Biweekly bolus 5-fluorouracil and leucovorin plus oxaliplatin in pretreated patients with advanced colorectal cancer: a dose-finding study

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The primary objective of this study was to determine the maximum tolerable dose (MTD) and dose-limiting toxicity (DLT) for bolus 5-fluorouracil (5-FU) administered on a biweekly schedule and in combination with fixed doses of leucovorin (LV) and oxaliplatin. The secondary objectives were to evaluate the toxicity profile and antitumor activity of this regimen for pre-treated patients with advanced colorectal cancer. A total of 26 patients with documented fluoropyrimidine-resistant, advanced colorectal cancer were enrolled into this phase I study. Fixed dose of oxaliplatin (85 mg/m^2) was delivered as an i.v. infusion over 2 h, followed by LV (20 mg/m^2) and 5-FU bolus every 2 weeks. The starting dose of 5-FU was 600 mg/m^2, which was then incremented by 100 mg/m^2 for each dose level. The DLT was determined for the first two treatment cycles, while toxicity and efficacy were evaluated throughout treatment. Six dose levels were tested. The MTD of 5-FU was deemed to be 1000 mg/m^2 since dose-limiting fatigue was noted for three of the five-patient cohort during the first two cycles of chemotherapy at dose level 6. The most frequent treatment-related toxicities during the study were neutropenia, vomiting, diarrhea, fatigue and neuropathy. In an intent-to-treat analysis, the objective response rate was 30.8% (95% confidence interval 11.8–49.8%) for the 26 patients. The combination of bolus 5-FU/LV and oxaliplatin every 2 weeks is a feasible and effective treatment at the recommended dosages. A phase II study, to more-precisely define activity and toxicity, is ongoing. *Anti-Cancer Drugs* 14:145–151 © 2003 Lippincott Williams & Wilkins.

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Introduction

Over the past 40 years, 5-fluorouracil (5-FU) has remained the most useful drug for the treatment of patients with advanced colorectal cancer [1]. Although i.v. administration of 5-FU is the most widely accepted mode of drug administration, the optimal schedule is still not established [2–5]. In a recent meta-analysis, a small, but statistically significant, survival advantage was demonstrated for continuous infusion 5-FU in comparison to the bolus protocol, with reduced gastrointestinal and hematological toxicity [6]. Nevertheless, bolus 5-FU represents a more economical and convenient treatment option, without the complications associated with indwelling central catheter and infusion pumps.

Oxaliplatin is a new third-generation platinum compound in the 1,2-diaminocyclohexane family, with notable activity for first- and second-line treatment for advanced colorectal cancer in combination with 5-FU [7–14]. The safety and efficacy of a variety of dosing regimens consisting of 5-FU, leucovorin (LV) and oxaliplatin have been evaluated, and marked antitumor efficacy was demonstrated for these combinations. Oxaliplatin's favorable safety profile has permitted the treatment of thousands of patients, with limited gastrointestinal and hematological toxicities noted, and no life-threatening toxicity or morbidity other than sporadic, acute pharyngolaryngeal dysesthesia or cumulative, self-limiting and mostly reversible neurosensory toxicity [7–14]. The optimal combination of oxaliplatin and 5-FU/LV is still under investigation, however, and despite over 40 years of clinical research, the best dosage and treatment schedule for the 5-FU and LV combination remains controversial. It is unlikely that oxaliplatin will be help to clarify the controversy regarding 5-FU/LV delivery. It should be noted, however, that most, if not all, available data on oxaliplatin and 5-FU have been obtained with high-dose 5-FU/LV infusion schedules. Furthermore, it has been suggested that the combination of oxaliplatin and high-dose continuous-infusion 5-FU/LV may be superior to bolus variants [15]. The combination of bolus 5-FU/LV and oxaliplatin has not been carefully investigated, however.

