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A Phase II Study of Celecoxib with Irinotecan, 5-Fluorouracil, and Leucovorin in Patients with Previously Untreated Advanced or Metastatic Colorectal Cancer

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Abstract

Objective—Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Cyclooxygenase-2 (COX-2) overexpression is associated with increased tumor invasiveness and proliferation in CRC, and COX-2 inhibition has demonstrated chemopreventive activity. This study investigated the addition of celecoxib, a selective COX-2 inhibitor, to the irinotecan 5-FU leucovorin (IFL) regimen for patients with previously untreated metastatic CRC.

Methods—47 patients enrolled in this single-arm phase 2 study received celecoxib at 400 mg orally twice daily in combination with weekly irinotecan (125 mg/m²), 5-fluorouracil (500 mg/m²), and leucovorin (20 mg/m²) for four weeks every six weeks. The primary endpoint was response rate as measured by RECIST. The protocol was amended midway to additionally exclude patients with ECOG performance status 2 and require all patients with specific cardiovascular risk factors to take daily aspirin (81mg).

Results—The objective response rate was 31.9% (95% CI: 19%–47%). Median progression-free survival was 8.7 months (95% CI: 5.8–10.6), and the median overall survival was 19.7 months

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(95% CI: 15.4–22.8). All cardiac events were observed prior to protocol modification. The median overall survival before and after protocol modification was 11.4 months versus 24.2 months, respectively ($P<0.0001$); tumor response rate and progression-free survival were not statistically different before or after protocol modification. The trial was halted after an interim analysis demonstrated that the primary endpoint would not be met.

Conclusion—Celecoxib plus IFL chemotherapy for patients with metastatic colorectal cancer is tolerable, but does not appear to increase the efficacy of IFL.

Keywords

colorectal cancer; celecoxib; cyclooxygenase-2 (COX-2) inhibitor; 5-fluorouracil (5-FU); irinotecan

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States, with approximately 135,430 cases and 50,260 deaths projected in 2017¹. Among patients with metastatic disease, the advancement in systemic treatment options has improved their expected median survival from 11–12 months with fluoropyrimidines alone in the 1990s to approximately 2.5 years with modern combination therapies^{2,3}. Progress in the treatment of metastatic colorectal cancer (mCRC) over the past two decades has been steady. However, even negative randomized clinical trials (RCTs) have been informative and have opened new avenues for investigation using different approaches with biologically active agents.

Prior to the widespread adoption of FOLFOX and FOLFIRI regimens in the United States, the IFL regimen, which incorporated bolus 5-fluorouracil (5-FU) infusion along with leucovorin (LV) and irinotecan, was a standard regimen with expected overall survival (OS) of 14.8 months vs. 12.6 months ($p=.04$), progression-free survival (PFS) of 7.0 vs. 4.3 months ($p=.004$), and response rate (RR) of 39 vs. 21% ($p<0.001$), when compared to irinotecan alone⁴. As subsequent RCTs optimized the combination chemotherapy backbone, incorporation of newer biologic agents targeting specific pathways (such as anti-angiogenic and anti-epidermal growth factor receptor targets) moved forward quickly to demonstrate improved efficacy⁵.

The cyclooxygenase-2 (COX-2) enzyme is overexpressed in the majority of colorectal cancers and promotes tumor growth, invasiveness, and metastasis⁶. Several non-steroidal anti-inflammatory drugs (NSAIDs), that inhibit COX-2 function to varying degrees, have demonstrated chemopreventive activity in CRC and adenoma development^{7–9}. To begin exploring COX-2 inhibition in combination with chemotherapy as a therapeutic strategy, a phase I trial of celecoxib, at doses up to 200 mg orally twice daily, in combination with 5-FU and leucovorin for patients with metastatic CRC did not increase toxicities expected from chemotherapy¹⁰. Moreover, 5-FU/LV did not affect COX-2 inhibition by celecoxib¹⁰.

Based upon the strong pre-clinical findings that COX-2 inhibition demonstrated antitumor activity^{11–14}, the clinical activity observed in chemoprevention trials^{7,8}, and the demonstrated safety in combining celecoxib with chemotherapy in mCRC¹⁰, we designed a

single-arm proof-of-concept phase II study evaluating the addition of celecoxib to IFL, the standard first-line chemotherapy in the U.S. at the time of the study implementation, for patients with previously untreated mCRC.

