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A Phase II Study of Oxaliplatin, Dose-Intense Capecitabine and High-Dose Bevacizumab in the Treatment of Metastatic Colorectal Cancer

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Abstract

Background—This study was designed to determine the efficacy and tolerability of a novel two-week regimen of capecitabine, oxaliplatin and bevacizumab in patients with chemo-naïve advanced colorectal cancer.

Patients and Methods—Nineteen patients with previously untreated advanced colorectal cancer received capecitabine at 1000 mg/m² BID on days 1–5 and 8–12 of a 14-day cycle and oxaliplatin at 85 mg/m² and bevacizumab at 10 mg/kg every 2 weeks. Due to unacceptable toxicities, the capecitabine dose was reduced to 850 mg/m². Thirty-one additional patients were treated at the lower capecitabine dose. Treatment continued until disease progression, persistent intolerable toxicity or physician and/or patient discretion.

Results—Overall, toxicities were better managed and tolerated at the 850 mg/m² capecitabine dose. The most common treatment-related grade 3 toxicities were diarrhea and sensory neuropathy. In the first nineteen subjects, the response rate was 63% [95% confidence interval (CI), 38–84%] and five patients had stable disease; median progression-free survival was 10.1 months (95% CI 5.7–19.5 months). In the subsequent 31 patients, the response was 42% (95% CI, 25%–61%); 11 patients had stable disease and median progression-free survival was 10.4 months (95% CI, 6.9–15.4); median overall survival was 24.8 months (95% CI 12.9–39.7).

Conclusions—This novel regimen of capecitabine at 850 mg/m² BID on days 1–5 and 8–12 and oxaliplatin at 85 mg/m² and bevacizumab at 10 mg/kg every 14 days is clinically active in

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Conflict of Interest

Dr. Bendell: Dr. Bendell has previously received honoraria from Genentech/Roche and Sanofi-Aventis. She also received research funding from Genentech/Roche and Sanofi-Aventis.

Dr. Morse: Dr. Morse serves as a consultant and receives honoraria from Genentech/Roche and previously received honoraria from Sanofi-Aventis.

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advanced colorectal cancer. The toxicity profile of this regimen is consistent with the standard every three-week dosing schedule.

Keywords

oxaliplatin; capecitabine; bevacizumab; phase II; metastatic colorectal cancer

Introduction

Colorectal cancer is a global health problem, ranking as the fourth most common cancer in men and the third most common cancer in women worldwide.¹

For decades, the anti-metabolite 5 fluorouracil (5FU) in combination with its biochemical modulator leucovorin (LV) had been the only available active treatment for metastatic colorectal cancer.^{2–4}

The clinical development of oxaliplatin (OHP)^{5–11} and irinotecan^{7, 12–16} in the 1990s has led to significant improvements in overall survival from 12–14 months with 5FU/LV alone to 15–20 months with the addition of these modern agents to 5FU/LV.^{11, 14, 16, 17}

The optimal incorporation of OHP with fluoropyrimidines has been extensively investigated. Combining OHP with the oral 5FU prodrug capecitabine (XELOX) is particularly attractive due to clinical evidence of synergy and the mostly non-overlapping toxicities between the two drugs as well as ease of administration and avoidance of protracted drug infusion.^{18–26} Randomized phase III trials have demonstrated non-inferiority of first line XELOX compared to FOLFOX.^{27–29} While capecitabine is usually administered daily for two weeks in a three week schedule in combination with OHP, there has been interest to explore alternative dose schedules.^{24, 30}

The addition of bevacizumab to first-^{31–34} and second-line chemotherapy³⁵ has improved clinical outcomes in multiple trials, including the XELOX and FOLFOX regimens.^{32, 35, 36} In addition, registry-based studies involving more general populations of advanced colorectal cancer patients have demonstrated overall survival in the range of 22.7 to 25.1 months.^{37, 38, 37, 38} The current consensus dose of bevacizumab in first-line setting is 2.5 mg/kg/week (5 mg/kg every two weeks or 7.5 mg/kg every three weeks). However, at the time the current study was initiated, the optimal dose of bevacizumab in colorectal cancer, particularly with an oxaliplatin-based regimen was still debated, as illustrated by the different doses of bevacizumab used in the first-line irinotecan plus 5FU/LV (IFL) (5mg/kg) and second-line FOLFOX studies (10mg/kg).^{35, 36} Reflecting these data, current FDA prescribing information recommends the 5mg/kg dose of bevacizumab with IFL and 10mg/kg with FOLFOX.³⁹ In addition, safety data with bevacizumab combined with capecitabine and oxaliplatin were not yet available and there were suggestions that alternative doses and schedules of capecitabine might improve this agent's side effect profile.^{24, 30}

For these reasons, we conducted a phase II study to evaluate the activity and feasibility of OHP and high dose bevacizumab given every two weeks in combination with capecitabine on days 1–5 and 8–12 every two weeks as front-line therapy for advanced colorectal cancer.