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In vitro assessment of the interaction between oxaliplatin and 5-FU/LV in colon cancer cell lines has demonstrated the greatest therapeutic synergy when oxaliplatin is followed by brief 5-FU exposure [16]. The combination of bolus 5-FU/LV and oxaliplatin may be superior to continuous infusion of 5-FU/LV. Further, bolus 5-FU has the advantage of patient convenience and it is also less labor intensive for medical staff. However, the combination of bolus 5-FU/LV with new agents such as irinotecan and oxaliplatin appears problematic, particularly given the safety concerns highlighted by the early termination of the two combined Mayo arms of the North Central Cancer Treatment Group N 9741 phase III trial for advanced colorectal cancer [17]. Nevertheless, Hochster *et al.* have recently reported a 64% response rate for 27 patients treated with oxaliplatin and a weekly bolus of 5-FU/LV as first-line chemotherapy for advanced colorectal cancer, with a favorable toxicity profile demonstrated [18]. Taking into consideration the synergistic effect of oxaliplatin and 5-FU, and the convenience associated with the combined delivery of the three drugs, we designed a phase I study using a biweekly schedule of concomitant oxaliplatin and bolus 5-FU/LV for patients with 5-FU-pretreated colorectal cancer. The objectives of this study were to define the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) for biweekly bolus 5-FU when administered with fixed-dose of LV and oxaliplatin, and to describe any preliminary evidence of antitumor activity and toxicity for patients with pretreated colorectal cancer.

Patients and methods

Eligibility criteria

Enrolled patients were required to have unresectable local advanced or metastatic colorectal cancer. The eligibility criteria for patients included histologically confirmed colorectal adenocarcinoma, age $\geq$18 and $\leq$75 years, bidimensionally measurable (at least $1.5 \times 1.5\,cm^2$) disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Additional criteria included adequate bone marrow (neutrophils $\geq$1500/mm^3; platelets $\geq$100 000/mm^3), liver and renal functions (GOT and GPT $\leq 5 \times$ upper normal limit, serum bilirubin $\leq$2.0 mg/dl and serum creatinine $\leq$2.0 mg/dl). Progression during or within 6 months of 5-FU/LV chemotherapy for advanced disease or during 5-FU-based adjuvant therapy must have been documented. Patients with active infection, concurrent major systemic disease or history of any other malignancy (except appropriately treated, localized cervical or epithelial skin cancer) were excluded. Patients who had been treated using the 5-FU/irinotecan regimens as first- or second-line chemotherapy were also eligible. Prior radiotherapy was allowed, provided the indicator lesion was outside the radiation port and at least 3 weeks had elapsed since completion of radiotherapy. Approval was obtained from our ethics review committee before initiation of the study and informed consent was obtained from all patients.

Study design

Oxaliplatin (85 mg/m^2) was delivered as an i.v. infusion over 2 h, with 5-FU and LV (20 mg/m^2) delivered as an i.v. bolus within 3 min of completion. The first 5-FU dose tested was 600 mg/m^2. Successive cohorts of patients were treated at progressively higher dose levels, in 100 mg/m^2 increments. All patients were observed for at least 4 weeks before being enrolled at the next dose level. Ondansetron 8 mg and dexamethasone 10 mg were administered before the oxaliplatin as antiemetic drugs, and no prophylactic granulocyte colony stimulating factors were used. Treatment courses were repeated every 2 weeks unless there was prior evidence of progressive disease, unacceptable toxicity or until a patient chose to discontinue treatment. Patients who did not respond to this salvage therapy were allowed to undergo further chemotherapy at the physician's discretion.

At least three patients were initially treated at each dose level. If none of them experienced any DLTs during the first two treatment cycles, the next cohort of three patients was treated at the next dose level. If any evidence of DLT was observed in the first three patients, three additional patients were recruited at the same dose level to fully establish safety before dosage was incremented. Dosage escalation was stopped if more than one-third of the patients in a given cohort experienced DLT; otherwise, 5-FU dosage was increased. The MTD was defined as the dose level immediately below which DLT was noted for more than one-third of patients during the first two cycles of treatment. A DLT was defined as any grade 3–4 non-hematological toxicity (except alopecia, nausea and vomiting), grade 4 vomiting, grade 4 hematologic toxicity or grade 3 hematological toxicity with complications (e.g. neutropenic fever or bleeding), or a recycling delay of over 2 weeks during the first two cycles.

