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ORIGINAL ARTICLE

# Combining capecitabine, oxaliplatin, and gemcitabine (XELOXGEM) for colorectal carcinoma patients pretreated with irinotecan: a multicenter phase I/II trial

**Se Hyun Kim · Sang Joon Shin · Sun Young Kim · Se Hoon Lee · Young Suk Park · Se Hoon Park · Kyung Hee Lee · Tae Won Kim · Yong Sang Hong · Joong Bae Ahn**

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**Abstract**
*Purpose* Capecitabine plus oxaliplatin (XELOX) is an effective second-line regimen for advanced colorectal carcinoma (CRC) patients pretreated with irinotecan. Previous studies have shown supra-additive anti-tumor activity of gemcitabine (GEM) when administered with oxaliplatin. We investigated the dose, toxicity, and efficacy of a second-line XELOXGEM regimen in CRC patients pretreated with irinotecan.
*Methods* Patients with metastatic or recurrent CRC who failed after a first-line irinotecan-containing regimen received escalating doses of gemcitabine (600, 800, 1,000 mg/m$^2$ d1, d8) followed by capecitabine (1,000 mg/m$^2$ b.i.d d1–14) and oxaliplatin (100 mg/m$^2$ d1) on a 21-day cycle.
*Results* A total of 38 patients were treated. At 800 mg/m$^2$, two of six patients experienced dose-limiting toxicities (diarrhea and thrombocytopenia). Therefore, the clinically recommended dose was defined as 600 mg/m$^2$ gemcitabine (d1, d8) followed by 1,000 mg/m$^2$ capecitabine (b.i.d dl–14) and 100 mg/m$^2$ oxaliplatin (d1). The most common grade 3/4 toxicities were neutropenia (32%), thrombocytopenia (13%), anemia (11%), and peripheral neuropathy (11%). Ten (26.3%) and 23 (60.5%) patients experienced partial response and stable disease, respectively. The median progression-free survival and overall survival were 5.4 months (95% CI 3.8–6.9 months) and 17.7 months (95% CI 8.4–26.9 months), respectively.
*Conclusions* The XELOXGEM triplet combination is an active and safe second-line regimen for advanced CRC patients pretreated with irinotecan.

**Keywords** Capecitabine · Colorectal carcinoma · Gemcitabine · Oxaliplatin · Second-line

S. H. Kim · S. J. Shin · J. B. Ahn (✉)
Department of Internal Medicine,
Cancer Metastasis Research Center, Yonsei Cancer Center,
250 Seoungsanno, 120-752 Seodaemun-gu, Seoul, Korea
e-mail: vvswm513@yuhs.ac

S. Y. Kim
Center for Colorectal Cancer, Research Institute and Hospital,
National Cancer Center, Gyeonggi-do, Korea

S. H. Lee · Y. S. Park · S. H. Park
Division of Hematology-Oncology, Department of Medicine,
Samsung Medical Center, Seoul, Korea

K. H. Lee
Department of Hematology-Oncology, College of Medicine,
Yeungnam University, Daegu, Korea

T. W. Kim · Y. S. Hong
Department of oncology, Asan medical center, Seoul, Korea

## Introduction

Colorectal carcinoma (CRC) is one of the most common cancers worldwide and is the leading cause for cancer-related deaths in developed countries. Approximately half of newly diagnosed CRC patients are metastatic and unresectable. Although various combination chemotherapies of 5-fluorouracil (5FU) with newer cytotoxic (irinotecan and oxaliplatin) or targeted (bevacizumab and cetuximab) agents have resulted in great improvements in clinical tumor response and survival, patients with metastatic CRC still experience disease progression and a dismal 5-year survival rate [1].

When an irinotecan-containing first-line treatment fails, a second-line oxaliplatin-containing regimen is considered the treatment of choice [2]. However, results of previous studies with capecitabine and oxaliplatin combination therapy in patients with metastatic CRC who had received a first-line irinotecan-containing chemotherapy showed a response rate between 12 and 16%, with a median overall survival (OS) of around 10 months [3–5]. These poor results stimulated investigators to search for new drugs or new combination regimens for patients with metastatic CRC in a second-line situation.

