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Combined Therapy with Weekly Irinotecan, Infusional 5-Fluorouracil and the Selective COX-2 Inhibitor Rofecoxib Is a Safe and Effective Second-Line Treatment in Metastatic Colorectal Cancer

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Abstract

The purpose of this study was to determine the tolerability and activity of rofecoxib (Vioxx®; Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com) combined with weekly irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com) and infusional 5-fluorouracil (5-FU) as second-line therapy in metastatic colorectal cancer (MCRC). Enrolled patients had previously treated metastatic disease, were aged ≥18 to ≤75 years, and had adequate performance status. A cycle of treatment consisted of i.v. irinotecan on days 1, 8, 15, and 22, rofecoxib at an oral dose of 50 mg/day, and infusional 5-FU at a fixed dose of 200 mg/m^2 per day for 5 weeks followed by 3 weeks of therapy with rofecoxib alone. In the dose-finding study, the starting dose of irinotecan was 87.5 mg/m^2 and further dose escalations were planned by increments of 12.5 mg/m^2 up to 125 mg/m^2. Forty-eight consecutive patients were enrolled in the study. Among the 15 cases enrolled in the dose-finding study, one patient experienced grade 3 reversible diarrhea as the dose-limiting toxicity, at the fourth dose level tested. Therefore, the dose of irinotecan for the phase II study was 125 mg/m^2, and 33 patients were enrolled and received a total of 75 cycles. Hematological side effects were moderate, with grade 4 neutropenia recorded in only two patients. The most common nonhematological toxicity was diarrhea, occurring in 25 patients (75.8%) and considered to be of grade 3 in 12 patients (36.4%). Sixteen patients achieved partial responses (48.5%; 95% confidence interval [CI], 30.8%–66.5%), and another 10 patients (30.3%) had stable disease. The median time to progression was 7 months (95% CI, 5–12) and the median overall survival (OS) was 18 months; the 1-year estimated OS rate was 69.4%. The unique schedule tested in this study is feasible, is well-tolerated, and has promising activity in patients with MCRC after progression on oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us)-based chemotherapy.
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Introduction

In the past 5 years, the efficacy of front-line chemotherapy for the treatment of patients with metastatic colorectal cancer (MCRC) has been improved by the use of combined treatments of irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com) or oxaliplatin

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(Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us) with fluoropyrimidines [1]. However, the 5-year survival rate remains poor at <10% [2, 3]. The clinical benefit of second-line therapy in patients with progressive disease remains unsatisfactory [4, 5]. Prospective, randomized phase III trials of second-line therapy suggested a superior response rate and palliation of tumor-related symptoms in patients treated with irinotecan compared with those receiving infusional 5-fluorouracil (5-FU) or best supportive care [6–8]. Two other studies, evaluating the efficacy of oxaliplatin combined with 5-FU and leucovorin in patients who failed first-line therapy, reported response rates of 9%–46% [9, 10]. The sequence of treatments including both oxaliplatin and irinotecan improved the median survival of patients by as many as 18–22 months [11]. Progress on the knowledge of colon cancer biology has favored the development of novel therapeutic anticancer strategies based on the identification of specific molecular targets [12]. Epidemiologic studies demonstrated a significantly lower incidence of invasive CRC in individuals taking acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs, related to the inhibition of cyclo-oxygenase (COX), a key enzyme in tumor cell transformation [13, 14]. Two isoforms of COXs are known: the constitutive COX-1 and the inducible COX-2, the latter being preferentially expressed in inflammatory and neoplastic tissues [14]. COX-2 expression is an early step in carcinogenesis, and it sustains tumor invasion by several mechanisms, including xenobiotic metabolism, (i.e., activation of benzo[a]pyrene), production of carcinogens (i.e., malondialdeyde), induction of angiogenesis, inhibition of apoptosis, impairment of immunoresponse, and enhancement of cell invasiveness by modulation of matrix metalloproteinases (MMPs) and adhesion molecules [15]. COX-2, absent in normal colonic epithelium, is overexpressed in 40% of colon adenomas [16] and up to 60%–90% of invasive cancers [17]. In patients with resected CRC, COX-2 overexpression correlates with tumor stage and poor prognosis [17]. Selective inhibitors of COX-2 (coxibs) induced a reduction in overall polyp burden in patients with familial adenomatous polyposis (FAP) [18], and randomized clinical trials showed that this activity was dose-dependent [19]. In experimental models, coxibs suppress tumor growth by blocking angiogenesis [20–22] and by inducing apoptosis [15]; moreover, COX-2 inhibition reduces liver metastasis formation [23]. A major challenge is to determine the optimal modality to integrate coxibs into conventional schedules of chemotherapy [24].

