Bi-weekly Capecitabine–Oxaliplatin (XELOX) plus Bevacizumab as First-line Treatment of Metastatic Colorectal Cancer –The PHOENiX Trial

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Abstract. *Aim: This phase II study assessed the efficacy and toxicity of an intermittent weekly capecitabine regimen in combination with oxaliplatin (XELOX) plus bevacizumab as a first-line treatment of metastatic colorectal cancer (mCRC). Patients and Methods: Patients with measurable mCRC who were to receive first-line chemotherapy were enrolled onto this disease-oriented multicenter phase II trial. Patients with mCRC were required to have Eastern Cooperative Oncology Group performance status of 0 to 1, to be aged >20 years, and to have adequate organ function. Localization of tumor, toxicities, response rate, progression-free survival (PFS) and time to progression (TTP) were studied. Capecitabine dose was 2,500 mg/m^2/day on days 1-7 (n=47) and was increased to 3,000 mg/m^2/day (n=5) in combination with oxaliplatin (85 mg/m^2) and bevacizumab (5 mg/kg), repeated every 2 weeks. Results: A total of 51 patients were enrolled from 14 institutions from December 2011 to July 2012. The median age was 66 (range=38-85) years, 29 (56.9%) had colonic cancer and 22 (43.1%) had rectal cancer in this study. Pertinent grade 3/4 toxicities were neutropenia (13.7%), peripheral neuropathy (13.7%), hypertension (13.7%), gastrointestinal perforation (3.9%), and hand-foot syndrome (5.9%). The response rate was 51% (one complete and 25 partial responses). Median PFS and TTP were 344 days and 196 days, respectively. Median overall survival has not been reached yet. Conclusion: The first-line treatment of mCRC using a biweekly combination of XELOX plus bevacizumab can also be administered safely and effectively in Japan. It is suggested that this regimen is an appropriate option for the treatment of mCRC.*

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Colorectal cancer (CRC) accounts for 9 to 10% of all cancers and is a common malignancy worldwide, being the third most common cancer in men and the second in women worldwide (1). In spite of the efforts for cure including cancer screening and early detection, many cases are too advanced to cure at the time of diagnosis. Therefore, the role of palliative chemotherapy is still important.

Approval of oxaliplatin, irinotecan, and some molecular targeting agents have brought dramatic changes in chemotherapy for CRC, significantly improving the response rate, progression-free survival (PFS), and overall survival (2-5). Capecitabine and oxaliplatin (XELOX) with/without bevacizumab is an effective regimen with good efficacy and has been used for standard first-line chemotherapy (6-8). In

some cases, chemotherapy becomes the cause of a specific adverse events and reduces patient quality of life. Seeking a balance between the efficacy and toxic profile, several doses and treatment schedules have been tested (9-12), although a considerable number of cases still suffer from adverse events which are certainly uncomfortable and might result in discontinuation of treatment. Hand-foot syndrome and diarrhea are symptoms associated with the capecitabine-containing regimens. In order to explore the balance of efficacy and adverse events, we performed a phase II trial of bi-weekly XELOX plus bevacizumab administration with a lower capecitabine dose intensity compared to previous study.

Patients and Methods

This study was a multicenter phase II clinical study to examine efficacy and safety of bi-weekly XELOX plus bevacizumab as the first-line therapy for patients with unresectable CRC.

Patient eligibility. Patients were entered into the study if they fulfilled the following inclusion criteria: i) histologically proven CRC; ii) metastatic and unresectable cancer with measurable lesion; iii) no prior chemotherapy or radiation therapy; iv) age 20 years or more; v) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1; vi) life expectancy of more than 2 months; vii) adequate bone marrow function (leucopenia >3,000/mm^3, platelet count >100,000/mm^3, and hemoglobin level >9.0g/dl), adequate renal function (creatinine clearance >50 ml /min) adequate hepatic function (bilirubin level <2.0 mg/dl and aspartate transaminase (AST)/alanine transaminase (ALT) <triple the normal upper limit); viii) no other severe medical conditions; ix) no active cancer in other organs.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. All patients gave their written informed consent, conforming to institutional guidelines, indicating that they were aware of the investigational nature of the study. This study was approved by the Ethics Committees of the participating institutions.

