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Retrospective analysis of capecitabine and oxaliplatin (XELOX) plus bevacizumab as a first-line treatment for Japanese patients with metastatic colorectal cancer

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Abstract. XELOX plus bevacizumab is an effective treatment strategy and has a manageable tolerability profile when administered to Japanese patients with metastatic colorectal cancer (mCRC). In this study, we retrospectively reviewed cases in which XELOX plus bevacizumab were administered in order to evaluate its efficacy and safety in clinical practice. In total, 40 patients with mCRC who presented at Fuchu Hospital received XELOX plus bevacizumab as a first-line treatment between September, 2009 and April, 2012. Eligible patients had histologically confirmed mCRC. XELOX consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily for 2 weeks of a 3-week cycle. Overall survival (OS) and survival benefit were analyzed when patients continued with XELOX plus bevacizumab beyond disease progression. The median progression-free survival (PFS) was 290 days [95% confidence interval (CI): 222-409 days] and the median OS was 816 days (95% CI: 490 days-not calculated). The response rate (RR; complete plus partial response) was 67.5%, and the disease control rate (RR plus stable disease) was 90%. The most common adverse events observed following administration of XELOX plus bevacizumab were neurosensory toxicity (82.5%), anorexia (50%), hypertension (45%) and a decrease in the platelet count (40%). The most common grade 3/4 adverse events were neurosensory toxicity (15%) and fatigue (15%). In conclusion, XELOX plus bevacizumab may be considered a routine first-line treatment option for patients with mCRC. Notably, the combination of capecitabine and bevacizumab was safe with an acceptable toxicity profile and induced a significant rate of disease control.

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Introduction

Colorectal cancer is the third most common type of cancer worldwide, with one million new cases diagnosed annually (1). In Japan, colorectal cancer is the second most common type of cancer and the third most common cause of mortality (2).

FOLFOX4, a bi-weekly schedule of intravenous bolus and infusion of 5-fluorouracil/folinic acid (5-FU/FA) plus oxaliplatin (Elplat®), is a widely used regimen for the first-line treatment of metastatic colorectal cancer (mCRC) (3,4). However, oral fluoropyrimidines can replace the intravenous fluoropyrimidine component of combination regimens. Capecitabine (Xeloda®) is an oral fluoropyrimidine with similar efficacy to bolus 5-FU/FA in the first-line treatment of mCRC and as adjuvant therapy for stage III colon cancer (5-7). The efficacy of capecitabine and a 3-week dose of oxaliplatin (XELOX regimen) has also been demonstrated to be inferior to 5-FU/FA plus oxaliplatin (FOLFOX4 or FOLFOX6) in the first- and second-line treatment of patients with mCRC (8-10). The addition of bevacizumab (Avastin®) to oxaliplatin-based chemotherapy significantly improved progression-free survival (PFS) by 20% in the first-line treatment of mCRC (11). XELOX plus bevacizumab is an effective treatment strategy and has a manageable tolerability profile when administered to Japanese patients with mCRC (12). In this study, we retrospectively reviewed cases in which XELOX plus bevacizumab was administered to evaluate its efficacy and safety in clinical practice.

Patients and methods

Patients. In total, 40 patients, 22 males and 18 females with a median age of 62.5 years, with mCRC presented at the Fuchu Hospital. These patients were administered XELOX plus bevacizumab as a first-line treatment between September, 2009 and April, 2012. Eligible patients had histologically confirmed mCRC. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and adequate hematological, liver and renal functions. Other assessments were carried out at the investigator's discretion.

Treatment. Oxaliplatin was purchased from Yakult Honsha Co., Ltd. (Tokyo, Japan) and capecitabine and bevacizumab

were purchased from Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan). XELOX consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily for 2 weeks of a 3-week cycle. The first dose of capecitabine was administered on the evening of day 1 and the last dose was administered on the morning of day 15. Bevacizumab at a dose of 7.5 mg/kg was administered as a 30- to 90-min intravenous infusion prior to oxaliplatin on day 1 of the 3-week cycle. Treatment was continued until disease progression, intolerable adverse events or the withdrawal of consent.

