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**ORIGINAL ARTICLE**

# Multicenter phase II study of oral capecitabine plus irinotecan as first-line chemotherapy in advanced colorectal cancer: A Korean Cancer Study Group Trial

TAE WON KIM[1], WON KI KANG[2], HEUNG MOON CHANG[1], JOON OH PARK[2], BAEK YEOL RYOO[3], JIN SEOK AHN[4], DAE YOUNG ZANG[4], KYUNG HEE LEE[5], YOON KOO KANG[1], SUNG ROK KIM[6] & HOON-KYO KIM[7]

[1]*Section of Oncology, Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea,* [2]*Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea,* [3]*Division of Hematology and Oncology, Department of Internal Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Science, Seoul, Korea,* [4]*Department of Internal Medicine, Hallym University College of Medicine, Hallym Sacred Heart Hospital, Anyang, Korea,* [5]*Division of Hematology-Oncology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea,*[6]*Department of Internal Medicine, Inje University College of Medicine, Sanggye Paik Hospital, Seoul, Korea, and* [7]*Department of Internal Medicine, The Catholic University College of Medicine, St Vincent's Hospital, Suwon, Korea*

**Abstract**

A phase II study was conducted to assess the efficacy and tolerability of capecitabine in combination with irinotecan (CAPIRI) in advanced colorectal cancer. Forty-seven patients with previously untreated metastatic or unresectable colorectal adenocarcinoma received capecitabine 1000 mg/m$^2$ twice daily on days 2–15 and intravenous irinotecan 100 mg/m$^2$ on days 1 and 8, every 21 days. A total of 268 cycles of chemotherapy (median 6: range 1–11) were administered. According to an intent-to-treat analysis, the overall response rate was 49% (95% CI, 35–63%). Median time to progression and overall survival were 7.5 months (95% CI, 4.8–10.2) and 19.5 months (95% CI, 15.7–23.8), respectively. The most common grade 3/4 adverse events were diarrhea (24%) and neutropenia (11%). There were no treatment-related deaths. These results indicate that CAPIRI has comparable activity and tolerability to FOLFIRI as first-line treatment for advanced colorectal cancer.

## Introduction

Colorectal cancer (CRC) is one of the most frequently encountered malignancies, third behind breast and cervical cancer in women and fourth after lung, stomach, and prostate cancer in men [1]. While 5-fluorouracil (5-FU)-based chemotherapy has been the mainstay of treatment for advanced CRC [2], infusion pumps and central venous catheters are necessary for optimal delivery, which add to the cost, morbidity, and inconvenience of treatment. However, the development of new cytoxotic agents (e.g. irinotecan and oxaliplatin) and an oral alternative to 5-FU (i.e. capecitabine) has changed the treatment of CRC in recent years.

Capecitabine (Xeloda®; Hoffmann-La Roche Inc, Nutley, NJ) is a novel oral fluoropyrimidine designed to mimic continuous infusions of 5-FU and deliver 5-FU to tumor cells. The recommended dose and schedule of capecitabine is 1250 mg/m$^2$ twice daily for 14 days every 3 weeks. Using this schedule as first-line single-agent therapy in patients with advanced CRC, two large randomized phase III studies have shown better tumor response rates and at least equivalent time to progression (TTP) and overall survival with capecitabine compared with intravenous (i.v.) bolus 5-FU/leucovorin (LV) [3,4]. In addition, capecitabine was better tolerated than 5-FU/LV, with a significantly lower rate of diarrhea, nausea, stomatitis, alopecia, and neutropenia.