Treatment plan and evaluation. The protocol treatment was started within 14 days after enrollment of patients who were deemed to be eligible. On day 1, bevacizumab at 5 mg/kg was administered by initial 90-minute intravenous infusion (which could be shortened to 60 minutes on the second occasion and to 30 minutes from the third), then oxaliplatin at 85 mg/m^2, followed by oral capecitabine 2000 mg/m^2/day on days 1-7, with 7 days of drug withdrawal thereafter. These 14 days constituted one cycle, and after the first course, capecitabine dose escalation up to 2500 mg/m^2/day was permitted providing no adverse events were seen in the previous courses (Figure 1). Protocol treatment was continued as long as it did not conflict with the criteria for discontinuing treatment. However, patients in whom disease became operable as a result of the efficacy of treatment were defined as having ended the protocol treatment (with the day of surgery defined as the end of protocol treatment).

Computerized tomography (CT)/magnetic resonance imaging (MRI) was performed every 8 weeks during the protocol treatment, in order to evaluate target and non-target lesions, and to check for the appearance of new lesions. Evaluation of tumor reduction was according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (13). Adverse events were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver. 3.0 (14) in all enrolled patients who received the protocol treatment at least once. The frequency and grade of the most serious clinical findings and laboratory test values in each cycle were tabulated. Patients were observed carefully for previously reported typical adverse drug reactions to capecitabine, bevacizumab and oxaliplatin, including hand-foot syndrome, diarrhea, myelosupression, hemorrhage, thrombosis, gastrointestinal perforation, increased blood pressure, allergy and peripheral neuropathy.

Definition of endpoints. In this study, the following definitions were used to assess the therapeutic effect: progression-free survival (PFS) defined as the period from the day of enrollment to the confirmation of progressive disease (PD) or death from any cause, whichever came first; time to treatment failure (TTF) as the period from the day of enrollment until the date of discontinuation of treatment, the date of PD confirmation, or the date of death, whichever came first; response rate (RR) as the percentage of patients whose best overall response was either complete (CR) or partial (PR) response; and overall survival (OS) as the period from the day of enrollment to the confirmation of death from any cause.

Statistical analysis plan. The primary endpoint of this study was PFS, while the secondary endpoints were TTF, RR, OS, relative dose intensity (RDI) and the safety. We set our goal at 10.5 months for median PFS as a result of reviewing various reports (2,3,9-12,15). Under this condition, the required sample size was 40 patients in order to be able to detect a difference between a threshold median PFS of 7 months and a target median PFS of 10.5 months using the South West Oncology Group Statistical Tool with one-sided alpha error of 5% and statistical power of 80% with 2 year enrollment and 2-year follow-up time (16). In order to account for dropout, the number of patients to be accrued was set at 45 patients in total.

Survival curves for PFS, TTF and OS were calculated using the Kaplan-Meier method. The 95% confidence intervals (95% CI) for median survival were estimated using Brookmeyer and Crowley method (17). RR was caiculated as a percentage and its 95% CI was calculated using the exact method. Dose-intensity for all treatment periods was calculated as the total cumulative dose divided by the duration of dosing {[(start date of last course) + (start date of first course) + 14]/7}. The RDI was calculated as the dose intensity divided by the planned dose intensity, multiplied by 100. Planned dose intensities were 7,000 mg/m^2/week for capecitabine, 2.5 mg/kg/week and 42.5 mg/m^2/week for oxaliplatin. When there was a patient who continued treatment, RDI was calculated as the last treatment course was the last course. All analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics. Fifty-three patients were enrolled from December 2011 to July 2012. Two out of the 53 patients were excluded due to withdrawal of their consent before starting the first treatment. Therefore, the efficacy and