Patients and Methods

Study Design and Entry Criteria

From September 2000 to May 2003, patients with previously untreated unresectable or metastatic colorectal cancer confirmed by biopsy were enrolled into this multi-center trial. The protocol was approved by each local institutional review board and was conducted in accordance with the Declaration of Helsinki. Patients were ineligible if they were candidates for further definitive resection or radiation. Prior adjuvant therapy with 5-FU (with or without leucovorin or levamisole) for previously resected disease was permitted, provided that the recurrence occurred more than 12 months from the end of adjuvant therapy, and patients had not experienced grade 3 or 4 toxicity from adjuvant chemotherapy.

Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (ECOG performance status 2 was excluded after protocol amendment), age 18 years or older, life expectancy of at least 12 weeks, ability to give informed consent, and measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0). Patients were required to have adequate hematologic, renal, and hepatic function (white blood cell count $\geq 3000/\text{mm}^3$, granulocytes $\geq 1500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, hemoglobin ≥ 8.0 gm, bilirubin ≤ 2.0 mg/dL, SGOT ≤ 3 times upper limit of normal, albumin ≥ 3.0 g/dL, and creatinine clearance ≥ 50 ml/min). At least 4 weeks must have elapsed from any major surgery.

Patients were excluded from study entry if they required daily full-dose NSAIDs, including aspirin > 81 mg daily, for any reason. Patients taking cardiac-preventive doses of aspirin, defined as ≤ 81 mg daily, were eligible. All previous full-dose NSAIDs were discontinued 14 days prior to first dose of celecoxib. Additional exclusion criteria were the following: significant cardiovascular or cerebrovascular disease, venous thromboembolism, interstitial lung disease, symptomatic pleural effusion or ascites, bleeding disorder, bowel obstruction, chronic malabsorption, extensive bowel resections, active peptic ulcer disease, brain metastases or leptomeningeal disease, active second malignancy, pregnancy or lactation, uncontrolled infections, other significant medical or psychiatric disorders, known allergy or contraindication to NSAIDs or sulfonamides, chronic steroid use, or concomitant investigational medications.

Due to emerging cardiotoxicity concerns found in other trials using celecoxib during the time of study conduct^{15,16}, an independent data safety and monitoring committee (DSMC) paused the study after 22 patients were accrued in order to perform an unplanned interim analysis for toxicity evaluation. After no additional toxicity events were found, the study continued with the protocol amended to exclude patients with ECOG performance status 2 and to require low-dose aspirin (≤ 81 mg) for patients with specific cardiovascular risk factors defined as age ≥ 65 years, hypertension with systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95 , hypercholesterolemia with total blood cholesterol ≥ 240 mg/dL, smoking

history, strong family history with a primary relative with myocardial infarction under age 55, or personal history of myocardial infarction, unstable angina, stroke, transient ischemic attack, peripheral vascular disease.

Therapy

Celecoxib was administered at 400 mg orally twice daily starting two weeks before chemotherapy (days 1 to 14). After the protocol amendment, patients with significant cardiovascular risk factors, were given aspirin 81mg orally once daily starting with the first dose of celecoxib. IFL regimen was administered intravenously once weekly for four weeks on days 15, 22, 29, and 36 of each treatment cycle after initial two weeks of celecoxib run-in. Celecoxib was given continuously throughout all six weeks. IFL consisted of irinotecan at a dose of 125 mg/m², 5-fluorouracil at a dose of 500 mg/m², and leucovorin at a dose of 20 mg/m². Treatment was continued until documentation of disease progression or until toxicities prohibited ongoing treatment, with a maximum of 24 months allowed on study drug.

Assessments

Tumor response by RECIST criteria was assessed every six weeks for the first three cycles then every three months, or every other cycle, for subsequent cycles. Confirmation of complete or partial response was performed by repeat assessment at least four weeks after response criteria was first met, and confirmation of stable disease required repeat assessment at least seven weeks after initial response criteria was met. Toxicity was assessed according to the NCI Common Toxicity Criteria (version 2.0).

Statistical Analysis

The primary endpoint was best objective response rate (complete or partial response). Secondary endpoints included PFS, OS, and grade 3 or higher adverse events. PFS was defined as the time from the study entry to a documented disease progression or death, which ever occurred first. Patients who were alive and without progression at the end of the study period were censored on the date of the last known progression-free assessment. Kaplan-Meier method was used to estimate PFS and OS, and 95% exact binomial confidence interval was used to estimate median PFS and OS. Statistical analyses were performed separately using patients enrolled before and after the protocol modification in order to explore differences in outcomes due to protocol modification. Fisher's exact test was used for categorical variables, and Wilcoxon rank sum test for continuous variables, and log rank test for survival outcomes. All analyses were performed using SAS version 9.0, and two-sided p values were reported.