Gemcitabine (2′,2′-difluorodeoxcycytidine) is a difluorinated analog of deoxycytidine. The compound inhibits tumor growth by interfering with DNA and RNA syntheses. Gemcitabine has shown antitumor activity against various tumor types including lung, ovary, pancreas, bladder, and breast cancer. Although a phase II trial of gemcitabine monotherapy failed to demonstrate antitumor activity against advanced CRC, a supra-additive effect was obtained with a combination of gemcitabine and oxaliplatin treatment in colon cancer cell lines. [6, 7]. In addition, CRC patients treated with a gemcitabine and oxaliplatin combination regimen showed promising tumor growth control without overlapping toxicities [8, 9].

Based on these findings, we designed and conducted a phase I/II clinical trial to investigate the toxicity profile and antitumor efficacy of a chemotherapy regimen combining capecitabine, oxaliplatin, and gemcitabine (XELOXGEM) in patients with metastatic or recurrent CRC pretreated with a first-line irinotecan-containing regimen.

## Patients and methods

### Patients

Patients with histologically confirmed metastatic or recurrent CRC pretreated with a first-line irinotecan-containing regimen were eligible for the study. Further inclusion criteria included age >18 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, at least one bidimensionally measurable lesion, and completion of any prior antitumor treatment (chemotherapy or radiotherapy) at least 4 weeks prior to study entry. In addition, subjects were required to have adequate organ function, as indicated by an absolute neutrophil count $\geq$1,500 $\times$ $10^9$/l, hemoglobin count $\geq$9 g/dl, platelet count $\geq$100 $\times$ $10^9$/l, serum creatinine <1.5 mg/dl, serum bilirubin <2 times the upper normal limit (UNL), and serum transaminase <3 times the UNL (<5 times the UNL in cases of liver metastases). Exclusion criteria included known central nervous system metastases, second primary tumors (except for non-melanoma skin cancer or in situ cervical cancer), uncontrolled inflammatory bowel disease, absorption disorder, and clinically significant cardiac disease. All patients submitted a written informed consent before registration.

### Treatment

Treatment consisted of gemcitabine at three dose levels (600 mg/m$^2$, 800 mg/m$^2$, and 1,000 mg/m$^2$) administered via i.v. over 30 min on day 1 (d1) and d8, oxaliplatin at 100 mg/m$^2$ i.v. over 120 min on d1, and capecitabine at 1,000 mg/m$^2$ orally twice daily from d1 to d14. Oxaliplatin was administered after gemcitabine infusion. This treatment was repeated every 3 weeks until disease progression or the onset of unacceptable toxicity. This treatment continued in responding patients at the discretion of the investigator.

At least three consecutive patients were treated at each dose level, and no intra-patient dose escalation was allowed. Escalation to the next dose level was permitted if no dose-limiting toxicity (DLT) was experienced by the end of the first or second cycle at the same dose level. If one of three patients experienced DLT during the first two cycles, three more patients were enrolled at the same dose level. If two or more patients experienced DLT, the previous dose level was determined as the clinically recommended dose (CRD). All patients in phase II part of the trial were treated at the CRD.

DLTs were defined as the following: grade 4 neutropenia, grade 3/4 febrile neutropenia, grade 3/4 thrombocytopenia, grade 3/4 anemia, grade 3/4 gastrointestinal symptoms (mucositis, vomiting, or diarrhea), grade 3/4 hand–foot syndrome (HFS), grade 3/4 peripheral neuropathy, grade 3/4 liver function abnormality including hyperbilirubinemia, inability to receive the d8 gemcitabine treatment, or any non-hematologic toxicity that required hospitalization. All adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Treatment was interrupted in the instance of any adverse event that was grade 2 or higher (except alopecia). If treatment was delayed for longer than 2 weeks, the patient was withdrawn from the study. If the adverse event resolved to grade 0–1, treatment was restarted. Dose modification was allowed for patients with grade 4 hematologic toxicity or grade 3 non-hematologic toxicity. In these cases, patients were treated at 80% of the previous event cycle dose. Dose modification of one drug was also allowed in cases of well-known causal relationships (capecitabine and HFS, oxaliplatin and peripheral neuropathy). The dose of gemcitabine on d8 was reduced by 20% in patients with grade 3 neutropenia or by 40% with grade 2 thrombocytopenia or grade 3 non-hematologic toxicity. The administration of gemcitabine on d8 was omitted in case of grade 4 neutropenia or grade 3 thrombocytopenia.