Correspondence: Won Ki Kang, Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, 50 Ilwon-Dong, Kangnam-Ku, Seoul 135-710, Korea. Tel: 82-2- 3410-3451. Fax: 82-2-3410-0041. E-mail: wkkang@smc.samsung.co.kr

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The topoisomerase I inhibitor irinotecan (CPT-11) has shown consistent efficacy in both chemotherapy-naive patients and 5-FU pretreated patients with advanced CRC [5,6]. The most frequent adverse events associated with irinotecan are neutropenia, delayed diarrhea, acute cholinergic syndrome, and nausea/vomiting. Two randomized phase III studies have shown that combining irinotecan with bolus or infusional 5-FU/LV regimens offers significant benefits compared with 5-FU/LV alone in terms of response rate and TTP [7,8], as well as overall survival in one trial [7]. However, an independent review of the data revealed a threefold higher early mortality rate associated with irinotecan/bolus 5-FU/LV combinations vs. other combinations [9].

The combination of irinotecan and oral capecitabine is compelling because the agents have different modes of action, only partially overlapping adverse event profiles, and administration of oral home-based capecitabine is much more convenient than hospital-based i.v. 5-FU/LV [10]. The early promise of adding capecitabine to irinotecan documented in preclinical studies [11] has been confirmed by encouraging results from phase I and II studies of capecitabine in combination with either weekly (CAPIRI) or 3-weekly (XELIRI) irinotecan [12–18]. The current phase II study was conducted to evaluate the efficacy and safety of the weekly CAPIRI regimen as first-line therapy in patients with previously untreated advanced CRC. The dose schedule of this study was based on a randomized phase II study in which irinotecan 120 mg/m$^2$ was given on days 1 and 8 with capecitabine 1000 mg/m$^2$ twice daily for 2 weeks every 3 weeks [15]. For safety reasons, we reduced irinotecan dose to 100 mg/m$^2$ (days 1 and 8).

## Material and methods

### *Study design and treatment*

The primary objective was to determine the overall response rate. Secondary objectives were to evaluate additional efficacy parameters and the safety profile of the combination.

Capecitabine was administered orally at 1000 mg/m$^2$ twice daily on days 2–15, followed by a 7-day rest period. Irinotecan was administered i.v. at a dose of 100 mg/m$^2$ over 90 minutes on days 1 and 8, every 21 days. Treatment was discontinued at any sign of disease progression, development of unacceptable adverse events or withdrawal of consent. Before irinotecan administration, patients received antiemetic therapy (serotonergic antagonists combined with i.v. dexamethasone 10 mg). For irinotecan-induced delayed diarrhea, high-dose loperamide therapy was administered orally at a starting dose of 4 mg for the first episode followed by 2 mg every 2 hours for at least 12 hours. The patient was allowed to stop loperamide only after a 12-hour diarrhea-free interval. No prophylactic use of granulocyte colony-stimulating factor and atropine was allowed.

### *Patient selection criteria*

Eligible patients had histologically confirmed unresectable advanced or metastatic adenocarcinoma of the colorectum and at least one bidimensionally measurable lesion (defined as $\geq 2 \times 2$ cm, as assessed by a physical or x-ray examination including chest x-ray or computed tomography (CT) scan). Other eligibility criteria were age 18–70 years and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were eligible if they had received: no prior chemotherapy or radiotherapy; one 5-FU-based adjuvant chemotherapy regimen that had finished at least 12 months before enrollment; and no radiotherapy within the 4 weeks before study entry. Adequate hematologic (absolute neutrophil count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L), hepatic (total bilirubin $\leq 1.5$ mg/dL and serum transaminases $\leq 2.5 \times$ upper normal limit [UNL] or $\leq 5 \times$ UNL in cases of hepatic metastases), and renal (serum creatinine $\leq 1.5$ mg/dL) function was required. Patients were excluded from the study if they had chronic diarrhea, unresolved bowel obstruction, severe uncontrolled medical conditions, or brain metastases. The protocol was approved by the local institutional review board of each center, and all patients gave written informed consent before enrollment.

### *Study assessments and dose modification*

A physical examination was carried out before each cycle of therapy. Complete blood counts and biochemical tests were performed before and on day 8 of each cycle. Safety was evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Hand–foot syndrome (HFS) was graded as described previously [19]. Patients were required to meet all of the following criteria to begin the next cycle of treatment: neutrophil count $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; and resolution or improvement of clinically significant non-hematologic adverse events to grade 1 or 0. Patients were excluded if treatment was delayed for 2 weeks.