The initial sample size estimate was based on a two-sided, one-sample binomial test with a 5% significance level, and power of 80%, to detect a 20% improvement in response rate in comparison with historical controls (response rate of 33% expected from IFL^{4,17}). Forty eight evaluable subjects were required, and after allowing for a 10% dropout, a target sample size was set to 54 subjects. After protocol modification requiring ASA 81mg for high-risk subjects, the sample size was increased to a total of 78 subjects in order to allow the equivalent statistical power for meeting the primary endpoint. However, because of slow

accrual, an unplanned interim analysis was performed which resulted in the study closure after it was found that the addition of celecoxib to IFL would not reach the target response rate even with the increased sample size.

Results

Patient Characteristics

A total of 49 patients met eligibility criteria, but two patients withdrew consent prior to receiving therapy. Of the 47 patients included in the analysis, 22 patients were enrolled on the original protocol, and 25 patients enrolled after the protocol amendment. Table 1 summarizes the baseline characteristics of all 47 patients. The mean age was 59.7 years, with a range of 21.4 to 80.1 years. Thirty four (72.3%) patients were male, 29 (61.7%) were Caucasian, and 45 (95.7%) patients had ECOG score of 0 or 1. Patient characteristics appeared similar between those on the original protocol and those from after the protocol amendment except more patients were Caucasian in the original group (77.1% vs. 48%, $p=.04$), and there was a non-significant trend toward better ECOG status in the post-protocol population. The median duration of chemotherapy treatment was 3 cycles (range 1–9 cycles) for all patients, 2.5 cycles (range 1–9) before the amendment versus 4.0 cycles (range 1–6) after the amendment ($p=.08$).

Efficacy

Data on best tumor response are summarized in Table 2. Overall response rate was 31.9%. One patient (2.1%) had a complete response as best overall response, while 14 patients (29.8%) had partial responses, 21 (44.7%) patients had stable disease, and three (6.4%) had progressive disease. No statistically significant difference was found in the response rates in patients accrued before or after the protocol amendment. Eight patients (17.0%) were not evaluable, but were included in the denominator for calculating response rate.

Median PFS for all 47 patients was 8.7 months (95% CI: 5.8–10.6), as detailed by Table 3 and Figures 1a/1b. PFS did not significantly differ between those enrolled before and after protocol modification (median 9.0 vs. 8.7 month, respectively; $P=0.34$). Six-month PFS was 68% (73% prior to modification and 67% after modification).

Median OS was 19.7 months, with median survival before protocol modification of 11.4 months, compared with 24.2 months after protocol modification ($P<0.0001$), which is detailed by Table 3 and Figures 2a/2b. One-year overall survival was 71%, with 46.7% prior to protocol modification, and 90.9% after protocol modification. Two patients in the pre-amendment portion of the study died during treatment: one from progressive disease, and one from toxicity.

Toxicity

Toxicity data was recorded for all 47 patients who received at least one dose of therapy. Table 4 lists the most common grade 3 or greater adverse events before and after protocol modification. Thirty nine patients (83%) experienced at least one grade 3 or higher adverse event, most commonly neutropenia (31.9%), followed by diarrhea (21.3%), nausea/vomiting

(12.8%), and infection (8.5%). The incidence of most adverse events was similar before and after protocol modification except grade 3 or greater cardiovascular and thromboembolic events. As summarized in Table 5, a total of ten grade 3 or greater cardiac events occurred in six patients prior to the protocol amendment, including grade 5 cardiac arrest (1 patient), atrial fibrillation (2 patients), myocardial infarction (1 patient), congestive heart failure (1 patient), cerebrovascular accident (2 patients), hypotension (1 patient), hypertension (1 patient), and premature ventricular contractions (1 patient). The one patient with heart failure also had hypotension and a myocardial infarction, and the one patient who had grade 3 hypertension also had a cerebrovascular accident and premature ventricular contractions. All six patients had at least one cardiovascular risk factor at baseline but would not have been excluded under the amended protocol and were not mandated to take aspirin 81mg until protocol modification. One of the six patients continued study treatment until disease progression. All significant cardiac adverse events occurred prior to protocol modification and none after ($p=0.02$). Two occurrences of deep venous thrombosis (DVT) occurred after protocol modification. The most common reason for study discontinuation was progressive disease, both before protocol amendment in 11 (50%) patients, and after in 13 (52%) patients. Toxicity as the predominant reason for study discontinuation was evident in 4 (18%) patients prior to protocol amendment, and in 3 patients (12%) afterwards.

