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Combination of Oxaliplatin, Fluorouracil, and Leucovorin in the Treatment of Fluoropyrimidine-Pretreated Patients with Metastatic Colorectal Cancer

There has been no standard therapy for patients with metastatic colorectal cancer who have failed to first-line fluorouracil-based treatment. The present study was designed to assess the efficacy and toxicities of a combination of oxaliplatin, 5-fluorouracil (5-FU) and leucovorin in fluoropyrimidine-pretreated patients with metastatic colorectal cancer. Chemotherapy consisted of oxaliplatin 85 mg/m^2 on day 1, followed by leucovorin 20 mg/m^2 and 5-FU 1,200 mg/m^2 on days 1 and 2. Treatment courses were repeated every two weeks. Thirty-nine patients were enrolled in this study. All patients previously received fluoropyrimidine-based chemotherapy. Thirty-one patients were assessable for response and 33 for treatment toxicity. Six patients required dose reduction of 5-FU due to grade III/IV cytopenia. Nausea/vomiting and peripheral neuropathy were common non-hematologic toxicities. Overall response rate was 42.0% including 3 complete response and 10 partial response. The median response duration was 91 days (range, 28-224+). The median duration of progression-free survival was 132 days (range, 40-308). A combination of oxaliplatin, 5-FU, and leucovorin showed high response rate in fluoropyrimidine-pretreated patients with metastatic colorectal cancer, but the duration of response was relatively short. It may be worthwhile to explore its therapeutic potential in the first-line treatment setting.

Key Words: *Colorectal Neoplasms; Oxaliplatin; Fluorouracil; Leucovorin*

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INTRODUCTION

Chemotherapy for colorectal cancer dates from the introduction of the fluoropyrimidines, fluorouracil (5-FU) (1) and its deoxyriboside, floxuridine (2). For years, 5-FU has been the standard chemotherapeutic agent for the treatment of patients with metastatic colorectal cancer (3, 4). However, 5-FU has achieved only 10% of objective responses, when given as a single agent for first-line treatment of metastatic disease (5, 6). Despite numerous attempts to increase the antiproliferative activity of 5-FU, including biochemical modulation with leucovorin or other modulators, modification of the administration schedule, increase of the dose intensity, and/or combination with other cytotoxic agents such as cisplatin, the superiority of any particular strategy has not yet been established (7-9). Although the acceptable tolerability of these regimens has supported their widespread clinical use, there has been only a modest activity and no evidence of any clear-cut survival advantage. Furthermore, there is no standard treatment for patients with metastatic colorectal cancer who have failed to respond to, or whose disease has progressed after, a first-line fluorouracil-based treatment (10). Survival is short and associated with weight loss, onset or worsening of tumor-related symptoms, and poor quality of life (11). Thus the need for new drugs and novel approaches in the treatment of metastatic colorectal cancer has been emphasized.

Oxaliplatin is a cisplatin analogue in the 1,2-diaminocyclohexane family of platinum compounds. Similar to cisplatin and carboplatin, the main mechanism of action is mediated by the formation of DNA adducts (12). Nevertheless oxaliplatin displays in vitro activity against cisplatin-resistant human tumor cells, including colorectal cancer cells (13). When used as a single agent, oxaliplatin achieved a 10% objective response rate in patients with metastatic colorectal cancer previously treated with 5-FU (14). In recent phase II studies, objective response rates of 20-24% were reported in patients with previously untreated metastatic colorectal cancer (15, 16). Preclini-

cal observations suggest that oxaliplatin has synergistic antitumor activity with 5-FU both in vitro and in vivo in murine leukemia cell cultures transplanted into mice and in human colonic xenografts either sensitive or resistant to 5-FU (12, 17). The combination of oxaliplatin plus 5-FU (±leucovorin) has been explored in the treatment of 5-FU-pretreated metastatic colorectal cancer patients. Significant antitumor activities have been observed with objective response rates consistently higher than 20% (18, 19).

The present study was designed to assess the efficacy and toxicities of a combination of oxaliplatin, 5-FU, and leucovorin in fluoropyrimidine-pretreated patients with metastatic colorectal cancer.