Dosage modification could be made on day 1 of a new cycle (on the basis of laboratory values obtained on that day and the adverse events encountered during the preceding cycle) or on day 8 (on the basis of adverse events observed since the start of the current cycle). Safety assessment and dose adjustments of capecitabine for HFS were as follows: no reductions for grade 1; a 25% reduction for grade 2; and a 50% reduction for grade 3 HFS [19]. Any patient who required more than a 50% dose reduction was withdrawn from the study.

Compliance with capecitabine was monitored by questioning patients and counting their remaining pills at each outpatient visit. The ratio of the actual administered dose to the scheduled dose was calculated. Dose intensity was defined as the total amount of drug given (mg/m$^2$) divided by the number of weeks of treatment.

### *Evaluation of response*

Tumors were measured every three cycles (9 weeks) until disease progression. Response to therapy was assessed according to WHO criteria [20], with complete response (CR) defined as complete disappearance of all clinically assessable disease for at least 4 weeks, and partial response (PR) as a decrease of at least 50% of the sum of the products of the diameters of any measurable lesion for at least 4 weeks. Duration of response was defined as the interval from the onset of CR or PR (whichever was recorded first) to the time point when any evidence of disease progression was encountered. TTP was calculated from the date of entry to disease progression and overall survival from the date of entry to death.

### *Statistical analysis*

Efficacy analyses were performed on the intention-to-treat population. The trial was conducted according to the optimal two-stage design [21]. Thirteen patients were included in the first stage, with at least four responses required to continue to the second stage. Thirty additional patients were included to a total sample size of 43. Thirteen responses were needed to conclude with 95% confidence that the response rate was $>40\%$. However, the accrual was continued to a total of 47 patients to compensate for potentially non-evaluable patients. The duration of response, TTP, and overall survival were estimated as secondary endpoints by the Kaplan–Meier method. We reported results with 95% confidence intervals (CIs).

## Results

### *Patient characteristics*

Between October 2001 and October 2002, 47 patients were enrolled in the study from seven Korean centers. Table I gives patient demographics and baseline disease characteristics. This was a typical first-line trial population, although only 6/47 (13%) had received prior adjuvant chemotherapy. In addition, despite almost one-third of patients having rectal cancer, only one had received prior radiotherapy. The median duration of follow-up at the time of analysis was 19.6 months (95% CI, 18.5–20.6 months)

### *Efficacy*

A total of 45 patients were evaluable for response. The remaining two patients were not assessable for response because they had been lost to follow-up. The overall response rate in the intent-to-treat

Table I. Patient demographics and baseline disease characteristics (n = 47).

| Characteristic | No. of patients | % |
|---|---|---|
| Age (years) | | |
| Median (range) | 55 (26–70) | |
| Sex | | |
| Male | 34 | 72 |
| Female | 13 | 28 |
| Performance status (ECOG scale) | | |
| 0 | 20 | 43 |
| 1 | 24 | 51 |
| 2 | 3 | 6 |
| Location of primary tumor | | |
| Colon | 33 | 70 |
| Rectum | 14 | 30 |
| Tumor differentiation | | |
| Well | 11 | 23 |
| Moderate | 30 | 64 |
| Poor | 2 | 4 |
| Unknown | 4 | 9 |
| Extent of disease | | |
| Metastatic | 41 | 87 |
| Recurrent | 6 | 13 |
| Previous adjuvant treatment | | |
| Chemotherapy | 6 | 13 |
| Radiotherapy | 1 | 2 |
| Metastatic sites | | |
| Liver | 39 | 85 |
| Lung | 9 | 19 |
| Cervical lymph node | 4 | 9 |
| Abdominal lymph node | 7 | 13 |
| Peritoneum | 5 | 11 |
| No. of organs involved | | |
| 1 | 30 | 64 |
| $\geq 2$ | 17 | 36 |

population (all patients) was 49% (95% CI, 35–63%), including two confirmed CRs and 21 confirmed PRs (Table II). The median duration of response in the 23 responding patients was 9.4 months (95% CI, 7.5–11.2 months). The median TTP and overall survival for all patients were 7.5 months (95% CI, 4.8–10.2 months) and 19.5 months (95% CI, 15.7–23.8 months), respectively (Figure 1). Some 40% of patients received oxaliplatin-based treatment as a salvage treatment; 32% received further capecitabine and 4% received further irinotecan.

