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ORIGINAL ARTICLE

# A phase II study of capecitabine, irinotecan, and bevacizumab in patients with previously untreated metastatic colorectal cancer

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**Abstract**
*Background* Previous phase III studies raised concern about the safety of the combination of capecitabine and irinotecan in patients with metastatic colorectal cancer (mCRC). We conducted a single arm phase II study to evaluate the safety and efficacy of bevacizumab in combination with dose-reduced capecitabine and irinotecan in patients with previously untreated mCRC.
*Patients and methods* Patients with previously untreated mCRC were eligible. Capecitabine was given at 1,000 mg/m2 orally twice daily for 14 days and dose was reduced to 750 mg/m2 for patients over 65. Irinotecan was given at 200 mg/m2 and bevacizumab was given at 7.5 mg/kg intravenously on day 1. The treatment cycle was repeated every 21 days. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival, response rate, and toxicity.
*Results* Fifty patients were enrolled, the median age was 58, and 54% were ECOG 0. The most common grade 3/4 adverse events included hand-foot syndrome (14%), neutropenia (12%), and diarrhea (10%). Response rate was 51% and disease control rate (response and stable disease) was 98%. Median PFS was 11.5 months (95% CI: 9.2–13.7), and 6 month PFS was 90% (95% CI: 77–98%).
*Conclusion* With modest dose reductions, the combination of capecitabine, irinotecan, and bevacizumab was well tolerated and resulted in favorable outcomes for patients with previously untreated mCRC.

**Keywords** Colorectal cancer · Capecitabine · Irinotecan · Bevacizumab · Phase II

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## Introduction

Colorectal cancer is the second leading cause of death related to cancer in North America and Europe [1, 2]. Historically, 5-fluorouracil (5-FU) with leucovorin was the only systemic treatment option for metastatic colorectal cancer (mCRC). More recently, there have been significant advances with the introduction of several new active agents including irinotecan, oxaliplatin, bevacizumab, and cetuximab/panitumumab [3–17]. In addition, the oral pro-drug of 5-FU, capecitabine (Xeloda®, Hoffman-La Roche Ltd.), has been demonstrated to be at least equally efficacious as 5-FU as a single agent and is also associated with less myelosuppression and mucositis [18–20]. Furthermore, capecitabine is more convenient as an extended intravenous infusion is not required and has been suggested to be potentially more cost effective [21].

The combination of capecitabine and irinotecan (XELIRI) has been extensively evaluated. There is no evidence of pharmacokinetic interactions between these two

agents and in initial studies the combination appeared to be well tolerated [22, 23]. Several phase II studies have been conducted to evaluate XELIRI as first-line therapy for mCRC [23–28]. In these studies, response rates ranged from 35 to 49%, similar to response rates seen with infusional 5-FU or bolus 5-FU and irinotecan in phase III trials. The most frequently observed severe toxicities were diarrhea and neutropenia. However, two subsequent randomized phase III trials raised concern about the potential toxicity of the capecitabine and irinotecan combinations with high rates of severe diarrhea and neutropenia, and several treatment-related deaths [29, 30]. It is not clear if the toxicity noted was related to the dose of capecitabine and/or irinotecan in these studies, but it is possible that dose reductions in one or both agents may result in reduced toxicity and still maintain efficacy for this combination.

In 2004, Hurwitz and colleagues demonstrated that the addition of bevacizumab to standard chemotherapy as first-line therapy for mCRC resulted in a significant survival advantage compared with chemotherapy alone [3]. In this study, progressive-free survival and overall survival were significantly improved (6.2–10.6 months, and 15.6–20.3 months, respectively) with the addition of bevacizumab to irinotecan and bolus 5-FU chemotherapy.

To evaluate the safety and efficacy of dose-reduced capecitabine and irinotecan given in combination with bevacizumab, we conducted a phase II study of this regime in patients with previously untreated metastatic or unresectable recurrent colorectal cancer.

## Patients and methods

### Patient selection

Patients were eligible if they had metastatic or unresectable recurrent colorectal cancer and had not received prior chemotherapy for metastatic or recurrent disease. They were required to be ≥18 years of age, eastern cooperative oncology group (ECOG) performance status ≤2; adequate organ function (absolute granulocyte count $\geq 1.5 \times 10^9$/L); platelet count $\geq 100 \times 10^9$/L; normal serum creatinine and bilirubin; aspartate aminotransferase and alanine transaminase ≤2.0 × the upper limit of normal (ULN), unless liver metastases were present (≤5 × ULN). Patients were required to have measurable disease by response evaluation criteria in solid tumors 1.0 [31].