Patients and Methods

Patient Selection

The eligibility criteria included histologically documented colorectal adenocarcinoma with evidence of metastatic disease not amenable to potentially curative treatment, no prior chemotherapy (except for adjuvant 5FU/LV based chemotherapy completed at least 6 months before study registration), age ≥ 18 years, Eastern Cooperative Group (ECOG) Performance Status 0–2, normal organ and marrow function as defined by: absolute neutrophil count (ANC) >2000/μl, platelets >100,000/μl, total bilirubin < 1.5X upper normal limit (UNL), aspartate transaminase (AST)/alanine transaminase (ALT) <2.5 XUNL (<5X UNL if known liver metastasis) and estimated creatinine clearance > 50 mL/min. Exclusion criteria included poorly controlled hypertension defined as >150/100 mmHg, arterial thromboembolic events within 6 months or venous thromboembolic event within 3 months before study registration, uncontrolled coagulopathy, major surgery within 4 weeks of the start of study treatment, current therapeutic anticoagulation (except for low dose prophylactic anticoagulation), current use of anti-platelet agents (except for aspirin <81 mg/day), proteinuria ≥ 500 mg/24-hours, lepto-meningeal or brain metastases, active cardiac disease, life expectancy <3 months, inability to tolerate oral medications and pregnancy or lactation. Women of childbearing potential were required to have a negative pregnancy test within 7 days prior to study entry; females and male subjects and/or female partners of male subjects were required to use medically adequate contraception throughout the study period. Written informed consent was required prior to study entry.

The study was approved by the Duke University Institutional Review Board and conducted at Duke University Medical Center and Duke Oncology Network in accordance with the Declaration of Helsinki and good clinical practice guidelines. Patient accrual was from September 2003 to June 2005; study follow-up continued through 2008.

Treatment schedule

Treatment was administered in 14 day cycles. The original protocol doses were oral capecitabine 1000 mg/m² every 12 hours on days 1–5 and 8–12; oxaliplatin 85 mg/m² intravenously over 2 hours on day 1; and bevacizumab 10 mg/kg intravenously over 30–90 minutes on day 1. After nineteen patients were enrolled, the starting dose of capecitabine was lowered to 850 mg/m² every 12 hours due to excessive toxicities; oxaliplatin and bevacizumab dosage and schedules remained unchanged. Treatment continued until disease progression, persistent unacceptable toxicity or discontinued at physician and/or patient discretion.

Patients were closely monitored for adverse events during protocol treatment and through the 30 day follow-up visit after the last dose of study drug. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 3.0 (NCI

CTCAE), Version 3.0.⁴⁰ Neurosensory toxicity was graded according to the Neurologic Toxicity Scale for Oxaliplatin. Treatment on day 1 of each cycle was delayed until recovery of ANC to $>1,500/\text{mm}^3$ and platelet count $> 75,000/\text{mm}^3$ and recovery from any clinically significant treatment-related non-hematologic toxicity (except alopecia) to baseline or grade 1, or bilirubin and AST/ALT to baseline or grade 1.

Dose reduction due to adverse events was performed for each drug as specified in the study protocol, which provided detailed algorithms to manage drug-specific toxicities such as oxaliplatin-related neuropathy, capecitabine-related diarrhea and hand-foot syndrome, bevacizumab-related hypertension, bleeding and thromboembolism as well as other treatment related toxicities.

Patient Evaluation

All patients completed an extensive medical history, baseline physical examination and clinical assessment prior to receiving study drug; toxicity and safety assessments were performed every two weeks prior to treatment and as clinically indicated. These assessments included vital signs, ECOG performance status, medical history, physical examination including neurosensory assessment, complete blood count (CBC), biochemistry including creatinine, AST, ALT, bilirubin, magnesium, urine protein to creatinine ratio. An electrocardiogram was performed at baseline and every 4 cycles. Tumor response was assessed via computed tomography scan or magnetic resonance imaging every 4 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.0).⁴¹ General symptom management and supportive care such as anti-diarrheal and anti-emetics agents were provided as clinically indicated to ensure optimal patient care.