Treatment was interrupted if grade 2-4 adverse events occurred. No dose modification of bevacizumab was performed. The dose of capecitabine was adjusted for grade 3 or 4 thrombocytopenia or neutropenia, febrile neutropenia or non-hematological toxicities of grade ≥2, according to the standard scheme described in detail by Doi *et al* (12). The dose of oxaliplatin was reduced to 100 or 85 mg/m^2 when patients experienced grade 3 or 4 thrombocytopenia or neutropenia, febrile neutropenia or a grade 3 non-hematological toxicity, grade 3 neurosensory toxicity lasting >7 days, or grade 2 neurosensory toxicity persisting between cycles. If grade 3 neurosensory toxicity persisted between cycles, oxaliplatin was discontinued. This treatment plan was almost identical to that of the NO16966 study (11).

If oxaliplatin and/or bevacizumab were discontinued, treatment with the remaining components were continued, such as capecitabine with or without bevacizumab subsequent to the discontinuation of oxaliplatin and XELOX or capecitabine after the discontinuation of bevacizumab. The continuation of oxaliplatin or bevacizumab without capecitabine was not permitted.

Evaluation of the methods. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v 1.0) by each attending phycisian. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v 3.0).

Statistical analysis. Statistical analyses were performed using the Statcel 2 software program (OMS, Saitama, Japan). The evaluation of response and progression was based on measurements reported by the radiologist. Complete and partial response required subsequent confirmation of response following an interval of at least 4 weeks. All clinical courses including subsequent chemotherapy were followed-up until death or last contact.The Kaplan-Meier method was used to evaluate the median duration of treatment, progression-free survival, and overall survival (OS). The median duration of treatment was calculated from the date that treatment was initiated to the date of disease progression or the cessation of treatment for any reason, whichever date occurred first. Progression-free survival was calculated from the date at which the treatement was started to the earlier date of disease progression or death. Without contradictory dates, patients who were lost to follow-up were assumed to have progressed at the last date of confirmation and to be progression-free. For patients whose treatments were ceased without progression and who had received subsequent surgery or an alternative treatment, progression-free survival was defined as the time from the initiation of treatment to the date of its cessation. OS was calculated from the date at which treatment was started to death or that of the last contact. Patients who were lost to follow-up were assumed to have succumbed to their disease at the last contact. The cutoff date was April 30, 2013 for progression-free survival and OS.

Table I. Patient characteristics.

Characteristics	No. of patients
Age (years)	
Median (range)	65.2 (51-79)
Gender (%)	
Male	22 (55)
Female	18 (45)
Eastern Cooperative Oncology Group performance status	
0 (%)	40 (100)
Primary tumor site (%)	
Colon	24 (60)
Rectum	16 (40)
Stage at first diagnosis (%)	
Local regional	24 (60)
Metastatic	16 (40)
Site of metastasis (%)	
Liver	20 (50)
Lung	9 (22.5)
Lymph node	17 (42.5)
Peritoneum	15 (37.5)
Local recurrence	3 (7.5)
Line of treatment (%)	
First	40 (100)
Prior adjuvant therapy (%)	
No	27 (67.5)
Yes	13 (32.5)

Results

Table I shows the characteristics of the 40 enrolled patients. The median age of the patients was 65.2 (range, 51-79 years). Of the 40 patients, 22 were male and 18 were female. The ECOG performance status was 0 in all 40 patients. The most common sites of metastasis were the liver, lungs, lymph nodes and peritoneum.

The median duration of treatment was 170.2 (range, 12-448 days) with a median of 8.0 (range, 1-21 treatment cycles). XELOX plus bevacizumab combination therapy was administered for a median of 6.5 (range, 1-18 cycles). Following the discontinuation of oxaliplatin, 4 patients (10%) continued with capecitabine and bevacizumab combination therapy and received a median of 3.2 (range, 1-5 cycles). Five patients (12.5%) received capecitabine monotherapy for a median of 7.7 (range, 4-12 cycles). One patient

Table II. Analysis of efficacy.

A, Endpoint		
Survival	Days	95% CI
Median progressive-free survival	290	222-409
Median overall survival	816	490-NC

B, Patient response	
Response rate	No. of patients (%)
Complete response	1 (2.5)
Partial response	26 (65)
Stable disease	9 (22.5)
Progressive disease	1 (2.5)
Not evaluable	3 (7.5)

NC, not calculated; CI, confidence interval.

Table III. The second and third line regimens used for patients receiving bevacizumab as the first-line treatment.

Line of treatment	Regimen	No. of patients (%)
Second line		n=19
	Combination with bevacizumab	7 (36.8)
	Chemotherapy only	4 (21.1)
	Combination with cetuximab/panitumumab	8 (42.1)
Third line		n=7
	Combination with bevacizumab	1 (16.7)
	Chemotherapy only	2 (33.3)
	Combination with cetuximab/panitumumab	4 (50)

received XELOX therapy for 2 cycles during the permanent discontinuation of bevacizumab (Fig. 1).