Exclusion criteria included concurrent other malignancies and any serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment. In addition, patients were excluded if they had metastasis of the central nervous system or a history of uncontrolled gastrointestinal bleeding, thromboembolism, hypertension, or proteinuria. The study was approved by the institutional ethics review board, and all patients provided written informed consent.

### Chemotherapy

Capecitabine was administered at a dose of 1,000 mg/m$^2$ orally twice daily for 14 days. Capecitabine dose was reduced to 750 mg/m$^2$ for patients over 65 years of age. Irinotecan was given at a dose of 200 mg/m$^2$ intravenously on day 1. Bevacizumab was given at 7.5 mg/kg IV on day 1. The treatment cycle was repeated every 21 days.

### Dose modifications for capecitabine

For grade 3 hematologic and non-hematologic toxicities, the capecitabine dose was decreased by 25% from baseline on the first occurrence, 50% from baseline on the 2nd occurrence, and capecitabine was permanently discontinued if it occurred a third time. For grade 4 hematologic and non-hematologic toxicities, the dose was decreased by 50% from baseline on the first occurrence and permanently stopped on the second occurrence.

### Dose modifications for irinotecan

For grade 3 hematologic and non-hematologic toxicities, the irinotecan dose was decreased by 25 mg/m2 from baseline on the first occurrence, 50 mg/m2 from baseline on the 2nd occurrence, and irinotecan was permanently discontinued if it occurred a third time. For grade 4 hematologic and non-hematologic toxicities, the dose was decreased by 50 mg/m$^2$ from baseline on the first occurrence and permanently stopped on the second occurrence.

### Dose modifications for bevacizumab

For the following events, bevacizumab was to be discontinued permanently: gastrointestinal perforation, arterial thromboembolic events, grade 3 or 4 hemorrhagic events, symptomatic grade 4 venous thromboembolic events, grade 4 hypertension, and grade 4 proteinuria. For grade 2 or 3 hypertension, bevacizumab was held until it improved to grade 1. For grade 3 and asymptomatic grade 4 venous thrombosis, bevacizumab was held for 2 weeks.

### Treatment of diarrhea

The protocol recommended that patients with severe diarrhea be closely monitored and given electrolyte and fluid replacement as medically indicated. Anti-diarrheal treatments (such as loperamide or lomotil) were recommended

to be promptly initiated as medically indicated. The use of subcutaneous octreotide was recommended for refractory chemotherapy-induced diarrhea when hospitalization was required.

### Study assessments

Baseline radiological investigations were done within 28 days prior to study treatment. Radiological assessments for tumor measurements were conducted after every third cycle (every 9 weeks). Tumor responses were assessed by radiologists independent of study investigators. Study treatment continued until unacceptable toxicity, patient request, or progression.

### Statistical considerations

The primary objective of this study was to determine the progression-free survival (PFS) of irinotecan, capecitabine, and bevacizumab in patients with previously untreated mCRC. Secondary endpoints included overall survival, response rate, time to progression, and toxicity.

In the study by Hurwitz et al. [3], the median PFS was 6.2 months for patients treated with irinotecan and 5-FU, and 10.6 months for patients treated with irinotecan, 5-FU, and bevacizumab. In this study, PFS was estimated with the Kaplan–Meier method and a 95% confidence interval for the median PFS was constructed. The combination of irinotecan, capecitabine, and bevacizumab would be considered to be of interest if the lower bound of the 95% confidence interval for the median PFS was >6.2 months.

Since the Kaplan–Meier method is a non-parametric estimate technique, power calculation is not possible. However, assuming exponential distribution, a null hypothesis of PFS = 6.2 months, and alternative hypothesis of PFS = 10.6 months, a two-sided test (alpha = 0.05) will have a 90% power to detect this difference if 45 patients were enrolled in the study. To be conservative, 50 patients were enrolled to ensure adequate power.

## Results

Fifty patients from Princess Margaret Hospital in Toronto, Canada, were enrolled over 18 months, from December 2006 to June 2008. The median age was 58, and the majority of patients (54%) were ECOG 0 (Table 1). Thirty-three (66%) had a colon primary, 16 (32%) had a rectal primary, and 1 (2%) had a colorectal cancer not otherwise specified. Seven (14%) patients received prior adjuvant chemotherapy. The median number of treatment cycles administered was 12 (range: 1–35), and the median follow-up time was 13 months.