Dosage modification

No intrapatient dosage escalation was allowed. Thus, patients were treated using the same dosage until a major response was achieved or progressive disease was documented. In the case of grade 1–2 non-hematological toxicity, or neutrophils $<$1500/mm^3 or platelets $<$75 000/mm^3 on the day of scheduled treatment, therapy was delayed until the toxicity subsided to baseline, and neutrophils and platelets recovered above the defined thresholds. In the next treatment cycle, adjustment of the dosage level was based on the highest grade of toxicity observed during the previous cycle. In the presence of grade 4 hematological toxicity, febrile neutropenia, grade 3–4 diarrhea, mucositis or fatigue,

chemotherapy was administered after recovery from the side effects and the 5-FU dose was decremented by one dose level (100 mg/m^2) in the subsequent cycles. An additional 5-FU dose reduction of one dose level was prescribed if the same toxicity recurred. The 5-FU dosage was also decremented by one level where patients required more than a 2-week delay for commencement of treatment. If the dosage was reduced because of toxicity, it was not increased subsequently. The oxaliplatin dose was reduced to 70 mg/m^2 on subsequent cycles of treatment if grade 2 neuropathy was detected. If neuropathy of grade 3 or above was encountered, chemotherapy was discontinued. In case of allergic reactions or the occurrence of laryngeal spasm, the duration of the oxaliplatin infusion was increased from 2 to 6 h. If the problem recurred, chemotherapy was stopped.

Patient evaluation

Prior to entry into the study, complete medical histories were obtained from all patients and physical examinations conducted. Laboratory studies included full blood and differential counts, serum chemistry, carcinoembryonic antigen (CEA), and chest X-ray, and abdominal and pelvic computed tomography (CT) examinations. Patients were seen by physicians at 2-weekly intervals during treatment for progress reports, physical examinations and toxicity assessments. Complete blood counts were performed weekly for the first two treatment cycles and before every chemotherapy infusion thereafter. Serum biochemistry and CEA were examined after every 2 cycles, with tumor reassessment performed after every four cycles thereafter using abdominal CT scan and/or chest X-ray. Where clinical evidence suggested disease progression during therapy, response was immediately re-evaluated. Standard WHO criteria were utilized for determination of tumor response, with toxic events noted prospectively and evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria graduations.

Statistical considerations

The primary end point of this study was determination of the MTD and DLT for biweekly bolus 5-FU when administered with fixed-dose oxaliplatin and LV. The DLT was assessed for the first two cycles for each enrolled patient at every dose level. The percentage of patients suffering from hematological and non-hematological toxicities during the entire treatment was also determined. All patients receiving at least one dose of the specified medication were included in the analyses of safety parameters and survival. The 95% confidence interval (95% CI) of the response rate was derived using binomial distribution. The interval to disease progression and the survival time were calculated using the Kaplan–Meier method, commencing from the start of chemotherapy [19].

Results

Patient characteristics

From June 2000 through May 2001, a total of 26 patients with advanced colorectal cancer were enrolled in the study (16 males and 10 females; median age 58 years; range 27–75). The liver was the predominant metastatic site (61.5%), with multiple metastatic sites determined for 16 patients (61.5%). Twelve (46.2%) had metastatic disease at the time of diagnosis. Elevated CEA on entry into the study was noted for 22 patients. Four patients had received 5-FU-based adjuvant chemotherapy and 15 patients received weekly high-dose 5-FU/LV (5-FU 2600 mg/m^2 24-h infusion) as first-line chemotherapy for metastatic disease. Additionally, 14 patients had undergone UFT/LV treatment for metastatic disease and 10 the irinotecan-based chemotherapy. Thirteen patients (50%) had received more than one line of chemotherapy for metastatic disease. A summary of the baseline characteristics is presented in Table 1.