Discussion

The addition of celecoxib to the IFL regimen (standard first-line chemotherapy in the US at the time of the study implementation) for patients with previously untreated metastatic colorectal cancer did not increase the tumor response rate beyond that expected for IFL alone^{4,17}. This finding was based on an unplanned interim analysis where the primary endpoint of increased response rate was unlikely to be achieved even if the target sample size were reached, which led to early termination of this trial. It should be noted that standard practice has adopted continuous 5-FU infusion regimens, such as FOLFOX or FOLFIRI, rather than the IFL regimen as the standard first-line chemotherapy backbone due to higher efficacy and less toxicity^{17,18}. In this study, PFS and OS seemed to be longer, 8.7 months and 19.7 months, respectively, when compared to historical data at the time the study was carried out. However, this may reflect available subsequent lines of therapy as well as improved supportive care. Nevertheless, we cannot exclude the possibility of added survival benefit with celecoxib, as it is possible that it may slow progression rather than provide tumor response. In fact, both regorafenib and trifluridine/tipiracil, which are FDA-approved for refractory metastatic colorectal cancer, have response rates of less than 2%, yet there is a survival benefit^{19,20}. Thus, additional research exploring drug targets in the COX-2 pathway remains warranted.

Since the completion of this study, there have been other trials testing celecoxib in mCRC. A single-arm phase II study in France, OPTIMOX2 found that while celecoxib at 400mg twice daily was safe to use with FOLFOX7, it did not increase the response rate nor PFS when compared to historical results with FOLFOX²¹. Likewise, a randomized phase II study in Italy, GOIM 9901, which started patients on first-line FOLFIRI with either celecoxib or placebo, demonstrated that celecoxib was safe to use without any added gastrointestinal or cardiovascular toxicity from celecoxib with FOLFIRI, but it did not improve response rates

nor time to progression ²². The EORTC 40015 study, which employed a two-by-two design comparing FOLFIRI to CAPIRI and celecoxib to placebo through a 1:1:1:1 randomization found increased toxicities, as eight treatment-related deaths from gastrointestinal and thromboembolic events resulted in early trial closure. However, the high incidence of grade 3 or higher events were thought to be related to capecitabine in combination with irinotecan rather than from celecoxib. Moreover, there may have been a trend towards lower response rates in the celecoxib arms, though early termination of the study limits definitive conclusions ²³. Nevertheless, due to these results in mCRC trials ^{21–23} and other studies demonstrating increased cardiovascular risks with COX-2 inhibitors ^{15,16}, ongoing trials at that time testing celecoxib in mCRC, such as the BICC-C study, closed the treatment arms containing celecoxib ²⁴.

Multiple studies have examined the cardiovascular risks with celecoxib and concluded that there is a dose-related increase in cardiovascular events and deaths ^{15,16,25}. This study similarly observed a number of cardiovascular events until the protocol was modified to exclude patients with modest functional status and to mandate use of low-dose ASA for those with risk factors for cardiovascular disease. The improvement in median survival from 11.4 months before protocol modification to 24.2 months after protocol modification likely reflects the advent of new treatment options after 2002, such as oxaliplatin and bevacizumab, rather than related to the protocol amendment. This suggestion is further supported by the lack of significant difference in PFS pre- and post-amendment. Cardiovascular risk is well recognized and regularly monitored when using other FDA-approved drugs for colorectal cancer, such as regorafenib and bevacizumab, and while it represents an unacceptable toxicity in chemoprevention trials, its use in incurable cancer is certainly still reasonable. Interestingly, aspirin has been observed to decrease CRC-specific mortality in patients with colorectal cancer, particularly if COX-2 expression were observed in the tumors ^{9,26}. Thus, non-selective NSAIDs rather than COX-2 inhibitors, particularly aspirin, could serve as a safer alternative.

Study conclusions made from this trial were limited by the rapidly changing landscape in metastatic colorectal cancer in the early 2000s, including the adoption of 5-FU continuous infusion over bolus, establishment of FOLFOX and FOLFIRI as the preferred chemotherapy backbone, FDA approval of bevacizumab and cetuximab, and recognition of cardiovascular risk from COX-2 inhibitors, which all contributed to slow accrual on this study. The single-arm design with a major protocol modification also made comparison to historical data difficult, and it also could have introduced an unintended selection bias enrolling healthier patients with fewer cardiovascular risk factors to participate in the trial post-protocol modification. Moreover, there was inadequate statistical power to examine the cardiovascular and gastrointestinal toxicity before and after protocol modification. Additionally, current relevant prognostic factors such as mutational status of RAS and BRAF, microsatellite instability, and site of primary tumor (right vs. left), were not known and thus not collected at the time of this study. Hence, it remains possible that such imbalances pre- and post-study modification could have influenced our findings.