**Table 1** Patient demographics and disease characteristics

| Characteristics | Enrolled patients ($n = 50$) |
|---|---|
| Age, years | |
| Median | 58 |
| Range | 35–72 |
| Gender | |
| Male | 34 |
| Female | 16 |
| ECOG performance status | |
| 0 | 43 |
| 1 | 7 |
| Site of primary | |
| Colon | 33 |
| Rectum | 16 |
| Undefined | 1 |
| Prior therapy number of treatment regimens | |
| 0 | 43 |
| 1[a] | 7 |

[a] Adjuvant chemotherapy

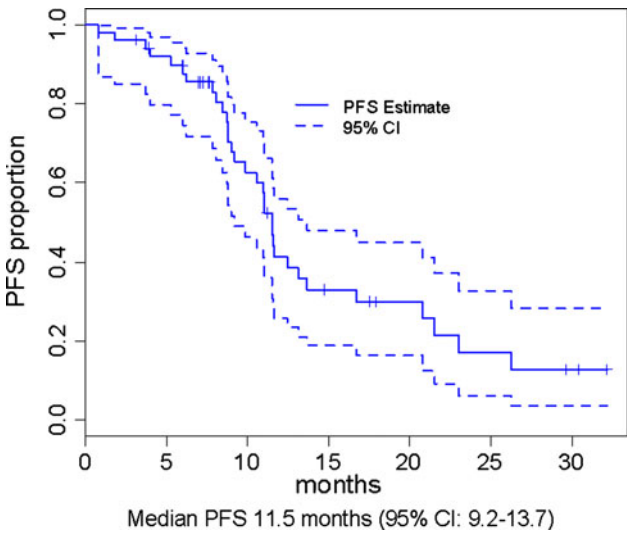


**Fig. 1** Kaplan–Meier curve of progression-free survival (PFS)

### Efficacy

All 50 patients enrolled were evaluable for the primary endpoint of PFS. Median PFS was 11.5 months (95% CI: 9.2–13.7), and 6 month PFS rate was 90% (95% CI: 77–98%) (Fig. 1). At the time of data analysis, median overall survival had not yet been reached (Fig. 2).

Forty-seven patients were evaluable for response. The best response was a partial response in 24 patients (51%). Twenty-two patients (47%) had a best response of stable disease. The disease control rate (response and stable

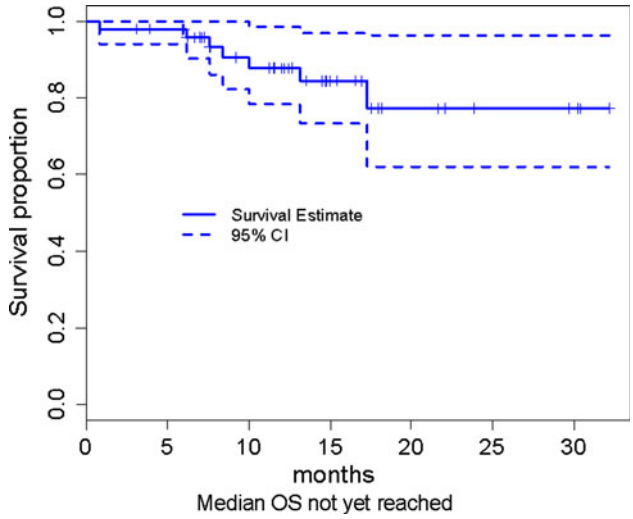


**Fig. 2** Kaplan–Meier curve of overall survival (OS)

disease) was 98%. Eight (16%) patients went on to undergo hepatic metastasectomy.

Safety

Adverse events are listed in Table 2. The most common adverse events (any grade) included fatigue (90%), hand-foot syndrome (80%), and diarrhea (78%). The most common grade 3 or greater adverse events included hand-foot syndrome (14%), neutropenia (12%), and diarrhea (10%). The only grade 4 toxicity was grade 4 neutropenia which occurred in 4 (8%) patients. There was one death from a case of small intestinal obstruction in which the patient declined surgical intervention. Dose modifications were common, with 56% of patients requiring dose reductions of capecitabine, and 36% of patients requiring dose reductions of irinotecan, within the first 6 months (eight cycles) of treatment. The dose of bevacizumab was modified in 36% of patients due to weight changes of greater than 10%.