Tumor response was evaluated according to the response evaluation criteria in solid tumors (RECIST) at every six-week interval (two cycles) during active treatment and every three months during follow-up.

### Study design and statistics

This open-label, uncontrolled multicenter trial consisted of two parts, phase I and phase II. In phase I, a modified Fibonacci design with inter-patient dose escalation and descriptive statistics were used to determine the CRD for phase II. DLTs were predefined in the protocol. In phase II, Simon's two-stage optimal design was used to determine the patient sample size to be enrolled. The primary endpoint was response rate, which was used to determine the antitumor activity of the experimental treatment. The response rates of interest were $P_0 = 10\%$ and $P_1 = 25\%$. If more than two responses were identified in the 14 patients in the first stage, the study continued to a total of 34 patients in the second stage. If there were more than six responses in the 34 patients in the second stage, this treatment was considered acceptable with alpha and beta errors of 0.05 and 0.20, respectively (80% power). Considering a follow-up loss rate of 10%, the total calculated sample size was 38 patients. Response and survival analyses were performed on the intention-to-treat (ITT) population. Survival was estimated using the Kaplan–Meier method.

The study was approved by the institutional review boards of the participating hospitals and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

## Results

### Patient characteristics

Thirty-eight patients with metastatic or recurrent CRC were recruited from five centers from January 2007 to July 2009. The baseline characteristics of all 38 patients are summarized in Table 1. The median age was 57 years, and more than half of the patients (57.9%) had metastatic disease at primary diagnosis. An irinotecan-containing regimen was administered previously as the first-line chemotherapy in all 38 patients (36 with 5FU/LV/irinotecan, 2 with capecitabine/irinotecan). All patients completed at least two cycles of first-line treatment, and the median number of cycles received was eight.

### Dose escalation and DLT

Nine patients were treated in phase I part of this study. The number of patients enrolled in each dose level and the dose-limiting toxicities (DLT) experienced are summarized in Table 2. No DLTs were reported for the first three patients at dose level 1 (gemcitabine, 600 mg/m$^2$). However, when gemcitabine was increased to dose level 2 (gemcitabine, 800 mg/m$^2$), DLTs were observed in two of the six patients, including grade 3 diarrhea and grade 4 thrombocytopenia. Therefore, the recommended dose was defined at dose level 1; capecitabine at 1,000 mg/m$^2$ b.i.d d1–14, oxaliplatin at 100 mg/m$^2$ d1, and gemcitabine at 600 mg/m$^2$ d1, d8.

**Table 1** Basic Characteristics (Total $n = 38$)

| | *n* | % |
|---|---|---|
| Phase | | |
| I | 9 | 23.7 |
| II | 29 | 76.3 |
| Age (median) | | 33–70 (57) |
| Gender | | |
| Male | 25 | 65.8 |
| Female | 13 | 34.2 |
| Performance status | | |
| 0 | 24 | 63.2 |
| 1 | 14 | 36.8 |
| Primary site | | |
| Colon | 18 | 47.4 |
| Rectal | 17 | 44.7 |
| Rectosigmoid | 3 | 7.9 |
| Disease status | | |
| Metastatic | 22 | 57.9 |
| Recurrent | 16 | 42.1 |
| Previous treatment | | |
| Surgery | 21 | 55.2 |
| Curative | 17 | 44.7 |
| Palliative | 4 | 10.5 |
| Radiation therapy | 8 | 21.1 |
| Chemotherapy | | |
| FOLFIRI | 36 | 94.7 |
| Other regimen | 2 | 5.3 |
| No. of cycles (median) | | 2–24 (8) |
| Site of metastasis | | |
| Liver | 25 | 67.6 |
| Lung | 14 | 36.8 |
| Peritoneal | 14 | 37.8 |
| Lymph node | 21 | 56.8 |
| Others | 8 | 21.6 |
| No. of treatment cycles (median) | | 2–20 (6.5) |
| Dose level 1 | | 2–20 (6.0) |
| Dose level 2 | | 4–18 (12.0) |

### Safety assessment

A total of 312 treatment cycles were administered to the 38 patients. The median number of treatment cycles per patient

**Table 2** Dose-limiting toxicities (DLT) according to dose level

| Dose level | X/O/G regimen (mg/m$^2$) | No. of patients | No. of cycles | DLTs on the first two cycles |
|---|---|---|---|---|
| 1 | 2,000/100/600 | 3 | 28 | None |
| 2 | 2,000/100/800 | 6 | 62 | Grade 4 thrombocytopenia ($n$ = 1)<br>Grade 3 diarrhea ($n$ = 1) |
| Total | | 9 | 90 | |