The present study represents the first reported phase I–II study of the combination of rofecoxib (Vioxx®; Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com) with conventional chemotherapy in MCRC. The aim of the study was to determine the feasibility, tolerability, and antitumor activity of such a regimen as second-line therapy.

Patients and Methods

Eligibility Criteria

Patients with histologically proven MCRC progressive after the oxaliplatin-based first-line chemotherapy regimen FOLFOX4 (5-FU, leucovorin, oxaliplatin) were eligible for the study. Major inclusion criteria included: age ≥18 and ≤75 years, Karnofsky performance status (KPS) score ≥50, at least one site of measurable metastatic lesion, adequate hematological reserve (ANC $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l; hemoglobin >10 g/dl), and normal hepatic and renal functions (serum bilirubin and creatinine levels ≤1.5 × the upper limit of normal). A negative pregnancy test was required before treatment in premenopausal women.

Exclusion Criteria

Patients were excluded if they had a previous history of tumors (other than basal cell carcinoma of the skin or adequately treated in situ carcinoma of cervix uteri); previous first-line chemotherapy with irinotecan; previous radiotherapy within 4 weeks; a history of active angina, myocardial infarction, or significant arrhythmias; acute infections; known allergy or intolerance to 5-FU or coxibs; therapy with acetylsalicylic acid, active gastroduodenal ulcer disease; brain or leptomeningeal metastases as the only site of measurable disease; and life expectancy ≤12 weeks. Pregnant or lactating women were ineligible. All patients gave written informed consent. The protocol was approved by the local ethical committees and the study followed the recommendations of the Helsinki Declaration.

Treatment Plan

A treatment cycle was 8 weeks long and consisted of 4 weeks of chemotherapy given in combination with rofecoxib in an outpatient setting followed by 4 weeks of therapy with rofecoxib only. Chemotherapy consisted of 5-FU by continuous i.v. infusion at a fixed dose of 200 mg/m^2 per day on weeks 1–4 in combination with irinotecan at an initial dose of 87.5 mg/m^2 by i.v. infusion over 60 minutes on days 1, 8, 15, and 22. Rofecoxib was given orally at a fixed dose of 50 mg/day. Each cycle was repeated every 8 weeks. If the leukocyte count was $\geq 2.0 \times 10^9$/l and/or the ANC was $\geq 1.0 \times 10^9$/l and platelet count was $\geq 75 \times 10^9$/l, full doses of chemotherapy were administered. If the leukocyte count was $< 2.0 \times 10^9$/l or ANC was $< 1.0 \times 10^9$/l or platelet count was $< 75 \times 10^9$/l, treatment with irinotecan and 5-FU was delayed by 1 week until recovery. If a patient required hospitalization for neutropenia and fever, both irinotecan and

5-FU were reduced by 25% for subsequent cycles. In cases of grade 3 or 4 nonhematological toxicities (excluding alopecia, nausea, and vomiting), treatment was delayed until the toxicity was resolved, and the doses of irinotecan and 5-FU were then reduced by 50%. No dose modification for rofecoxib was planned.

Concomitant Medications

Antiemetic agents were allowed at the discretion of the treating physician. Premedication with atropine was given for irinotecan-related cholinergic symptoms. Growth factors were allowed only in cases of grade 4 or febrile neutropenia. Oral antibiotic therapy was administered if the ANC was $<0.5 \times 10^9$/l without fever. For febrile neutropenia, hospital admission was recommended with the administration of an i.v. empiric antibiotic therapy (cephalosporin and aminoglucoside). Loperamide (Imodium®; McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, PA, http://www.mcmeilcampusrecruiting.com) was administered for diarrhea.