*Safety*

Patients received a total of 268 treatment cycles (median 6; range 1–11 cycles), of which 266 were administered to the 47 patients who were assessable for safety. Most adverse events were mild to moderate in intensity (Table III) and manageable through either dose interruption or reduction (see below). The most common adverse events are shown in Table III. With the exception of diarrhea (24%) and neutropenia (11%), no grade 3/4 adverse events occurred in $\geq$ 5% of patients. Only three patients experienced febrile neutropenia and there were no treatment-related deaths. Overall 15 (32%) patients and 49 (18%) cycles required a dose reduction of irinotecan at day 1. Dose reductions or omissions of irinotecan at day 8 were needed in 73 (27%) cycles. The most common reasons for the dose modification of irinotecan (days 1 or 8) were neutropenia (48 cycles) and diarrhea (46 cycles). A total of 34 cycles (13%) were delayed, mainly by neutropenia (22 cycles; 8%). Three patients discontinued chemotherapy due to toxicity. Three out of five patients equal to or over 65 years experienced grade 3/4 adverse events (2 patients: grade 3 diarrhea, 1 patient: grade 4 neutropenia). There was a higher incidence of dose reductions required with irinotecan than with capecitabine. The median dose intensity over all treatment cycles was 8631 mg/m$^2$/week (range 4109–9333) for capecitabine and 57 mg/m$^2$/week (range 24–67) for irinotecan; these figures correspond to 95% and 85% of the planned dose intensities, respectively (Figure 2). Compliance with capecitabine was 95% during all cycles of treatment.

Table II. Response rates: intention-to-treat analysis.

| Response | No. of patients | % |
|---|---|---|
| Overall response | 23 | 49[1] |
| Complete | 2 | 4 |
| Partial | 21 | 45 |
| Stable disease | 13 | 28 |
| Progressive disease | 9 | 19 |
| Not evaluable | 2 | 4 |

[1]95% CI = 35–63%.

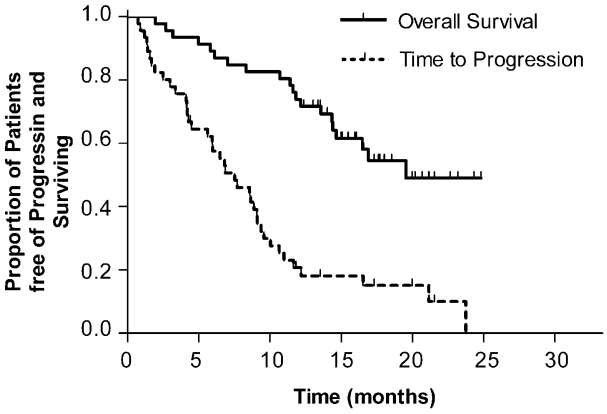


Figure 1. Kaplan–Meier curves for time to disease progression and overall survival for the intent-to-treat population (n = 47).

## Discussion

Our results indicate that CAPIRI is highly effective as first-line chemotherapy for advanced CRC. The overall response rate (49%), median TTP (7.5 months), and overall survival (19.5 months) are similar to results previously reported with irinotecan plus infusional 5-FU/LV combinations and compare favorably with those with bolus regimens [7,8,22]. Our findings are also consistent with those from a number of phase I/II trials evaluating XELIRI/CAPIRI regimens (capecitabine at 1000 mg/m$^2$ for 2 weeks plus irinotecan at 240–250 mg/m$^2$ on day 1 or 80–100 mg/m$^2$ on days 1 and 8) [12–18].

