation strategy seems appropriate, starting with single agents, or with a well-tolerated two-drug combination. However, distinguishing the patients of group 3 from those of other groups, is clinically very difficult.

Since 2009, the patients' serum carcinoembryogenic antigen (CEA) value on the treatment day was not higher than that before the initial chemotherapy and they did not wish to receive intensive chemotherapy, we prospectively scheduled the next chemotherapy one month later. The aim of the current study was to evaluate the usefulness of such monthly chemotherapy for patients with unresectable metastatic colorectal cancer categorized as ESMO group 3.

Patients and Methods

Patients. Between January 2009 and December 2011, 10 patients with unresectable metastatic colorectal cancer who received monthly chemotherapy were enrolled in the study. Fourteen patients with unresectable metastatic colorectal cancer were given regular-interval oxaliplatin with oral S-1 (tegafur, gimeracil, oteracil potassium: SOX) or oxaliplatin with oral capecitabine (XELOX), assigned in the same period as the control group. These 14 patients were reported in the previous study of our group (2).

Patients also had to have adequate organ function (4,000≤ leukocytes<12,000/mm^3; thrombocytes ≥100,000/mm^3; serum total bilirubin ≤1.5 mg/dl; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <100 IU/l; and creatinine ≤1.5 mg/dl). Patients with a history of drug hypersensitivity, serious surgical and non-surgical complications, or active secondary cancer were excluded. Pregnant or lactating women were also excluded.

Table I. *Clinicopathological features of the patients.*

Case no.	Gender	Age (years)	Recurence site	Chemotherapy line	Chemotherapy regimen	Serum CEA (mg/ml)					
						Before	6 mo.	12 mo.	18 mo.	24 mo.	30 mo.
1	Male	78	P, H	1st	SOX	16.7	7.7	10.8	11.2	17.7	-
2	Male	74	P	1st	SOX	8.9	1.8	2.2	3.4	-	-
3	Male	78	L	1st	Pmab	65.2	14.6	41.6	98.9	134.2	-
4	Male	70	L, H	2nd	XELIRI	9.5	4.8	5.6	6.9	16.3	21.8
5	Female	64	L	2nd	XELIRI	30.4	10.9	12.4	14.8	16.4	-
6	Female	60	P	2nd	XELIRI	49.8	8.8	10.2	-	-	-
7	Female	74	L	2nd	XELIRI	36.6	12.2	14.6	15.3	18.2	-
8	Male	79	P	3rd	Pmab+CPT	44.1	12.8	13.5	14.2	21.6	-
9	Male	64	P, H	3rd	Pmab+CPT	65.5	15.3	21.3	24.2	26.4	54.1
10	Female	68	P, H	3rd	Pmab+CPT	65.9	4.5	6.9	11.9	-	-

P: Peritoneal dissemination, H: liver metastasis, L: lung metastasis, CEA: carcinoembryonic antigen. SOX: S-1 + oxaliplatin, Pmab: panitumumab, CPT: irinotecan, XELIRI: capecitabine plus irinotecan. before: before chemotherapy, mo.: months after surgery.

Treatment schedule. Physical examination, routine blood analysis, and serum CEA measurement were performed every month before chemotherapy. Computed tomography (CT) was performed every three months or when their serum CEA value on the treatment day was higher than that before the initial chemotherapy. The chemotherapy would be repeated as long as possible until the patients' serum CEA value on the treatment day was higher than that before the initial chemotherapy or rapid tumour growth were detected by CT. The response of measurable and assessable disease sites was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) [3].

For the first-line treatment, two regimens, SOX or panitumumab therapy, were employed. In SOX therapy, oxaliplatin at 130 mg/m^2 was administered on the first day, followed by 14-day administration and 13-day withdrawal of oral S-1 (Taiho Pharmocentical, Tokyo, Japan) at 80 mg or 100 mg per day according to the body surface area (BSA): 80 mg/day for BSA<1.5 m^2; and 100 mg/day for BSA>1.5 m^2. S-1 was administered orally twice daily after meals.

In panitumumab therapy for Kirsten rat sarcoma viral oncogene homolog (KRAS) wild-type colorectal adenocarcinoma, panitumumab at 6 mg/kg was administered on the first day followed by a 27-day rest period.

For second-line treatment, irinotean with oral capecitabine (XELIRI) was employed. Irinotecan at 120 mg/m^2 was administered on the first day, followed by 14-day administration and 13-day withdrawal of oral capecitabine (Xeloda; Hoffmann-La Roche, Basel, Switzerland) at a dose of 2,400 mg for those with BSA <1.5 m^2 or 3,000 mg for those with BSA ≥1.5m^2. Capecitabine was administered orally twice daily after meals.

As the third-line treatment for KRAS wild-type colorectal adenocarcinoma, irinotecan with panitumumab therapy was selected. Irinotecan at 120 mg/m^2 and panitumumab at 6 mg/kg were administered on the first day, followed by a 27-day rest period.

Statistical analysis. All data were analysed using the Statistical Package for Social Sciences (SPSS 18). The survival rate was calculated by the Kaplan-Meier method, and statistical significance was determined by the generalized Wilcoxon test. A *p*-value of less than 0.05 indicates statistical significance.