Patient Evaluation

The pretreatment evaluation was performed within 4 weeks before therapy and included a complete history and physical examination, CBC and serum chemistries, electrocardiogram, and tumor assessment with total body computed tomography (CT), bone scan, and skeletal bone x-rays, if necessary. During treatment, a CBC, physical examination, and toxicity evaluation were performed every week; hepatic and renal function tests were performed every 2 weeks. Patients were first evaluated for toxicity and response at week 8, repeating the staging procedures, and then every cycle. Patients with stable disease or an objective response continued treatment until toxicity or progression, for a maximum of six courses (48 weeks).

Evaluation of Toxicity and Response

Toxicities were graded according to the National Cancer Institute (NCI) common toxicity criteria (version 2.0, published on April 30, 1999). The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were adopted to assess objective response [25], and responses were confirmed by two independent investigators.

Statistical Methods and Study Design

The response rate was defined as the frequency of patients with a complete or partial response among all evaluable patients. The intention-to-treat (ITT) population included all the enrolled patients. All confidence intervals (CIs) cited are two-sided 95% exact intervals, calculated using the binomial formula. Response duration was measured from the day of its initial documentation until disease progression. Time to progression (TTP) was calculated from the study entry until the last follow-up or evidence of disease progression; overall survival (OS) was measured from the day of entry until the last follow-up or death. TTP and OS were analyzed by the Kaplan-Meier product-limit method.

In the dose-finding study, escalating doses of irinotecan were planned by increments of 12.5 mg/m^2, and the following levels were evaluated: 87.5 mg/m^2, 100 mg/m^2, 112.5 mg/m^2, and 125 mg/m^2. No dose escalation was allowed in the same patient. A minimum of three patients was enrolled at each dose level. If one of the first three patients at a given dose level experienced a dose-limiting toxicity (DLT), three additional patients were to be enrolled. If an additional patient experienced a DLT, no further dose escalation was allowed, and that dose level was considered to be the maximum-tolerated dose (MTD). The dose level before the MTD was then recommended for the phase II study. DLT was defined as the occurrence of one or more of the following toxicities during the first cycle of treatment: grade 4 neutropenia lasting ≥4 days; febrile neutropenia, defined as an ANC $<1 \times 10^9$/l with fever (≥38°C) or any systemic infection requiring hospitalization and parenteral antibiotic treatment; grade 3 thrombocytopenia; and any grade 3 or 4 nonhematological toxicity, excluding grade 3 alopecia, nausea, and vomiting.

The phase II part of the trial was designed as an open-label, uncontrolled study. With the available sample of 33 patients, the asymptotic half-width of the confidence interval (precision) for the estimated response probability is, at most, 17%.

Calculation of Dose Intensity

The time on treatment was calculated as the sum of the intervals between the start of treatment cycles, assuming an 8-week duration for the last cycle. The actual dose intensity (DI) of each drug was calculated by dividing the total dose (mg/m^2) administered by the time on treatment (weeks). The relative DI of each drug was calculated as the ratio between the actual DI and the planned DI per cycle.

Results

Patient Characteristics

From October 2001 to February 2004, 48 patients were enrolled in the two centers involved in the study. Fifteen patients were treated with escalating doses of irinotecan (from 87.5 mg/m^2 to 125 mg/m^2) in combination with fixed 5-FU and rofecoxib, and 33 patients were treated with the dose of irinotecan established in the

phase II study. The main characteristics of the patients are reported in Table 1. In the phase II study, 22 patients (66.7%) had two or more metastatic sites, and 24 patients (84.8%) had liver disease.

Dose-Escalation Study

Four dose levels were tested, as summarized in Table 2. At the first three dose levels, no patient experienced a DLT. At the fourth dose level of irinotecan (125 mg/m^2), one patient of the first three enrolled experienced reversible grade 3 diarrhea lasting 3 days as a DLT. The patient was a 64-year-old man with a KPS score of 50 and peritoneal metastases, previously treated with the FOLFOX4 regimen. Three further patients were enrolled at this dose level without grade 3 or 4 toxicities. Consequently, the MTD level was not reached in the planned dose levels, and the recommended dose of weekly irinotecan in the combined schedule was 125 mg/m^2, allowing a weekly dose density of 62.5 mg/m^2 during the cycle. Overall, seven patients achieved partial responses with a median duration of response of 5 months (range, 3–10).