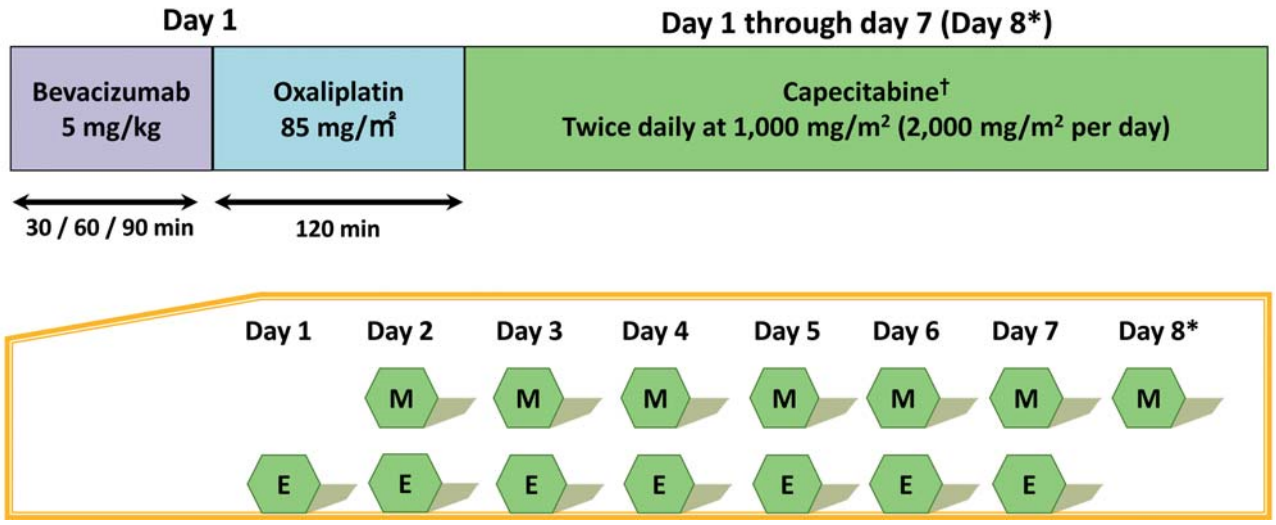

Figure 1. *Treatment. M, Morning; E, evening. *Patients who started capecitabine treatment from the evening of day 1, the last dose was given on the morning of day 8. †Increase of capecitabine to 2,500 mg/m²/day was allowed at the discretion of the investigator if no safety concern was found.*

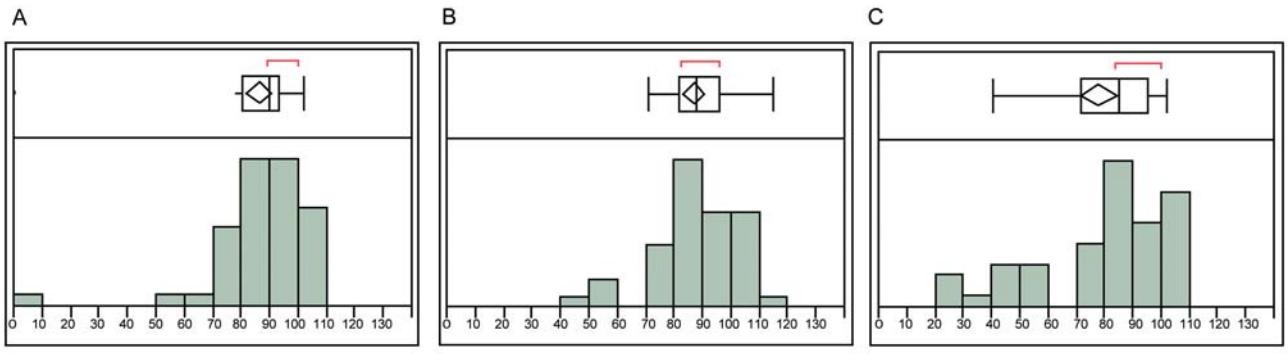

Figure 2. *Relative dose intensity (RDI) of each agent used in regimen of bi-weekly capecitabine-oxaliplatin (XELOX) plus bevacizumab as first-line treatment of metastatic colorectal cancer. A: Bevacizumab all courses, median RDI= 89.8% (mean=86.3%, range=0-102.4%); B: capecitabine all courses, median RDI =88.1%, (mean=86.9%, range=47.2-115.3%); C: oxaliplatin all courses, median RDI= 85.1%, (mean=78.1%, range=21-102.4%).*

safety were evaluated in 51 patients. Thirty-one patients were males and 20 females. All enrolled patients received the protocol treatment at least once. Data cut-off was August 2013, and the median observation period was 428 days. Characteristics of the patients are described in Table I. The median age was 66 (range=38-85) years.

Treatment status. Fifty-one patients started the protocol treatment. The median number of treatment courses was 11 (range=1-35). Fifty patients finished the protocol treatment and treatment for one patient was still ongoing at the time of data cutoff. Reasons for discontinuing treatment were disease progression in 13 cases, adverse events in 12 cases, conversion to surgery in 11 cases, patients' wish in six cases, and other reasons in eight cases. Median RDI values for capecitabine, oxaliplatin, and bevacizumab were 88.1%, 85.1% and 89.8%, respectively (Figure 2).