*X* capecitabine, *O* oxaliplatin, *G* gemcitabine

**Table 3** Toxicity profiles per patient according to NCI-CTC v3.0

| | Dose level 1 ($n$ = 32) | | | | Dose level 2 ($n$ = 6) | | | | Total ($n$ = 38) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 3/4 | | Grade 1/2 | | Grade 1/2 | | Grade 3/4 | | Grade 3/4 | | All grades | |
| | $n$ | (%) | $n$ | (%) | $n$ | (%) | $n$ | (%) | $n$ | (%) | $n$ | (%) |
| *Hematologic* | | | | | | | | | | | | |
| Neutropenia | 8 | 25 | 9 | 28 | 1 | 17 | 3 | 50 | 12 | 32 | 21 | 55 |
| Febrile neutropenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anemia | 8 | 25 | 4 | 13 | 2 | 33 | 0 | 0 | 4 | 11 | 14 | 37 |
| Thrombocytopenia | 5 | 16 | 3 | 9 | 1 | 17 | 2 | 33 | 5 | 13 | 11 | 29 |
| *Non-hematologic* | | | | | | | | | | | | |
| General | | | | | | | | | | | | |
| Fatigue (Asthenia) | 11 | 34 | 0 | 0 | 4 | 67 | 0 | 0 | 0 | 0 | 15 | 39 |
| Skin | | | | | | | | | | | | |
| Rash | 9 | 28 | 0 | 0 | 1 | 17 | 0 | 0 | 0 | 0 | 10 | 26 |
| Hand–foot syndrome | 9 | 28 | 2 | 6 | 2 | 33 | 0 | 0 | 2 | 5 | 13 | 34 |
| GI | | | | | | | | | | | | |
| Nausea and vomiting | 21 | 66 | 0 | 0 | 3 | 50 | 1 | 17 | 1 | 3 | 25 | 66 |
| Stomatitis | 7 | 22 | 0 | 0 | 1 | 17 | 0 | 0 | 0 | 0 | 8 | 21 |
| Diarrhea | 12 | 38 | 0 | 0 | 3 | 50 | 1 | 17 | 1 | 3 | 16 | 42 |
| Neurology | | | | | | | | | | | | |
| Peripheral neuropathy | 14 | 44 | 3 | 9 | 5 | 83 | 1 | 17 | 4 | 11 | 23 | 61 |

was 6.5 (range: 2–20 cycles), and the majority of adverse events were mild to moderate. Treatment-related toxicity profiles per patient are summarized in Table 3. The predominant grade 3/4 adverse events observed in the patients were neutropenia (12 patients, 32%), thrombocytopenia (five patients, 13%), anemia (four patients, 11%), and peripheral neuropathy (four patients, 11%).

Thirty-two patients were treated at the CRD with a total of 243 cycles. In this group, the most frequent grade 3/4 adverse events were neutropenia (nine patients, 28%), thrombocytopenia (three patients, 9%), and peripheral neuropathy (three patients, 9%). Neither febrile neutropenia nor hemorrhagic complications were observed in these patients. Grade 3 peripheral neuropathy was observed in three patients who received cumulative oxaliplatin doses of 780 mg/m$^2$, 1,060 mg/m$^2$, and 1,140 mg/m$^2$, respectively. Oxaliplatin was permanently discontinued in two patients with continuous grade 3 peripheral neuropathy. Two patients (6%) experienced grade 3 HFS during treatment, and capecitabine was permanently discontinued in one of these patients with recurrent episodes despite dose reduction.

Two patients (1 patient at dose level 2) required hospitalization due to diarrhea (grade 2–3) and dehydration after the second cycle of treatment. One patient died due to pulmonary thromboembolism after the fourth cycle of chemotherapy during phase II of the study. The event was not considered to be treatment-related.