**Table 2** Possibly related grade 3 or 4 adverse events

| Adverse event (grade 3–4) | *n* (%) |
|---|---|
| *Non-hematologic* | |
| Hand and foot syndrome | 7 (14) |
| Diarrhea | 5 (10) |
| Hypertension | 3 (6) |
| Dehydration | 2 (4) |
| Nausea | 2 (4) |
| Thrombosis | 2 (4) |
| Abdominal distension | 1 (2) |
| Abdominal pain | 1 (2) |
| Alopecia | 1 (2) |
| Anal exam abnormality | 1 (2) |
| Anorexia | 1 (2) |
| Fatigue | 1 (2) |
| Vascular access complication | 1 (2) |
| Small intestinal obstruction[a] | 1 (2) |
| Proteinuria | 1 (2) |
| *Hematologic* | |
| Neutropenia | 6 (12) |
| Hypokalemia | 2 (4) |
| Elevation in bilirubin | 1 (2) |
| Hypophosphatemia | 1 (2) |
| Hyponatremia | 1 (2) |

[a] One grade 5 event

## Discussion

There have been significant improvements in outcomes for mCRC with the incorporation of multiple new active agents. Several studies have demonstrated the benefit of adding bevacizumab to 5-FU-based chemotherapy, but there are limited data on the use of bevacizumab in combination with capecitabine and irinotecan (XELIRI). In our trial, a regimen consisting of dose-modified capecitabine and irinotecan with bevacizumab showed promising activity and was well tolerated.

Although results from initially phase II studies were promising, two subsequent randomized phase III trials raised significant concern about the toxicity of the capecitabine and irinotecan combination. The BICC-C study is a phase III study comparing FOLFIRI, mIFL, and CapeIRI (Capecitabine 1,000 mg/m$^2$ twice daily on days 1–14, irinotecan 250 mg/m$^2$ on day 1). The CapeIRI arm is associated with significant toxicity, including a rate of grade 3/4 diarrhea of 47.5% and grade 3/4 neutropenia of 31.9% [29]. The EORTC 40015 study compared FOLFIRI with CAPIRI (capecitabine and irinotecan given at the same doses and schedule as in the BICC-C study) with or without celecoxib and the study was closed early due to higher than expected patient deaths, especially on the CAPIRI arm [30].

In the current study, a dose-modified XELIRI regimen was used, with the dose of irinotecan reduced from 250 mg/m$^2$ to 200 mg/m$^2$ for all patients and the capecitabine dose reduced from 1,000 mg/m$^2$ to 750 mg/m$^2$ twice daily in patients over the age of 65. Two other studies of XELIRI and bevacizumab have been recently published or presented, and they also utilized lower doses of irinotecan. Garcia-Alfonso and colleagues performed a phase II study the combination of biweekly capecitabine and irinotecan with bevacizumab (irinotecan 175 mg/m$^2$ on day 1, capecitabine 1000 mg/m$^2$ twice daily on days 2–8, bevacizumab 5 mg/kg on day 1) [32]. This regimen was relatively well tolerated with the most frequent

**Table 3** Efficacy data from capecitabine, irinotecan, and bevacizumab combination studies

| | Renouf et al. | Garcia-Alfonso et al. [32] | Ducreux et al. [33] |
|---|---|---|---|
| Number of patients | 50 | 46 | 72[a] |
| Response rate | 51% | 67% | 58% |
| Disease control rate | 98% | 94% | Not reported |
| Median progression-free survival | 11.5 months | 12.3 months | Not reported |
| Six-month progression-free survival | 90% | Not reported | 79% |

[a] 72 Patients enrolled in the XELIRI-bevacizumab arm of this study

grade 3/4 adverse events being diarrhea (7%), asthenia (7%), vomiting (7%), and nausea (9%). In addition, Ducreux and colleagues presented preliminary results from a phase II study comparing FOLFIRI with bevacizumab versus dose-modified XELIRI and bevacizumab (irinotecan 200 mg/m$^2$, capecitabine 1000 mg/m$^2$, bevacizumab 7.5 mg/kg, every 3 weeks), and demonstrated similar toxicity for the two regimens [33]. In the XELIRI-bevacizumab, arm rates of grade 3/4 neutropenia and diarrhea were 17 and 12%, respectively. The results of these two studies are comparable to the rates of grade 3/4 neutropenia and diarrhea noted in our study (12 and 10%, respectively). These toxicity results compare favorably to the grade 3/4 neutropenia and diarrhea noted in a phase IV study of FOLFIRI and bevacizumab (29 and 12%, respectively) [34].

The efficacy results noted in our study were also comparable to those noted by Garcia-Alfonso and colleagues [32], and by Ducreux and colleagues [33] (Table 3). In addition, the median PFS of 11.5 months from our study compares favorably with those from the Hurwitz study (median PFS of 10.6 months) [3], the ECOG 9699 study of FOLFOX or XELOX and bevacizumab (median PFS 9.4 months) [6], and a phase IV study of FOLFIRI and bevacizumab (median PFS 11.1 months) [34].

In summary, with modest dose reduction, the combination of bevacizumab, irinotecan, and capecitabine was well tolerated. Furthermore, treatment efficacy was not compromised since outcomes in the current study compared favorably with those from other first-line trials. This combination may be considered another option for first-line therapy in patients with mCRC.

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