Efficacy. The median PFS was 344 days (11.3 months; 95% CI=226-439 days) (Figure 3). The pre-specified upper critical value was 9.2 months, and our statistical hypothesis in this phase II study was therefore met. The median TTF was 196 days (95% CI=146-218 days) (Figure 4), while the median OS has not yet been reached (Figure 5). Twenty-five patients had PR (49.0%) and 21 had SD (41.2%); two patients had PD (3.9%) as the best response and two patients could not be evaluated (3.9%). The objective RR was 51.0% (95% CI=36.6% to 65.3%) for this trial (Table II).

Table I. *Study patients' characteristics (n=51).*

	n=51	%
Median age, years	66 (38-85)	
Gender		
Male	31	60.8
Female	20	40.2
Performance status		
0	42	82.4
1	9	17.6
Diagnosis		
Primary	33	64.7
Recurrence	18	35.3
Location		
Colon	29	56.9
Rectum	22	43.1
Histological type		
Well-differentiated	12	23.5
Moderately differentiated	31	60.8
Poorly differentiated	4	7.8
Mucinous adenocarcinoma	3	5.9
Unknown	1	2
Measurable lesion		
Liver	34	66.7
Lung	21	41.2
Lymph node	18	35.3
Pleura	5	9.8
Other	5	9.8

Toxicity. The main adverse drug reactions of grade 3 or higher in the 51 patients of the safety analysis set are listed in Table III. Grade 3-4 neutropenia occurred in 13.7% (seven patients), peripheral neuropathy 13.7% (seven patients), hypertension 13.7% (seven patients), GI perforation 3.9% (two patients), and HFS 5.9% (three patients). Treatment-related death was not observed, including none from GI perforation. Discontinuation of protocol due to adverse events occurred in 13 cases, most of which were due to worsening neuropathy after 10 courses of oxaliplatin administration.

Discussion

Advances in chemotherapy have certainly improved the survival time of patients with mCRC. Capecitabine and oxaliplatin are key drugs for the management of mCRC. Oral capecitabine monotherapy has been shown to have superior antitumor activity to bolus fluorouracil with leucovorin (Mayo Clinic regimen) in this setting, with higher response rates (26% *vs*. 17%, $p<0.0002$) and at least equivalent TTP and OS in two large randomized studies (3, 18, 19, 20). The addition of oxaliplatin to oral capecitabine monotherapy can lead to higher response rates and TTP in both first- and second-line treatment of advanced colorectal cancer (2, 21).

Table II. *Response rate of patients treated with bi-weekly capecitabine-oxaliplatin (XELOX) plus bevacizumab as first-line treatment of metastatic colorectal cancer.*

	n=51	
Response	n	%
CR	1	2%
PR	25	49%
SD	21	41.20%
PD	2	3.90%
NE	2	3.90%
CR + PR	26	51
CR+PR+SD	47	92.1

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Table III. *Incidence of adverse events of patients treated with bi-weekly capecitabine–oxaliplatin (XELOX) plus bevacizumab as first-line treatment of metastatic colorectal cancer.*

	n=51			
	≥G3		All	
Adverse event	n	(%)	n	(%)
WBC	4	7.8	11	21.6
Neutropenia	7	13.7	11	21.6
Hemoglobin	0	0	28	54.9
PLT	0	0	19	37.3
T-Bill	0	0	15	29.4
AST	1	2	28	54.9
ALT	1	2	19	37.3
ALP	0	0	19	37.3
Fatigue	-		26	51
Anorexia	2	3.9	27	52.9
Nausea	1	2	19	37.3
Vomiting	0	0	2	3.9
Diarrhea	0	0	13	25.5
Stomatitis	1	2	18	35.3
Alopecia	-		3	5.9
Hypertension	7	13.7	12	23.5
Proteinurea	1	2	12	23.5
Constipation	0	0	5	9.8
Neuropathy	7	13.7	41	80.4
Hand-foot syndrome	3	5.9	25	49
GI hemorrhage	0	0	2	3.9
Nasal hemorrhage	0	0	4	7.8
Thrombosis artery	0	0	0	0
Thrombosis venous	0	0	0	0
GI perforation	2	3.9	2	3.9
TRD	0	0	0	0

WBC: White blood cell count, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GI: gastrointestinal, TRD, treatment-related death.