Results

Patients' characteristics. Between January 2009 and December 2011, 10 patients were enrolled in the study. Their characteristics are summarized in Table I. For the first-line treatment, two patients who received SOX were given chemotherapy for more than 18 months and a patient who received panitumumab-alone was given chemotherapy for more than 24 months. As second-line treatment, all four patients received chemotherapy for more than 12 months. For the third-line treatment, one of the three received chemotherapy for more than 30 months.

Comparison of survival between monthly chemotherapy and SOX or XELOX. In comparison of progression-free survival (PFS) between patients who received monthly chemotherapy (MC) and patients who received SOX or XELOX, PFS of patients who received MC was significantly better than that of those who received SOX or XELOX ($p<0.01$) (Figure 1). By comparing survival periods between the two groups within 30 months after starting chemotherapy, the survival period of the patients who received MC was significantly better than that of those who received SOX or XELOX ($p<0.05$) (Figure 2).

Discussion

5-Fluorouracil/folinic acid (5-FU/FA)-plus-oxaliplatin (FOLFOX4 or FOLFOX6) has been the standard systemic regimen for first-line treatment of patients with metastatic colorectal cancer (4-6). This regimen has an administration interval of every-two-weeks, while the interval of XELIRI (7), SOX (2, 8), and XELOX (2, 9) is usually every-three-weeks. In the presence of certain adverse effects such as

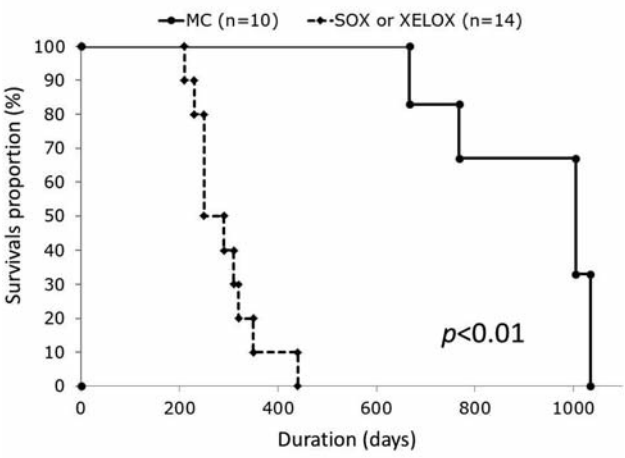

Figure 1. *Comparison of progression-free survival (PFS) between patients who received monthly chemotherapy (MC) and those who received SOX or XELOX. PFS of patients who received MC was significantly better than that of those who received SOX or XELOX (p<0.01).*

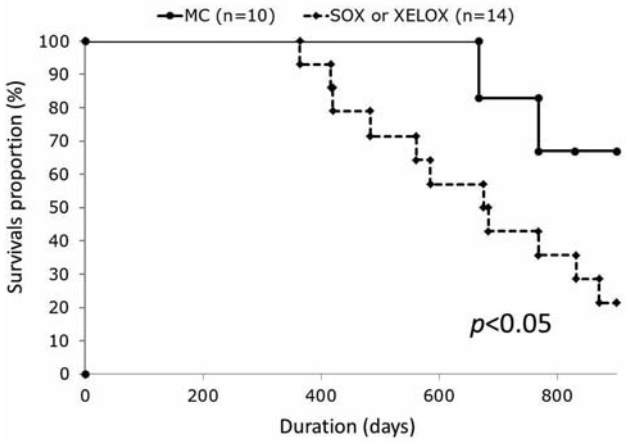

Figure 2. *Comparison of survival between patients who received MC and those who received SOX or XELOX. The survival of the patients who received MC was significantly better than that of those who received SOX or XELOX within 30 months after starting chemotherapy (p<0.05).*

leukopenia, the administration interval has been extended. However, there is no report on the correlation to between prolongation of the administration interval and antitumour effects.

In ESMO consensus guidelines for the management of patients with colon and rectal cancer, first-line treatment of advanced disease has been divided into four groups (1). These four groups are conceptually acceptable, while distinguishing patients of group 3 from those in other groups is clinically difficult.

Since 2009, we have prospectively administered monthly chemotherapy when the patients' serum CEA value on the treatment day were not higher than those before the initial chemotherapy, and when the patients did not want to receive intensive chemotherapy. The PFS and the survival period of patients who received MC was significantly better than that of those who receiving SOX or XELOX for the same period, within 30 months after starting chemotherapy. As the patients with very slow tumour growth received MC, their survival period was better than that of patients who received SOX or XELOX. These patients can be classified as ESMO group 3. In the present study, all participants had abdominal dissemination or lung metastasis. Their number of unresectable lesions was low, or the size of the lesions was small. According to the size and the number of unresectable lesions in the abdominal cavity or lung, we may judge the patients' eligibility for inclusion in group 3.

Since the patients determined as belonging to group 3 in this study were found to have better prognosis than these receiving intensive chemotherapy, future controlled trials examining the effects of anticancer agents may require our attention with regard to the distribution rate of group 3 patients in each group.

In conclusion, some selected patients with very slow tumour growth rates, may be judged as being in group 3, for whom the novel MC presented herein seems effective.

Conflicts of Interest

We declare that we have no conflict of interests.

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