A randomized phase II trial by the Swiss Group for Clinical Cancer Research enrolled 75 patients who received either a weekly CAPIRI regimen or a

Table III. Adverse events per patient.

| | Grade[1] (% of patients) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Hematologic | | | | |
| Anemia | 39 | 33 | 0 | 0 |
| Leukopenia | 28 | 15 | 2 | 2 |
| Neutropenia | 15 | 33 | 9 | 2 |
| Thrombocytopenia | 2 | 0 | 0 | 0 |
| Non-hematologic | | | | |
| Nausea | 67 | 22 | 2 | 0 |
| Vomiting | 13 | 33 | 4 | 0 |
| Stomatitis | 11 | 17 | 0 | 0 |
| Diarrhea | 24 | 20 | 22 | 2 |
| HFS | 52 | 15 | 4 | – |

HFS = hand-foot syndrome. [1]NCI-CTC, except for grading of HFS.

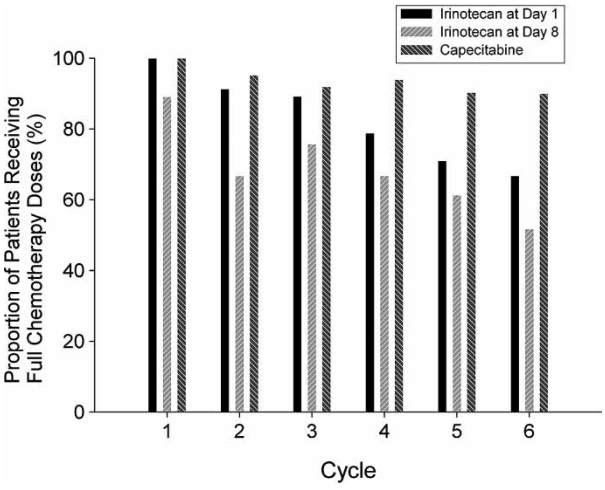


Figure 2. Proportion of patients receiving full chemotherapy doses during respective treatment cycles.

3-weekly XELIRI regimen as first-line therapy. Recently presented data indicate that the weekly CAPIRI regimen leads to more frequent grade 3/4 diarrhea but a lower rate of grade 3/4 neutropenia and alopecia than the 3-weekly XELIRI regimen [17]. However, the response rate and TTP data are inferior those seen with 3-weekly XELIRI, perhaps because of the lower dose intensity of irinotecan. Findings from three other studies [14,15,18] have also shown a higher rate of grade 3/4 diarrhea with the weekly CAPIRI schedule. While reducing the irinotecan dose in the elderly [18] appears to improve safety, efficacy is impaired. Therefore, reverting to the standard 3-weekly XELIRI regimen might have a better therapeutic ratio.

In our study, diarrhea was the main adverse event with CAPIRI, which is consistent with previous findings. A number of early deaths have been reported at an irinotecan dose of 100 mg/m$^2$ administered on days 1 and 8 [14]. While no treatment-related mortality was observed on day 60 in the present study, the peak incidence of grade 3/4 diarrhea was noted during the first treatment cycle, and the dose intensity of irinotecan dropped after the second cycle of treatment. In addition, three out of five patients equal to or over 65 years suffered from grade 3/4 adverse events. It has been reported that several agents, such as neomycin [23], bicarbonate [24], and the 'Kampo' product [25], might be capable of preventing irinotecan-induced diarrhea. However, adequately powered randomized trials are needed to verify these approaches. Until then, irinotecan dose reductions are likely to be necessary in elderly and frail patients.

In conclusion, our findings suggest that CAPIRI is as effective as FOLFIRI with a similar safety profile when administered as first-line treatment for advanced CRC. Phase III trials of this combination in patients with previously untreated metastatic CRC or Duke's C colon cancer are currently under way.

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