Study Design and Statistical Methods

This was an open-label, multicenter, non-randomized phase II trial to assess the safety, tolerability and efficacy of capecitabine, oxaliplatin and bevacizumab in previously untreated patients with recurrent or metastatic colorectal cancer. The primary endpoint was overall response (complete and partial response) as defined by RECIST criteria (version 1.0), based on an intent-to-treat analysis. Secondary endpoints included time to progression, progression free survival, overall survival, safety and tolerability. Progression free survival was defined as the interval between start of treatment and the date of disease progression or death, censoring for loss to follow-up or start of new line of treatment (for patients who discontinued study treatment for reasons other than disease progression). A modified Simon 2-stage design was used. The null hypothesis was a response rate 30% versus an alternative favorable response 50%, with a one-sided significance level of 0.10 and power of 0.82. Twelve patients were to be enrolled in stage 1 and the treatment deemed inactive if 2 or fewer patients showed response. If 3 or more patients responded, 16 more patients were to be enrolled in the second stage.

Based on the toxicities seen in the first nineteen patients, the protocol was amended to reduce the starting dose of capecitabine and increase the sample size for the revised dosing combination. An additional thirty-one patients were recruited to evaluate the same primary endpoint with a revised one-sided alpha of 0.11 and a power of 0.86.

The exact method was used to calculate 90 and 95% confidence interval of proportions. Survival duration was calculated using the Kaplan Meier method.

Patients who discontinued study treatment prematurely prior to the first response assessment were classified as having progressive disease.

Results

Patient characteristics

A total of 50 evaluable patients were enrolled in two different cohorts based on capecitabine dosing; nineteen patients were enrolled in cohort 1 at capecitabine 1000 mg/m² BID, and thirty-one patients were enrolled in cohort 2 at capecitabine 850 mg/m² BID. Table 1 lists the baseline patient demographics. The median age among both cohorts was 55 (range 24–81), and a majority had good baseline performance status. The patients in cohort 1 were predominantly male while cohort 2 was predominantly female. No patient in either cohort received prior oxaliplatin in the adjuvant setting. The majority of patients had colonic primary tumors with 1–2 sites of metastatic disease and presented with elevated carcinoembryonic antigen at baseline. All patients were evaluable for toxicity and tumor response.

Adverse Events

Treatment-related toxicities are listed in Table 2.

For both cohorts, the most common grade 3 toxicities were diarrhea and sensory neuropathy although the number of grade 3 diarrhea events in cohort 2 was significantly lower compared to cohort 1 (37% vs. 16%). Grade 3 hematological toxicity was very uncommon (3–5%), and none of the patients developed neutropenic fever. Other grade 3 toxicities were vomiting, fatigue, hypertension, and bowel perforation. Common grade 1 to 2 toxicities included anemia, anorexia, diarrhea, nausea, vomiting, fatigue, hand-foot syndrome, and sensory neuropathy. In cohort 2, the frequency of grade 1–2 hand-foot syndrome was significantly lower compared to cohort 1, 26% vs. 74%, respectively. Serious possible treatment-related events included congestive heart failure, angina, seizure and hypotension with syncope all affecting one patient each.

Dose delays and interruptions

Almost all patients in cohort 1 required at least one capecitabine dose reduction and/or dose delay primarily due to hand-foot syndrome and/or diarrhea; four patients required oxaliplatin dose delay and/or reduction, and one patient had oxaliplatin discontinued due to grade 3 peripheral neuropathy. One patient was withdrawn from study due to treatment-related grade 3 diarrhea and weight loss and another for persistent intolerable grade 2 hand-foot syndrome.

In cohort 2, capecitabine dosage was reduced in fourteen of thirty-one patients and held for nine patients. One patient required oxaliplatin dose reduction and seven patients required oxaliplatin dose delay. One patient was withdrawn due to treatment-related grade 3 diarrhea and weight loss, and two additional patients were removed from study due to severe adverse

events unrelated to study treatment (bowel perforation due to a sigmoid diverticulum and acute cholecystitis).

Bevacizumab-related dose delays were due to expected toxicities such as hypertension (n=2) and delayed wound healing (n=2) and prophylactic delays for planned minor surgical procedures (n=2) and were usually of short duration.

Efficacy

Table 3 summarizes the best radiographic response. In cohort 1, the response rate was 63% (95% confidence interval (CI), 38–84%; 90% CI 42–81%). One patient had a complete response (5%), 11 patients had a partial response (58%) and 5 patients had stable disease (26%) as their best response. In cohort 2, the response was 42% (95% CI, 25%–61%; 90% CI 27–58%); no complete response was observed, 13 patients had a partial response (42%) and 11 patients had stable disease (35%). In the combined cohort of 50 patients, 1 had complete response (2%), 24 had a partial response (48%), 16 had stable disease (32%) and 9 had progressive disease (18%), yielding an overall response of 50% (95% CI, 36%–64%; 90% CI 38–62%).