The mean relative dose intensities of capecitabine, oxaliplatin, and gemcitabine calculated among the 32 patients treated at CRD were 89, 82, and 84%, respectively. Among 243 cycles, the full planned doses of capecitabine, oxaliplatin, and gemcitabine were administered in 222 cycles (91%), 173 cycles (71%), and 150 cycles (62%), respectively. The dose of gemcitabine on d1 and d8 was reduced in 92 cycles (37.9%) and 22 cycles (9.1%), respectively. The administration of gemcitabine on d8 was omitted in 9 cycles (3.7%) due to grade 4 neutropenia or grade 3 thrombocytopenia.

**Table 4** Best objective responses during treatment

| | Dose level 1 | | Dose level 2 | | Total | |
|---|---|---|---|---|---|---|
| | *n* = 32 | (%) | *n* = 6 | (%) | *n* = 38 | (%) |
| Complete response | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Partial response | 8 | 25.0 | 2 | 33.3 | 10 | 26.3 |
| Stable disease | 19 | 59.4 | 4 | 66.7 | 23 | 60.5 |
| Progressive disease | 5 | 15.6 | 0 | 0.0 | 5 | 13.2 |

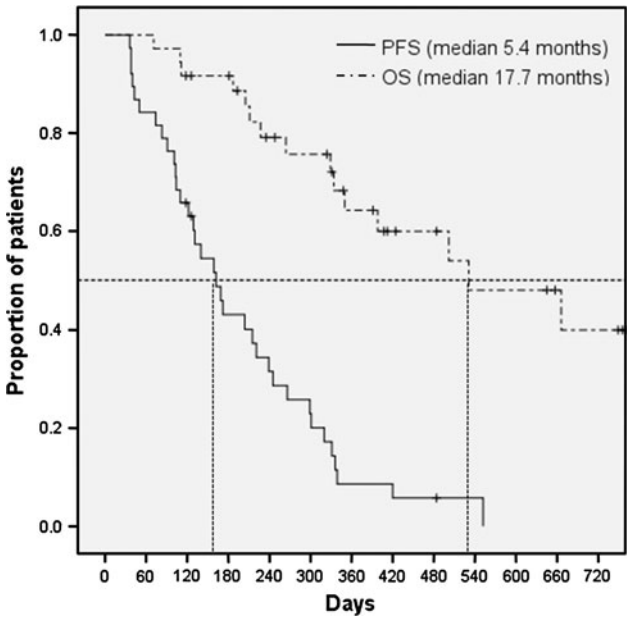


**Fig. 1** Kaplan–Meier estimates of progression-free survival and overall survival of enrolled patients (ITT population). *ITT* intention-to-treat; *PFS* progression-free survival; *OS* overall survival

### Efficacy assessment

All 38 patients with measurable disease were available for the assessment of tumor response. Table 4 summarizes the best responses of all patients treated at each dose level. No complete response was reported among the 38 patients on this study, whereas ten (26.3%) patients achieved a best response to partial response, for an overall objective response rate of 26.3% (95% CI, 13.2 to 42.1%) by intention-to-treat analysis. Twenty-three patients (60.5%) showed stable disease and five (13.2%) demonstrated progressive disease. Among the 32 patients treated at CRD, eight (25.0%) achieved a partial response and 19 patients (59.4%) showed stable disease.

After a median follow-up duration of 11.4 months (range: 2.4–31.0), the median PFS was 5.4 months (95% CI 3.8–6.9 months) in 38 patients (Fig. 1). Among the 32 patients at CRD, the median PFS was 4.7 months (95% CI 3.3–6.1 months), with four patients censored (3 patients remained progression-free and continued treatment, one patient was lost to follow-up without evidence of progressive disease). The median OS of the enrolled patients was 17.7 months (95% CI 8.4–26.9 months). The causes for death were disease progression in 14 patients (93.3%) and pulmonary embolism in one patient (6.7%).

## Discussion

To the best of our knowledge, this is the first study to report the efficacy and tolerability of capecitabine, oxaliplatin, and gemcitabine (XELOXGEM) combination chemotherapy in patients with advanced CRC who failing to respond or progressing to first-line irinotecan-containing chemotherapy. Although there is no large-scale phase III study of gemcitabine-containing regimens in patients with CRC, Correale et al. [8] reported a promising response (CR + PR 42%) of GOLF (gemcitabine, oxaliplatin, leucovorin, and 5-FU) combination therapy in patients with metastatic CRC. In addition, Ziras et al. [9] demonstrated the antitumor activity and favorable toxicity profile of a gemcitabine plus oxaliplatin (GEMOX) treatment as a second-line therapy for patients with metastatic CRC (PR 17.7%, SD 23.5%).