Dosage-escalation results

A total of six dose levels were tested (Table 2). At the first three dose levels, combining oxaliplatin 85 mg/m^2, LV 20 mg/m^2 with 5-FU at either 600, 700 or 800 mg/m^2, no DLT was observed. When the 5-FU dosage was incremented to 900 mg/m^2, dose-limiting grade 3 diarrhea and grade 4 neutropenia were each noted for one patient, while a further increase to 1000 mg/m^2 caused grade 4 neutropenia for one patient and grade 3 fatigue for another. The final increase in 5-FU dose to 1100 mg/m^2 produced grade 3 fatigue for three subjects in the five-patient cohort. Therefore, the MTD was established at 5-FU 1000 mg/m^2 with LV 20 mg/m^2 as an i.v. bolus with oxaliplatin 85 mg/m^2 administered as a 2-h infusion, administered every 2 weeks.

Table 1 **Patient characteristics ($N = 26$)**

Characteristics	*N*	%
Male/female	16/10 (26)	
Median age (range)	58 (27–75)	
Primary tumor		
colon	13	50.0
rectum	13	50.0
Performance status (ECOG)		
0	5	19.2
1	18	69.2
2	3	11.6
Metastatic sites		
liver	16	61.5
lung	6	23.1
peritoneum	9	34.6
lymph nodes	6	23.1
others	11	42.3
Synchronous metastasis	12	46.1
Prior chemotherapy regimen		
1	13	50.0
2	11	42.3
3	2	7.7

Table 2 **Dose escalation results**

Level	5-FU dose (mg/m^2)	No. of patients	DLT no.	Type of DLT	Response
1	600	3	0		0
2	700	3	0		1 PR
3	800	3	0		1 PR
4	900	6	2	G3 diarrhea, G4 neutropenia	2 PR
5	1000	6	2	G3 fatigue, G4 neutropenia	2 PR
6	1100	5	3	G3 fatigue (3 patients)	2 PR

G, grade; PR, partial response.

Table 3 **Worst toxicities during the first two cycles**

Toxicity	Level 1 ($n=3$)	Level 2 ($n=3$)	Level 3 ($n=3$)	Level 4 ($n=6$)	Level 5 ($n=6$)	Level 6 ($n=5$)
Neutropenia						
grade 1–4	0	0	1	3	4	1
grade 3/4	0	0	1	1	2	0
Anemia						
grade 1–4	0	1	1	2	2	2
grade 3/4	0	0	0	0	0	0
Thrombocytopenia						
grade 1–4	2	0	0	0	1	2
grade 3/4	0	0	0	0	0	0
Nausea/vomiting						
grade 1–4	1	2	2	3	4	5
grade 3/4	0	0	0	0	0	1
Diarrhea						
grade 1–4	1	1	1	3	2	3
grade 3/4	0	0	0	1	0	0
Mucositis						
grade 1–4	2	0	0	0	2	1
grade 3/4	0	0	0	0	0	0
Fatigue						
grade 1–4	2	2	0	0	2	5
grade 3/4	0	0	0	0	1	3
Neuropathy						
grade 1–2	1	0	2	1	2	2

Safety profile

During the study, 192 treatment cycles of 5-FU/LV and oxaliplatin were administered, with a median treatment duration of six cycles (range 3–16). The treatment-related adverse events for all 26 patients for the first two and for all treatment cycles, respectively, are listed in Tables 3 and 4. The most-frequent treatment-related adverse events were neutropenia, thrombocytopenia, fatigue, gastrointestinal toxicity and neuropathy, with the majority of toxicities mild to moderate in intensity. Grade 3/4 neutropenia was observed infrequently during the first two cycles, but occurred in 50% of patients (grade 4: 23.1%) during the overall treatment. Only two episodes of febrile neutropenia occurred and one patient died of neutropenia with septicemia. Grade 3/4 diarrhea developed for 7.7% of the patients; however, it was resolved quickly with loperamide treatment and all patients continued treatment after full recovery. Although grade 3 fatigue was observed for four patients, it was typically mild for dosage levels at or below the MTD. A total of 22 patients (84.6%) complained of sensory neuropathy, with the cause attributed to the oxaliplatin administration. Two patients (7.7%) developed grade 3 peripheral neuropathy and eight (30.8%) the grade 2. In accordance with the treatment plan, chemotherapy was delayed at least once for 14 of the patients (53.8%). Treatment delays occurred more frequently after the sixth cycle of chemotherapy because of neutropenia, thrombocytopenia or fatigue. A decrement of one 5-FU dosage was required for five patients as a consequence of severe neutropenia, diarrhea or fatigue, with two requiring a two-level decrement.