At the final data cut-off date of August 31, 2012, the median duration of follow-up was 500.5 days. Seventeen patients (42.5%) succumbed to disease progression and two patients were still receiving medication.

The analysis of efficacy is presented in Table II. The median PFS was 290 [95% confidence interval (CI): 222-409 days] and the median OS was 816 (95% CI: 490 days-not calculated). The response rate (RR; complete plus partial response) was 67.5% and the disease control rate (RR plus stable disease) was 90%.

Table III shows the second- and third-line regimens used for patients treated with bevacizumab in the first-line regimen. Results revealed that 36.8% of patients who were treated with bevacizumab in the second-line regimen were administered bevacizumab continuously. A total of 42.1% of patients in the second-line regimen were administered combination chemotherapy with cetuximab or panitumumab.

Table IV. Incidence of common adverse events.

	Grade 1-4	Grade 3-4
Adverse event	No. of patients (%)	No. of patients (%)
Hypertension	18 (45)	0 (0)
Neurosensory toxicity	33 (82.5)	6 (15)
Anorexia	20 (50)	3 (7.5)
Fatigue	12 (30)	6 (15)
Hand-foot syndrome	15 (37.5)	0 (0)
Nausea/vomitting	7 (17.5)	0 (0)
Diarrhea	2 (5)	0 (0)
Oral ulcer	7 (17.5)	0 (0)
Allergic reaction	2 (5)	2 (5)
Hiccups	1 (2.5)	1 (2.5)
Neutrophil count decreased	12 (30)	0 (0)
Platelet count decreased	16 (40)	0 (0)

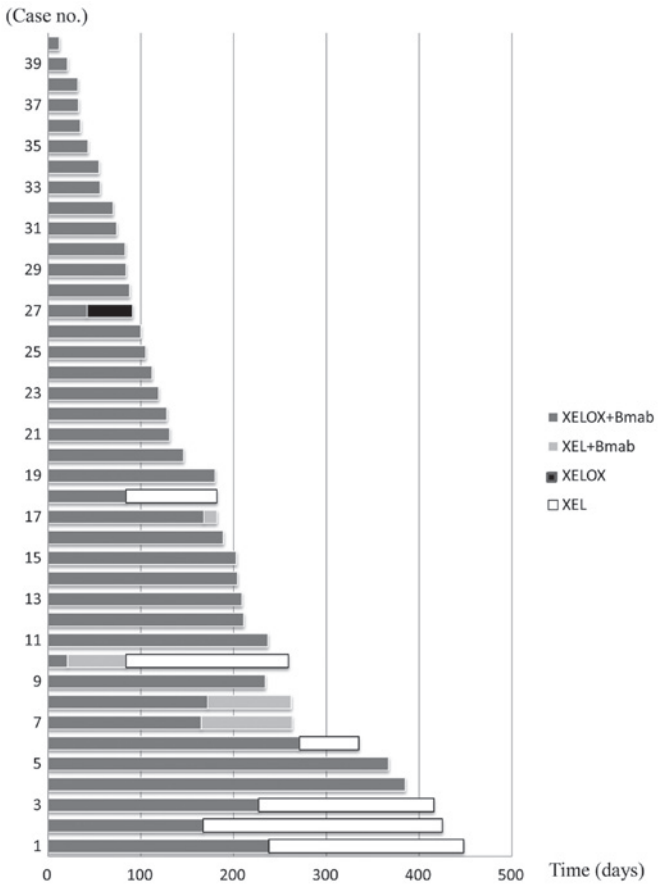

Figure 1. Period of treatment of XEL(OX) ± bevacizumab (Bmab).

The adverse events that occurred in all 40 patients are provided in Table IV. The most common adverse events with XELOX plus bevacizumab were neurosensory toxicity (82.5%), anorexia (50%), hypertension (45%) and a decrease in the platelet count (40%). The most common grade 3/4 adverse events were neurosensory toxicity (15%) and fatigue (15%). Regarding patients receiving XELOX plus bevacizumab, dose reductions were required for capecitabine in 6 patients (15%) due to hand-foot syndrome (n=5) and diarrhea (n=1). Capecitabine doses were reduced to 75% of the starting dose in all 6 patients. Dose reductions were required for oxaliplatin in 10 patients (25%) due to neurosensory toxicity and the oxaliplatin dose was reduced to 100 mg/m^2 in all of these patients.