The primary objective of phase I of this study was to determine the CRD of XELOXGEM. Two DLTs (diarrhea and thrombocytopenia) were observed at dose level 2 (gemcitabine 800 mg/m$^2$) and precluded further increase in dosage. The CRD for phase II consisted of three-week cycles of gemcitabine at 600 mg/m$^2$ i.v. over 30 min on d1 and d8, oxaliplatin at 100 mg/m$^2$ i.v. over 120 min on d1, and capecitabine at 1,000 mg/m$^2$ orally twice daily from d1 to d14. Two studies evaluated the DLT and maximum tolerated dose (MTD) of XELOXGEM using different dosing and scheduling. Tan et al. [10] reported a MTD for oxaliplatin at 100 mg/m$^2$ plus gemcitabine at 800 mg/m$^2$ on d1 and d15, with capecitabine at 800 mg/m$^2$ b.i.d. d1–7 and d15–21 on a 28-day cycle with grade 3 fatigue and dyspnea in patients with advanced upper gastrointestinal malignancies. Another study determined the CRD for a phase II trial as a three-week regimen of oxaliplatin at 130 mg/m$^2$ on d1, capecitabine at 650 mg/m$^2$ b.i.d. d1–14, and gemcitabine at 1,000 mg/m$^2$ on day d1 and d8 with diarrhea and thrombocytopenia as the dose-limiting DLTs (similar to our results) in patients with advanced pancreatic carcinoma [11]. Both studies were mainly designed for the treatment of pancreatobiliary carcinomas; thus, a relatively higher dosage of gemcitabine was used compared to that in the current trial.

Adverse events observed with XELOXGEM were mild to moderate in severity in most patients. The main treatment-related adverse events were neutropenia,

thrombocytopenia, diarrhea, and peripheral neuropathy. Although the rate of grade 3/4 neutropenia in the present trial (28%) was higher than that of XELOX (5–7%), the rate was lower than that of FOLFOX4 (35–43%) [4, 12]. Despite the addition of gemcitabine, only one of 38 patients (3%) experienced grade 3 diarrhea and four of 38 patients (11%) reached grade 3 peripheral neuropathy. The rate of HFS in the current trial (all grade, 34%; grade 3, 5%) was similar to that reported with XELOX (all grade, 29%; grade 3, 5%) [13]. Of note, there were no treatment-related deaths or withdrawals due to delayed treatment.

The present study provides evidence for the efficacy of XELOXGEM combination therapy in patients with metastatic CRC. Ten of 38 patients (26.3%) had objective tumor regression, matching the primary endpoint of phase II. An additional 23 patients (60.5%) showed stable disease with a tumor growth control rate of 86.8%. The median PFS and OS of the enrolled patients were 5.4 and 17.7 months, respectively. While the general limitations of a cross-study comparison should be taken into account, these findings showed a higher response rate to XELOXGEM treatment than that of XELOX (between 12 and 16%) in patients with metastatic CRC who had received a prior irinotecan-containing regimen, such as FOLFIRI or XELIRI, as a first-line treatment [3–5].

There is potential for the use of XELOXGEM as a first-line treatment, especially in patients with potentially curable liver metastasis. Previous neoadjuvant studies investigated the efficacy of adding bevacizumab to XELOX. However, thromboembolism, bleeding, and wound healing were matters of great concern with this treatment [14, 15]. XELOXGEM regimen also has an advantage over irinotecan-containing triplet regimens, such as FOLFOXIFI or XELOXIRI, as they cause grade 3/4 diarrhea in 20–24% of treated patients that can be life threatening [16, 17].

Similar to other phase II trials, the results of the current trial were limited by a small sample size and must be confirmed through a larger phase III trial, such as a head-to-head comparison with XELOX treatment. The possibility of selection bias with relatively good performance status might be another limitation of this study. However, the primary objective of this trial was to determine response rate, not survival time, which is less affected by performance status.

In conclusion, the results of this study showed that XELOXGEM treatment is safe and effective in patients with CRC previously treated with a first-line irinotecan-containing chemotherapy. The present results also indicate that a subclinical dose of gemcitabine may have a potential role as an enhancer to a XELOX regimen without adding serious toxicity. The current combination chemotherapy regimen is worthy of further investigation.

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**Conflict of interest** None.

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