Response and survival

Although establishing the response rate was not the main aim of this study, the antitumor response was assessed (Table 5). Eight patients achieved partial responses lasting from 4.4 to 12.1 months (median 6.1). This represents a 30.8% response rate (95% CI 11.8–49.8%) among the 26 intent-to-treat populations. There were 10 patients with stable disease (38.4%) and seven with disease progression (26.9%). One patient was not evaluated, expiring early in the treatment program as a consequence of toxicity, despite good response for the

Table 4 **Maximum severity of toxicity in all courses given ($N = 26$)**

Toxicity	National Cancer Institute Common Toxicity Criteria grade				
	1	2	3	4	Percent of grade 3/4
Leukopenia	3	11	2	1	11.5
Neutropenia	1	3	7	6	50.0
Anemia	12	7	1	2	11.5
Thrombocytopenia	11	5	2	0	7.7
Vomiting	13	3	1	0	3.8
Mucositis	2	5	2	0	7.7
Diarrhea	6	8	1	1	7.7
Alopecia	2	0	–	–	0
Neurological	12	8	2	0	7.7
Fatigue	5	7	4	0	15.4
Infection	0	0	1	1	7.7
Allergy	0	2	0	0	0

One patient died of neutropenia with septicemia in cycle 4 (drug-related death, 3.8%).

Table 5 **Objective response rates ($N = 26$)**

	N	%
Complete response	0	0
Partial response	8	30.8
Stable disease	10	38.4
Progressive disease	7	26.9
Not evaluable	1	3.9

first two cycles. No responses were observed at the first dosage level; however, responding patients were found in all subsequent five dose levels. Two of the partial response patients with metastatic disease confined to the liver underwent thermoablative treatment for residual disease. CEA levels decrease for 54.6% of the subjects, with levels that were normalized or decreased by more than 50% were found in 36.4% of subjects with elevated CEA levels at baseline (eight of 22). The response rate for the irinotecan-pretreated patients was 20%.

As of June 2002, 18 patients had died and eight survived, with a median survival of 9.9 months (95% CI 6.7–13.1). The median time to progression was 4.6 months (95% CI 2.0–7.2). The overall survival rate was 46.1% at 1 year after therapy. The median survival time from the diagnosis of metastatic disease was 20.9 months.

Discussion

Oxaliplatin is the first platinum compound demonstrated active against advanced colorectal cancer; however, single-agent activity against this cancer is limited. The efficacy of oxaliplatin has been evaluated in phase II studies, which demonstrated 10 and 12–24% response rates for 5-FU-pretreated and chemonaive patients with advanced colorectal cancer, respectively [20–22]. Preclinical and clinical studies have demonstrated a synergistic interaction between oxaliplatin and 5-FU [23,24]; however, the challenge to determine the optimal dosage and schedule for the combination of oxaliplatin and 5-FU remains unanswered. Several phase II and III studies have confirmed the activity of oxaliplatin and 5-FU/LV, delivered using either constant or chronomodulated continuous infusion [7–14]. The combination of oxaliplatin and bolus 5-FU, however, has not been extensively explored. In an *in vitro* study of the synergistic interaction between oxaliplatin and 5-FU on colon cell lines, it has been demonstrated that the 5-FU/oxaliplatin combination is more cytotoxic when 5-FU exposure is brief (2 h) [16]. This result fails to confirm the widely held belief that, in combination with oxaliplatin, continuous 5-FU exposure is superior to the short, discrete variant. Therefore, combining oxaliplatin with bolus 5-FU/LV instead of infusional 5-FU/LV provides an encouraging alternative in view of the synergy of the interaction and the practicality of the administration of these three drugs.