Discussion

Results of this study have demonstrated the safety and efficacy of XELOX with bevacizumab in combination with oxaliplatin 130 mg/m^2 plus oral capecitabine 1,000 mg/m^2 in Japanese patients. Of particular significance are our novel results demonstrating the safety and efficacy of the international standard-dose XELOX with bevacizumab in Japanese patients. No fatal adverse events occurred and any complications arising were managed successfully using appropriate support care and drug cessation/dose reductions.

The results of randomized controlled trials in patients with advanced colorectal cancer demonstrated that the median OS was 16-23 months in patients who received bevacizumab with fluoropyrimidine-based chemotherapy, including 5-FU/FA, irinotecan plus 5-FU/leucovorin (IFL), 5-FU/IFL plus oxaliplatin (FOLFOX) and capecitabine plus oxaliplatin (XELOX), as first-line chemotherapy (11,13,14).

Previous randomized or observation trials that included the XELOX plus bevacizumab regimen as first-line therapy have been conducted mainly in North America and Europe (11,15,16). The NO16966 study (10,15) demonstrated a longer PFS and OS in the XELOX plus bevacizumab arm than that with the XELOX plus placebo arm in the subgroup analysis, which reported a median PFS of 9.3 vs. 7.4 months, hazard ratio (HR)=0.77 (95% CI: 0.63-0.94, P=0.0026) and a median OS of 21.6 vs. 18.8 months (HR was not shown) (15). Furthermore, another phase III trial (CAIRO2) reported a RR of 50.0%, a median PFS of 10.7 months and a median OS of 20.3 months in the XELOX plus bevacizumab arm (16). A Japanese clinical trial of XELOX plus bevacizumab in patients with mCRC reported that the median OS was 27.4 months and that the median progression-survival was 11.0 months (12). In this study, the median OS was 816 days, the median PFS was 290 days and the RR was 67.5%. These efficacy results are similar to those obtained in first-line therapy with XELOX plus bevacizumab.

The safety profile observed in the present study was similar to that observed in previous clinical trials with Western patients, including the NO16966 study (11,16,17). Notably, the incidence of grade 3/4 diarrhea and nausea/vomiting was 0%, which is markedly lower than that reported with XELOX plus bevacizumab in previous phase II and III studies (19-21%) (11,16,17). A lower incidence of diarrhea and nausea/vomiting has been reported in other studies of Japanese or Asian patients treated with fluoropyrimidine-based chemotherapy (18,19). The reason for this regional variation remains unclear; however, it is hypothesized that differences in dietary folate intake is a potential explanation (20). The incidence of all grades of hand-foot syndrome (37.5%) was similar to that in the XELOX plus bevacizumab arm of the NO16966 study (39%) (15).

Approximately 90% of patients with severe peripheral neuropathy reportedly improve 20 weeks following the discontinuation of oxaliplatin (3). The results of the OPTIMOX-1 study demonstrated that a 'stop-and-go' approach employing an oxaliplatin-free interval resulted in decreased neurotoxicity, but did not affect OS in patients receiving FOLFOX as initial therapy for mCRC (21). The antitumor effects of capecitabine used alone on mCRC have been reported to be similar to those of intravenous 5-FU/IFL therapy (22). Capecitabine and bevacizumab therapy showed a RR of 34% and median PFS and OS were 10.8 and 18 months, respectively (23). Regarding peripheral neuropathy, the overall incidence of peripheral neuropathy in our study (82.5%) was similar to that in the XELOX plus bevacizumab arm of previous studies (84-93%) (12,15). In the present study, following the discontinuation of oxaliplatin, 4 patients (10%) continued with capecitabine and bevacizumab combination therapy and received a median of 3.2 (range, 1-5 cycles). Five patients (12.5%) received capecitabine monotherapy for a median of 7.7 (range, 4-12 cycles). One patient received XELOX therapy for 2 cycles during the permanent discontinuation of bevacizumab. Peripheral neuropathy disappeared and successful tumor control was achieved (partial response continued).

In conclusion, findings of this study have demonstrated that the survival benefit of XELOX plus bevacizumab in Japanese patients with mCRC was similar to that observed in previous clinical trials from Western countries. Therefore, XELOX plus bevacizumab may be considered a routine first-line treatment option for patients with mCRC. Additionally, the combination of capecitabine and bevacizumab was found to be safe with an acceptable toxicity profile, and induced a significant rate of disease control.

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