The secondary study endpoint was progression-free survival (PFS) in cohort 2, which was the revised dose and schedule deemed tolerable. The median PFS for this cohort was 10.4 months (95% CI, 6.9–15.4) (Figure 1). When both cohorts were combined, the median progression-free survival among the 50 patients remained essentially unchanged (10.3 months, 95% CI, 7.5–12.7 months) (Figure 2). Calculated time to progression and PFS produced identical results in this study since disease progression and censoring for progression occurred before any death events. The median PFS among the nineteen patients in cohort 1 was 10.1 months (95% CI 5.7–19.5 months); the median overall survival for cohort 1 was 19.6 months (95% CI, 13.3–30.2 months). The median overall survival for cohort 2 was 24.8 months (95% CI 12.9–39.7) (Figure 3). When both cohorts were combined, the median overall survival was 23.3 months (95% CI, 14.3–31.8) (Figure 4). The median duration for partial response in the combined cohort was 10.8 months (range 5.6–17.7).

Discussion

This study explored a novel regimen of capecitabine, oxaliplatin and bevacizumab. The 5 day on/2 day off schedule was intended to potentially improve capecitabine-related toxicities by scheduling more frequent treatment breaks, while maintaining a dose intensity similar the standard 14 day on/7 day off schedule. The starting dose of capecitabine found to be well tolerated in patients accrued in the United States has been reported to be lower than the doses tolerated in Europe, a topic which has been extensively reviewed.^{28, 31, 32, 42–45} The doses of capecitabine found tolerable in the current study of capecitabine, oxaliplatin and bevacizumab are similar to the capecitabine doses that were tolerable in the TREE 1 and TREE 2 studies.³¹ At a dose of 1000 mg/m², capecitabine was not well tolerated; however, at the reduced dose of 850 mg/m² capecitabine was generally well tolerated.

In this phase II study, we were unable to administer oxaliplatin, dose-intense capecitabine and bevacizumab as specified in the initial protocol due to a high frequency of all grade diarrhea, hand foot syndrome, nausea and vomiting. In the initial cohort of 19 patients, grade 3 to 4 diarrhea occurred in approximately one-third of patients, and most patients required dose reductions and/or dose delay of capecitabine. Bevacizumab at 10mg/kg every two weeks was well tolerated with only six treatment-related delays.

At the reduced capecitabine dose, toxicities were overall more manageable and better tolerated, however, nearly half of the patients still required dose reductions and about one third of patients required dose delays primarily due to hand-foot syndrome and diarrhea. The objective response in this second cohort was 42% (95% CI, 25%–61%) and the median PFS was 10.4 months (95% CI, 6.9–15.4). When efficacy endpoints were calculated with both cohorts combined, the results were not substantially different.

Since the inception of this study, a number of other trials have been published examining the efficacy of capecitabine or 5FU in combination with oxaliplatin and bevacizumab as first-line therapy for metastatic colorectal cancer. Our results are comparable to the results found in these larger randomized phase II–III studies. In NO16966, 1401 patients with metastatic colorectal cancer were randomized in a 2×2 factorial design to first-line XELOX versus FOLFOX4 and then to bevacizumab versus placebo.³² Among the 699 patients in the bevacizumab group, objective response was 47%, median progression-free survival was 9.4 months and median overall survival was 21.3 months. In patients accrued primarily in the United States, the TREE 1 and 2 studies, the incidence of grade 3 or 4 toxicities among the 72 patients in the XELOX arm in TREE 2 was 56%.³¹ The overall response for XELOX in combination with bevacizumab was 46%, the median time to progression 10.3 months and the overall survival 24.6 months.³¹

The results of our study contrasts with those of a randomized phase II trial by Scheithauer et al, who found that patients with advanced colorectal cancer who received first-line dose-intensive capecitabine administered on days 1–7 and 14–21 every 4 weeks in conjunction with oxaliplatin had higher response rate and progression-free survival compared to those who received conventional XELOX, without any increase in toxicities.²⁴ However, a subsequent large randomized comparison of every 2 week with every 3 week XELOX plus bevacizumab in US patients found that the two regimens were similar in efficacy and tolerability although non-significant trends in efficacy and tolerability favored the more standard every 3-week regimen.⁴⁴ The results of the novel XELOX plus bevacizumab regimen used in this study are consistent with these larger studies using more standard regimens.