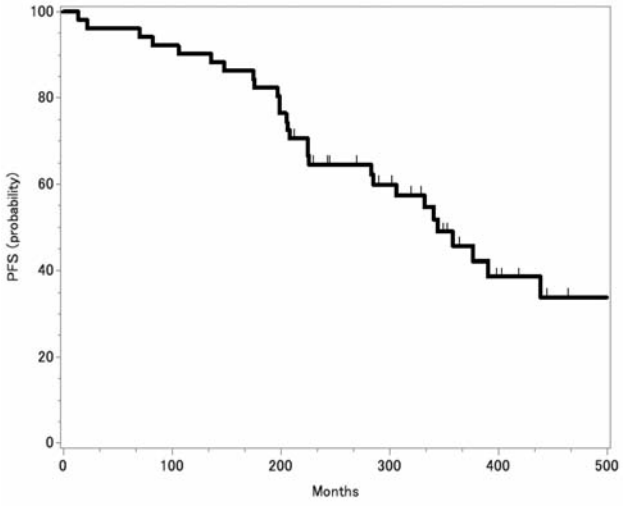

Figure 3. *Progression-free survival (PFS) of all enrolled patients. Events: 29/51, median PFS=44 days (95% confidence interval=226-439 days).*

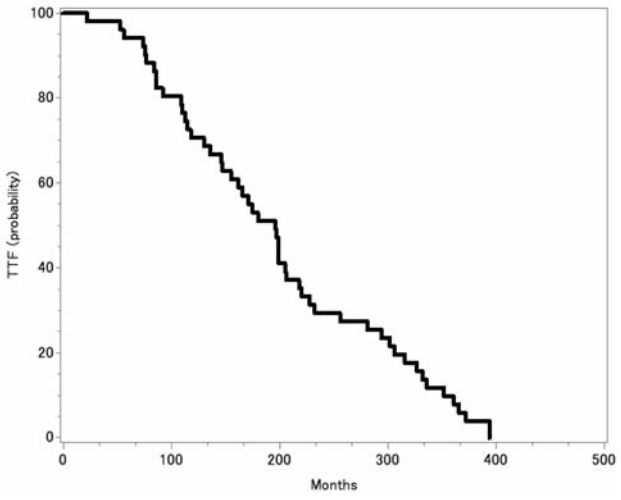

Figure 4. *Time-to treatment failure (TTF) of all enrolled patients. Events: 50/51, median TTF=196 days (95% confidence interval=146-218 days).*

Recently, the standard chemotherapies for treating advanced CRC have become FOLFOX or XELOX regimens and additional molecular targeting therapies. Standard combination chemotherapy with biological therapies has a significant benefit for patients (22, 23). XELOX with/without bevacizumab has been widely accepted for first-line treatment of mCRC, with good efficacy in RR and PFS (2, 3, 15). Patients with mCRC were given XELOX plus bevacizumab using a standard tri-weekly cycle or a dose-dense biweekly cycle schedule (9, 10). The latter phase II clinicial trial was conducted to determine if a regimen of intermittent XELOX with bevacizumab given as a dose-dense, bi-weekly cycle was superior to the standard regimen given as a tri-weekly cycle in terms of the PFS outcomes of patients with mCRC (10). To ensure efficacy, previous XELOX trials, in both bi-weekly and tri-weekly regimens, had set their dose at rather potent intensity (2, 9-12, 15), and consequently, considerable hand-foot syndrome and diarrhea had been observed.

However, capecitabine may differ in character from oxaliplatin. In animal model experiments, a higher therapeutic index (ratio of the 50% toxic dose and the 50% effective dose) compared to other fluoropyrimidine agents has been reported (24), suggesting that less dosage may still maintain good efficacy with a less toxic profile. In fact, *post hoc* analysis of some large trials reported that the subset of patients receiving a reduced dose of capecitabine by adverse events showed same or even higher efficacy compared with the subset given the scheduled dose (25). Moreover, the synergic effect of capecitabine and oxaliplatin might be stronger in a bi-weekly than in a tri-weekly regimen. However, some patients suffer