Hochster *et al.* have recently reported a 64% response rate for 27 patients treated with oxaliplatin and a weekly bolus of 5-FU/LV as first-line chemotherapy for advanced colorectal cancer [18]. Analysis of their data suggests that weekly bolus 5-FU/LV treatment also has a synergistic cytotoxicity in combination with oxaliplatin. Ravaioli *et al.* have also demonstrated that monthly 5-day courses of bolus 5-FU/LV plus oxaliplatin are a safe and effective combination [25]. The result of the current study demonstrates that concomitant administration of bolus 5-FU/LV with oxaliplatin on a biweekly schedule is a promising new treatment option for patients with advanced colorectal cancer. Further, a recommended schedule was established, with 5-FU 1000 mg/m^2, LV 20 mg/m^2 plus oxaliplatin 85 mg/m^2 administered as an i.v. bolus or 2-h infusion every 2 weeks. This regimen is more convenient in comparison to continuous 5-FU infusion schedules, with only one visit to the clinic required every 2 weeks for drug administration.

Although establishing the response rate was not the primary objective of this study, the activity of this regimen was encouraging. In an intent-to-treat analysis, a clinical response was demonstrated for eight patients

(30.8%). Importantly, these results were achieved for a heavily pretreated cohort of patients bearing a heavy tumor burden. Additionally, 10 (38.4%) of our 26 patients had undergone irinotecan-based chemotherapy. Despite these adverse factors, a response rate of 30.8% was still obtained, which compares favorably with other second-line studies of advanced colorectal cancer treated using oxaliplatin, 5-FU and LV. Further, the survival rate for our patients is comparable to that of other second-line studies adopting either oxaliplatin or irinotecan-based chemotherapy. Another encouraging observation is the relatively high response rate observed for patients, despite the prior failure of both 5-FU and irinotecan treatments.

Clearly, efficacy and safety are important considerations when attempting to identify the most suitable treatment option for individual patients. Other important factors in treatment assessment are patient convenience and the impact on quality of life. As metastatic colorectal cancer is incurable, symptom palliation and the optimization of quality of life are critical aspects for evaluation of therapy. The significant disadvantage of continuous infusion 5-FU/LV regimens is the need for implantable access devices and portable infusion pumps. Implantable access devices are associated with complications such as infections, bleeding, deep vein thrombosis, pulmonary embolism and pneumothorax, in addition to the considerable cost burden. From a practical viewpoint, a biweekly administration of 5-FU/LV and oxaliplatin as an i.v. bolus or short infusion is more convenient for both patient and physician, and convenient as outpatient therapy.

With regard to observed toxicity in this trial, the main treatment-related adverse events consisted of neutropenia, fatigue, gastrointestinal toxicity and neuropathy. Although grade 3/4 neutropenia was uncommon (15.4%) in the first two courses, it was more frequent (50%) after the first two courses of treatment. However, only two episodes of febrile neutropenia were noted during the treatment program. The duration of neutropenia was usually short and it responded well to dosage modification. In this trial, fatigue or asthenia was the other frequently encountered treatment-related toxicity, however, it was usually mild at or below the MTD. In the phase III study of de Gramont *et al.*, the patients with advanced colorectal cancer receiving oxaliplatin in combination with a bimonthly schedule of LV and bolus-plus-continuous-infusion 5-FU, the most common toxicities were grade 3/4 neutropenia (41.7%), grade 3/4 diarrhea (11.9%), grade 3/4 mucositis (5.8%) and grade 3 neurosensory toxicity (18.2%) [7]. Similar hematological toxicity but less diarrhea and mucositis were noted for our new regimen, while the complications associated with an indwelling device for continuous infusion were avoided.

In conclusion, this phase I study has demonstrated that fortnightly bolus 5-FU/LV and oxaliplatin is an active and well-tolerated regimen for patients with heavily pretreated, advanced colorectal cancer. Fatigue, diarrhea and neutropenia are the DLTs for this regimen. Additionally, encouraging activity was demonstrated for the management of pretreated, advanced colorectal cancer patients, probably comparable to, or arguably better than, high-dose continuous-infusion 5-FU/LV schedules. Based on the results of this study, the recommended dose for phase II trials is 5-FU 1000 mg/m^2 and LV 20 mg/m^2 plus oxaliplatin 85 mg/m^2, administered every 2 weeks. A phase II study, which aims to more precisely define activity and toxicity, is ongoing.

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