In conclusion, this novel regimen of capecitabine at 850 mg/m², on days 1–5 and 8–12 of a 14-day cycle and oxaliplatin at 85 mg/m² and bevacizumab at 10 mg/kg every 2 weeks is active and tolerable in the first-line treatment of metastatic colorectal cancer. As with other XELOX plus bevacizumab regimens, toxicity management is critical for patient safety, especially when tumor control can be maintained for nearly a year. While the results of this novel regimen are promising, the standard every 3-week XELOX plus bevacizumab regimen described by Saltz et al remains the consensus dosing for these agents.³²

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Figure 1.
Progression free survival, cohort 2 (months)

Figure 2.
Progression free survival, combined cohort (months)

Figure 3.
Overall survival, cohort 2 (months)

Figure 4.
Overall survival, combined cohort (months)

Table 1

Baseline Patient Characteristics

Characteristics	Initial Cohort (n=19) No. (%)		Second Cohort (n=31) No. (%)	
Sex				
Male	14	(74)	13	(42)
Female	5	(26)	18	(58)
Ethnicity				
Caucasian	16	(84)	22	(71)
African American	2	(11)	5	(16)
Others	1	(5)	4	(13)
Age				
Median	55		55	
Range	24–76		27–81	
ECOG performance status				
0–1	18	(95)	30	(97)
2	1	(5)	1	(3)
Primary site				
Colon	15	(79)	22	(71)
Rectum	1	(5)	3	(10)
Missing	3	(16)	6	(19)
Prior adjuvant				
Yes	3	(16)	6	(19)
No	12	(63)	6	(19)
Missing	4	(21)	19	(61)
No. of metastatic sites				
1	8	(42)	6	(19)
2	4	(21)	7	(23)
3	4	(21)	11	(35)
Missing	3	(16)	7	(23)
Baseline CEA				
2.5 ng/ml	3	(16)	1	(3)
> 2.5 ng/ml	14	(74)	27	(87)
Missing	2	(11)	3	(10)

Table 2

Selected Treatment Related Toxicities

Treatment Related Toxicities	Initial Cohort (n=19) No. (%)		Second Cohort (n=31) No. (%)	
Non-hematologic				
Anorexia				
Grade 1–2	15	(79)	16	(52)
Grade 3–4	0	(0)	1	(0)
Bowel perforation				
Grade 1–2	1	(5)	0	(0)
Grade 3–4	0	(0)	1	(3)
Diarrhea				
Grade 1–2	9	(47)	15	(48)
Grade 3–4	7	(37)	5	(16)
Nausea				
Grade 1–2	13	(68)	15	(48)
Grade 3–4	1	(5)	1	(3)
Vomiting				
Grade 1–2	7	(37)	11	(35)
Grade 3–4	1	(5)	2	(6)
Fatigue				
Grade 1–2	15	(79)	22	(71)
Grade 3–4	1	(5)	1	(3)
Hand foot syndrome				
Grade 1–2	14	(74)	8	(26)
Grade 3–4	1	(5)	3	(10)
Hypersensitivity				
Grade 1–2	0	(0)	0	(0)
Grade 3–4	1	(5)	0	(0)
Hypertension				
Grade 1–2	2	(11)	2	(6)
Grade 3–4	0	(0)	2	(6)
Infection				
Grade 1–2	7	(37)	6	(19)
Grade 3–4	1	(5)	0	(0)
Proteinuria				
Grade 1–2	5	(26)	6	(19)

Treatment Related Toxicities	Initial Cohort (n=19) No. (%)		Second Cohort (n=31) No. (%)	
Grade 3–4	0	(0)	0	(0)
Sensory neuropathy				
Grade 1–2	14	(74)	16	(52)
Grade 3–4	2	(11)	5	(16)
Hematological				
Anemia				
Grade 1–2	15	(79)	20	(65)
Grade 3–4	0	(0)	0	(0)
Missing	4	(21)	3	(10)
Neutropenia				
Grade 1–2	3	(16)	1	(3)
Grade 3–4	1	(5)	1	(3)
Thrombocytopenia				
Grade 1–2	2	(11)	3	(10)
Grade 3–4	0	(0)	0	(0)

Table 3

Best Radiographic Response.

Cohort Level	No of Patients	Complete Response	Partial Response	Stable Disease	Progressive Disease
1*	19	1	11	5	2
2*	31	0	13	11	7

* Cohort 1: Capecitabine at 1000 mg/m²; Cohort 2: Capecitabine at 850 mg/m²