Table 1. Characteristics of the patients

	Phase I	Phase II
Total number	15	33
Median age (years)	63	64
Range	35–73	44–74
Performance status score		
0	11 (73.3%)	20 (60.6%)
1	3 (20%)	13 (39.4%)
2	1 (6.7%)	0
Responders to first-line chemotherapy	4 (26.7%)	13 (39.4%)
Number of metastatic sites		
One	7 (46.7%)	11 (33.3%)
Two or more	8 (53.3%)	22 (66.7%)
Metastatic sites		
Liver	13 (86.6%)	28 (84.8%)
Lymph nodes	5 (33.3%)	9 (27.3%)
Lung	3 (20%)	12 (36.4%)
Bone	1 (6.6%)	1 (3.0%)
Peritoneum	1 (6.6%)	8 (24.2%)

Phase II Study

Safety

A total of 75 cycles of therapy was administered to 33 patients, with a median of 2.3 cycles per patient (range, 1–6). Fifty-seven cycles (76.0%) were given at full doses of chemotherapy. In 12 cycles (16%), thirty-two administrations of irinotecan and 5-FU were reduced by 25%. Because of toxicity at the date of the planned recycle, a delay of a week on day 7, 15, and/or 22 occurred in 16 cycles (21.3%). The planned DI of irinotecan was 62.5 mg/m^2 per week, and the mean delivered dose was 59.6 mg/m^2 per week. The planned DI of 5-FU was 125 mg/m^2 per week, and the mean delivered dose was 119.6 mg/m^2 per week. The relative DIs were 0.95 for both the drugs. G-CSF support was needed in only five cycles (6.7%). Rofecoxib was administered as scheduled in all but one patient, who interrupted the drug after 12 weeks of treatment due to epigastric pain that resolved after drug discontinuation. A median of 16 weeks of treatment with rofecoxib was administered (range, 8–52 weeks). Hematological and nonhematological toxicities are summarized in Table 3 and Table 4, respectively. Hematological toxicity was mild, as grade 4 neutropenia without fever was observed in only two patients. No episode of neutropenic fever occurred. Grade 2 anemia occurred in four patients. Diarrhea was the most common nonhematological toxicity, occurring in 25 patients (75.8%), and it was the main cause of dose reductions and/or treatment delay. In 12 patients (36.4%), it was of grade 3. Alopecia occurred in 36.4%, vomiting occurred in 30.3%, and asthenia occurred in 12.1% of patients; no case of hand-foot syndrome was observed. Worsening of a peripheral neuropathy resulting from previous oxaliplatin-based therapy was observed in two patients. No cardiac, thromboembolic, gastrointestinal, and/or renal toxicity correlated to rofecoxib was observed.

Antitumor activity

Objective responses and survival data are summarized in Table 5. No complete response was achieved. Sixteen patients achieved partial responses (48.5%, 95% CI, 30.8%–66.5%) and 10 patients (30.3%) had disease stabilization, with an overall disease control (objective response plus stable disease) rate of 78.8%. A response rate of 45%

Table 2. Dose escalation results

Level	Irinotecan dose (mg/m^2)	No. of patients	Dose-limiting toxicity	Toxicity	Objective response
I	87.5	3	0	–	2
II	100	3	0	–	1
III	112.5	3	0	–	1
IV	125	6	1	Grade 3 diarrhea	3

Table 3. Hematologic toxicity according to National Cancer Institute grade

	Assessable patients, *n* (%) (*n* = 33)			Assessable cycles, *n* (%) (*n* = 75)		
Toxicity	1–2	3	4	1–2	3	4
Leukopenia	7 (21.2%)	2 (6.1%)	1 (3%)	10 (13.3%)	2 (2.7%)	1 (1.3%)
Granulocytopenia	7 (21.2%)	2 (6.1%)	2 (6.1%)	9 (12%)	6 (8%)	2 (2.7%)
Thrombocytopenia	0	0	0	0	0	0
Anemia	11 (33.3%)	0	0	15 (20%)	0	0