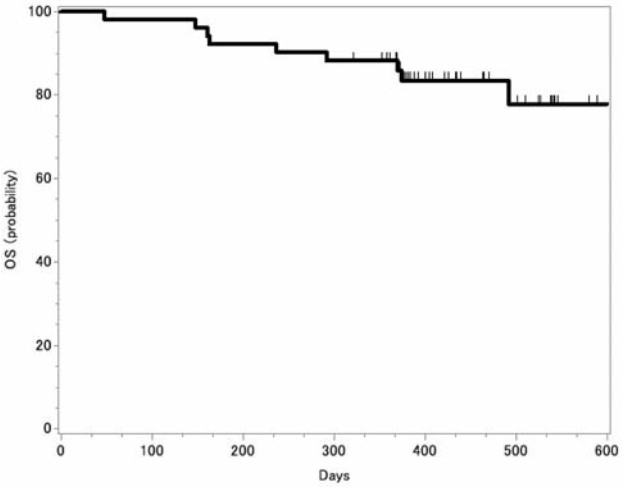

Figure 5. *Overall survival (OS) of all enrolled patients. Events: 11/51, median overall survival, not reached, (95% confidence interval=not reached).*

from substantial adverse events, including hand-foot syndrome, diarrhea, and neurotoxicity, which would be barriers to continuing long-term treatment or even be a reason to preclude possible next-line chemotherapy.

We performed a phase II trial of bi-weekly XELOX plus bevacizumab administration with a lower capecitabine dose intensity compared to previous reports. Points of interest in this study were to investigate whether efficacy and safety of bi-weekly XELOX treatment were acceptable in the first-line setting for Japanese patients with advanced CRC. This phase II

trial of a bi-weekly XELOX regimen (2,000 mg/m^2 capecitabine on days 1-7 plus 85 mg/m^2 oxaliplatin on day 1, every 2 weeks) plus bevacizumab treatment (5 mg/kg) was performed. The RR in this study was 51% (95% CI=36.6-65.3%) and the disease control rate was 92.1.0%. As for prognosis, the median PFS was 344 days (95% CI=226-439 days), and the median TTF was 196 days (95% CI=146-218 days), while the median OS has not yet been reached. With respect to the RR and median PFS, this study result was comparable or better to the results of first-line XELOX regimen plus oxaliplatin reported by Saltz *et al*. (49%, 9.4 months) (2), Hochster *et al*. (46%, 9.1 months) (9), Scheithauer *et al*. (49%, 6.0 months) (10) and by Doi *et al*. (71.9%, 11.0 months) (15).

Regarding the prognosis and the RR, our results are comparable to those reported for other regimens. The main grade 3 or greater toxic effects were leucopenia (8%), neutropenia (14%), anorexia (4%), hypertension (14%), neuropathy (14%), hand-foot syndrome (6%) and GI perforation (4%). In our study, the bi-weekly XELOX regimen appeared to have reduced toxicity compared with previous reports of other regimens (3, 5, 24-26).

As described, the given dose of capecitabine in our trial was 14,000 mg/m^2 for 2 weeks, which is two-thirds equivalence of the conventional regimens. In spite of the lower dose setting, the results seemed to be almost identical. Moreover, the RR and disease control rate were not inferior to other conventional XELOX studies. These favorable results are almost the same as those from other recent trials concerning oxaliplatin-based first-line treatment in mCRC (2, 3, 15, 27) and would support our hypothesis that the capecitabine also has good efficacy even in the lower dose setting. The RDI in this trial were 85.1% for oxaliplatin, 89.8% for bevacizumab, and 88.1% for capecitabine. Considering the efficacies, this regimen would be promising if it shows better tolerability with fewer adverse events or improved quality of life. This less-toxic profile of capecitabine might lead to better patient satisfaction, less incidence of treatment patient-initiated discontinuation, and consequently, good RDI with on-schedule treatment without dose reduction. We suppose good efficacy in our trial is partly due to this good RDI with long-term treatment compliance, and the strategy of maintaining a lower dosage may be more adequate than the strategy using near dose-limiting toxicity dose, which may sometimes require unexpected treatment interruption.

This phase II clinical trial was conducted to determine if a regimen of intermittent XELOX with bevacizumab given as a dose-dense, bi-weekly cycle was superior to the standard regimen given as a tri-weekly cycle in terms of PFS outcomes of patients with mCRC. Tolerable and sustainable dose setting of capecitabine might also have enough potential to ensure long SD with satisfactory quality of life due to the substantial accumulative dose in long and steady scheduled treatment.

In conclusion, our findings suggest that a bi-weekly XELOX regimen provides an effective, tolerable and safe first-line treatment for patients with mCRC. This regimen might be one of the better options for mCRC treatment, especially in order to avoid discontinuation of the scheduled treatment by severe subjective complications due to capecitabine.

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