In conclusion, the addition of celecoxib to IFL did not improve response rates compared to what is expected from IFL alone. It may be that despite preclinical antitumor effects and

chemopreventive activity for premalignant lesions, celecoxib has less impact upon larger disease burden and only more of a disease control (or cytostatic) effect. Celecoxib may also be more clinically relevant in a microscopic tumor disease state. Interestingly, there is an ongoing Alliance/SWOG 80702 study testing the benefit of celecoxib to adjuvant FOLFOX in stage III colon cancer, a disease state that at most has only microscopic disease rather than overt metastatic disease and these results are eagerly awaited (<https://clinicaltrials.gov/show/NCT01150045>). However, because our trial was unable to meet its primary endpoint in addition to safety concerns, it remains to be seen what the ultimate role, and in what clinical context, the modulation of the COX-2 pathway will play in the treatment of colorectal cancer.

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Figure 1.

Figure 1a. Progression-free survival for all 47 patients.

Figure 1b. Progression-free survival for patients in the original protocol vs. revised protocol.

Figure 2.

Figure 2a. Overall Survival for all 47 patients.

Figure 2b. Overall Survival for patients in the original protocol vs. revised protocol.

Table 1

Patient Baseline Characteristics

	Overall N=47	Pre-Modification N=22	Post-Modification N=25	P-value
Mean age (range)	59.7 (21.4–80.1)	61.1	58.5	NS
Sex:				
Male	34 (72.3%)	17 (77.3%)	17 (68%)	NS
Female	13	5	8	
ECOG				
0	31 (66%)	13 (59.1%)	18 (72%)	NS
1	14 (29.8%)	7 (31.8%)	7 (28%)	
2	2 (4.3%)	2 (9.1%)	0	
TNM Stage at Diagnosis:				
Locally-advanced	10 (21.2%)			
Metastatic	28 (62.2%)	13 (61.9%)	15 (62.5%)	NS
Unknown	9 (19.1%)			
Race:				
Caucasian	29 (61.7%)	17 (77.3%)	12 (48%)	0.04
Black	4 (8.5%)	2 (9.1%)	2 (8.0%)	
Hispanic	7 (14.9%)	1 (4.6%)	6 (24%)	
Asian	5 (10.6%)	1 (4.6%)	4 (16%)	
Other	2 (4.3%)	1 (4.6%)	1 (4%)	

*
NS=not significant

Table 2

Objective Response Rates

Best Tumor Response	Overall N=47	Pre-Modification N=22	Post-Modification N=25
Complete Response	1 (2.1%)	0 (0%)	1 (4%)
Partial Response	14 (29.8%)	6 (27.3%)	8 (32%)
Complete and Partial	15 (31.9%)	6 (27.3)	9 (36%)
Stable Disease	21 (44.7%)	8 (36.4%)	13 (52%)
Progressive Disease	3 (6.4%)	3 (13.6%)	0 (0%)
Not Evaluable	8 (17%)	5 (22.7%)	3 (12%)

Table 3

Progression-Free Survival and Overall Survival

	Overall (N=47)	Pre-Modification (N=22)	Post-Modification (N=25)	P-value
Median Progression-Free Survival	8.7 months	9 months	8.7 months	0.34
Median Overall Survival	19.7 months	11.4 months	24.2 months	<0.0001
1-Year Overall Survival	71%	46.7%	90.9%	<0.0001

Table 4

Most Common Grade 3/4 Adverse Events

	Pre-Modification	Post-Modification	P-value
Neutropenia	8 (36.4%)	7 (28.0%)	0.76
Diarrhea	4 (18.2%)	6 (24.0%)	0.73
Nausea/Vomiting	4 (18.2%)	2 (8.0%)	0.40
Infection	1 (4.5%)	3 (12%)	0.61

Table 5**Most Common Cardiovascular (CV) Toxicity by Grade**

	Pre-modification	Post-modification
Grade 3/4/5 CV Events	10	2
Atrial fibrillation *	2	0
Cardiac arrest ***	1	0
Cerebrovascular accident **	2	0
Congestive heart failure *	1	0
Deep venous thrombosis *	0	2
Hypertension *	1	0
Hypotension *	1	0
Myocardial infarction **	1	0
Premature ventricular contractions *	1	0
Grade 1/2 CV Events	10	13
Flushing	1	2
Hypertension	0	2
Hypotension	1	1
Palpitations	1	0
Phlebitis	1	0
Peripheral Edema	4	8
Pulmonary Edema	1	0
Sinus Tachycardia	1	0

* Grade 3 CV toxicity

** Grade 4 CV toxicity

*** Grade 5 CV toxicity