Table 4. Nonhematological toxicity according to National Cancer Institute grade

	Assessable patients, *n* (%) (*n* = 33)			Assessable cycles, *n* (%) (*n* = 75)		
Toxicity	1–2	3	4	1–2	3	4
Phlebitis	1 (3.0%)	0	0	1 (1.3%)	0	0
Vomiting	10 (30.3%)	0	0	13 (17.3%)	0	0
Diarrhea	13 (39.4%)	12 (36.4%)	0	21 (28%)	12 (16%)	0
Mucositis	2 (6.1%)	0	0	4 (5.3%)	0	0
Fever	1 (3.0%)	0	0	1 (1.3%)	0	0
Liver	1 (3.0%)	0	0	1 (1.3%)	0	0
Neuropathy	1 (3.0%)	1 (3.0%)	0	1 (1.3%)	1 (1.3%)	0
Gastric pain	1 (3.0%)	0	0	1 (1.3%)	0	0
Cystitis	2 (6.1%)	0	0	2 (0.7%)	0	0
Asthenia	4 (12.1%)	0	0	7 (9.3%)	0	0
Alopecia	12 (36.4%)	0	0	20 (26.7)	0	0

Table 5. Treatment results

Clinical end points	No. of patients	Months	95% confidence interval
Partial response	16 (48.5%)		30.8%–66.5%
Stable disease	10 (30.3%)		
Progressive disease	7 (21.2%)		
Time to progression		7	5–12
Median overall survival		18	17–undefined

was observed among the 20 patients not responsive to the first-line oxaliplatin-based chemotherapy. After a median follow-up of 10 months (range, 4–19), 10 patients died of disease progression and 23 patients were alive, 10 of whom were still in response. The median TTP was 7 months (95% CI, 5–12). The median OS was 18 months (95% CI, 17–undefined); the 12-month estimated probability of OS was 69.4%. Kaplan-Meier estimated progression-free survival and OS curves are shown in Figure 1.

Discussion

The present study was conducted to explore the feasibility, tolerability, and activity of a novel combined therapeutic regimen containing a coxib as second-line therapy for MCRC. The schedule of chemotherapy was designed to minimize the side effects of the cytotoxic drugs [26–29]. We planned on performing a dose escalation of irinotecan because of the

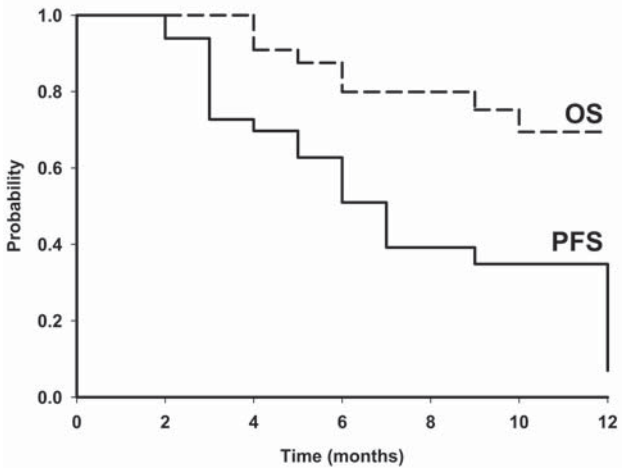

Figure 1. Kaplan-Meier–estimated progression-free survival (PFS) and overall survival (OS) curves.

innovative schedule of administration. Rofecoxib was chosen for its favorable selectivity for the target enzyme, and its dosage was selected based on the preclinical evidence of dose-dependent antitumor activity [19]. The main rationale for testing coxibs in combination with cytotoxic drugs is based on several findings. First, COX-2 is involved in CRC progression, its overexpression is associated with mutations of the *APC* gene [30], and it correlates with recurrence, poor survival, and a higher probability of liver metastases in invasive CRC [17, 31]. Second, coxibs block angiogenesis by the downregulation of several growth factors (vascular endothelial growth factor, nitric oxide synthase (NO_s), interleukin-6, and others) [19–21, 32–34] and suppress tumor cell invasiveness associated with COX-2–induced MMP-11, MMP-2, and MMP-9 [35] as well as with $\alpha_v\beta_3$ integrin-dependent activation of small GTPases involved in cellular adhesion [36]. Coxibs also inhibit endothelial cell spreading and migration in vitro and fibroblast growth factor-2–induced angiogenesis in vivo [37]. Indeed, coxibs induce apoptosis through decreased expression of cyclines A–B_1 and overexpression of $p21^{waf1}$ and $p27^{kip1}$ [37–40]. Finally, Pai et al. found a link between prostaglandin-E_2–induced activation of MMP-2 and MMP-9 and activation of epidermal growth factor receptor (EGFR), suggesting crosstalk between COX-2 and EGFR [41].

Our choice to use rofecoxib was mainly based on the pharmacodynamic study by Baigent and Patrono [42], who demonstrated a 10-times-greater specificity of rofecoxib compared with celecoxib to the target COX-2, particularly when the two compounds were tested at high doses, similar to those to be used in cancer patients [24].

In our study, as far as toxicity is concerned, we did not observe negative interactions among the drugs. Hematological toxicity was moderate, with only four cycles associated with grade 4 and three cycles associated with grade 3 hematological toxicities. Grade 3 diarrhea occurred in 12 patients and in 12 cycles of therapy and resolved in a few days with hydration and loperamide. Its frequency was lower than that reported in other irinotecan-based schedules, suggesting a possible protective role of rofecoxib in the control of this side effect, in agreement with the results of experimental data [43]. No cardiac or thrombotic toxicity was observed in our study, probably related to the fact that no patient received the drug for more than 1 year. The recent withdrawal of rofecoxib and valdecoxib (Bextra®; Pfizer Pharmaceuticals) by the U.S. Food and Drug Administration was related to the potential cardiac side effects of long-term therapy with such drugs.

Our novel schedule of therapy was associated with a promising overall response rate and with a disease control of 78.8%. The efficacy of this novel schedule as second-line therapy of MCRC compares favorably with the results of the more active chemotherapy combinations reported in the literature [6–10], also taking into account the characteristics of the series evaluated, with more than 80% of cases with liver metastases and 66.7% of the patients with two or more metastatic sites. Indeed, the regimen does not present cross-resistance with front-line oxaliplatin-based chemotherapy. In fact, the response rate was similar in the two subgroups of patients responsive or not to previous therapy. Also, both the TTP of 7 months and the OS of 18 months compare favorably with the literature data [44].

A recently published phase II study of irinotecan and infusional 5-FU, given with a different schedule without coxibs, found a similar response rate in a larger cohort of patients, but this was a first-line chemotherapy study and higher incidences of grade of 3–4 hematological and nonhematological toxicities were reported [45].

Blanke et al. reported, at the 36th Meeting of the American Society of Clinical Oncology, the preliminary results of a phase II study of the combination of celecoxib, another COX-2 inhibitor, and weekly schedules of irinotecan (125 mg/m^2), 5-FU (500 mg/m^2), and leucovorin (20 mg/m^2) [46]. However, three patients experienced a stroke ($n = 2$) or myocardial infarction ($n = 1$), suggesting a possible cardiovascular toxicity correlated with the schedule. A good response rate was reported in the 18 assessable patients: 28% partial response rate and 56% stable disease rate. The results of our phase II study coupled with those reported by Blanke et al. [46] suggest that the strategy of combining irinotecan-based chemotherapy with coxibs warrants further evaluation, because it is associated with promising antitumor activity.

Appropriate prospective phase III studies are needed for a proper evaluation of the antitumor activity of combined treatments with coxibs. Also, pharmacokinetic and pharmacodynamic studies with the use of surrogate biomarkers, aimed to identify the subsets of patients with higher likelihoods of response, are warranted to better rationalize the clinical use of such regimens.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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Combined Therapy with Weekly Irinotecan, Infusional 5-Fluorouracil and the Selective COX-2 Inhibitor Rofecoxib Is a Safe and Effective Second-Line Treatment in Metastatic Colorectal Cancer

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