PATIENTS AND METHODS

Patients

Eligibility criteria were as follows: 1) histologically proven colorectal adenocarcinoma, 2) relapsed or progressed disease after fluoropyrimidine-based chemotherapy, 3) bidimensionally measurable metastatic lesion(s), 4) Karnofsky performance status of 70 or more, 5) adequate bone marrow, renal and hepatic function, and 6) radiologic assessments performed within 30 days before the start of treatment.

Complete blood cell counts, chemistry, and carcinoembryonic antigen (CEA) blood levels were obtained initially and every four weeks thereafter. According to the location of measurable lesion(s), computed tomography (CT) scans of the abdomen/pelvis and/or chest, and chest radiography were obtained within one month before the onset of therapy and every twelve weeks thereafter. Subjective symptoms, physical examination findings, and all adverse reactions were recorded before each treatment cycle.

Chemotherapy regimen

Chemotherapy consisted of oxaliplatin 85 mg/m^2 administered as a 2-hr intravenous infusion on day 1, followed by leucovorin 20 mg/m^2 given as intravenous bolus injection and 5-FU 1,200 mg/m^2 given as a 6-hr intravenous infusion on days 1 and 2. Treatment courses were repeated every two weeks. Treatment was given until disease progressed, unacceptable toxic effects developed, or the patient refused further treatment.

Toxicities and dosage modification

The toxicities of each course were recorded before the start of the next course and were graded according to the WHO criteria (20). 5-FU dose was reduced by 20% in subsequent courses if cytopenia or gastrointestinal toxicities of more than grade II were observed in the previous cycle. If a patient had peripheral neuropathy of grade II, treatment was delayed until recovery of neurotoxicity. Oxaliplatin was discontinued if any neurotoxicity of more than grade II was observed. The treatment toxicity was assessed by the highest grade of each toxic effect seen per patient. Patients who received more than three courses were considered assessable for treatment toxicity.

Assessment of response

The primary efficacy end point was response rate. Response was assessed after every twelve weeks and was defined according to the following WHO criteria: 1) complete response (CR), complete disappearance of all symptoms and signs of disease for a minimum of four weeks, 2) partial response (PR), a 50% or more reduction in the sum of the products of the perpendicular diameters of each measurable lesion without appearance of any new lesion for a minimum of four weeks, 3) stable disease (SD), no appearance of new lesions of disease or less than 50% decrease or less than 25% increase in the described measurements, and 4) progressive disease (PD), more than 25% increase in the measurements and/or appearance of new lesions.

The secondary efficacy end points included the duration of response, progression-free survival (PFS), and overall survival (OS).

Statistical considerations

The duration of response was counted from the onset of documented response to the date of disease progression. PFS and OS were calculated from the start of treatment to the time of progression and death, respectively. Kaplan-Meier curves were drawn for PFS and OS.

RESULTS

Patient characteristics

Between May and December 1999, a total of 39 patients were enrolled in this study. Thirty-one patients were assessable for response and 33 for treatment toxicity. Eight patients were removed from the study before the treatment effect or toxicity was evaluated. The reasons were economic problem in two patients and patient's refusal of further chemotherapy in six. Patient

Table 1. Patient characteristics

Characters	No. of patients
No. of patients	39 (100%)
Age, yr, Median (range)	57 (33-75)
Sex	
Male	23 (59%)
Female	16 (41%)
Karnofsky performance status	
90-100	16 (41%)
70-80	23 (59%)
Location of primary tumor	
Colon	21 (54%)
Rectum	18 (46%)
No. of involved metastatic sites	
1	4 (10%)
2	14 (36%)
≥3	21 (54%)
Location of metastases	
Liver	36 (92%)
Lung	19 (49%)
Peritoneum	4 (10%)
Others	23 (59%)
Prior chemotherapy	
Adjuvant	9 (23%)
Palliative	30 (77%)
No. of prior chemotherapy regimens	
One	14 (36%)
Two	21 (54%)
Three or more	4 (10%)
Prior chemotherapy regimens	
5-FU/leucovorin	34 (89%)
Doxifluridine/leucovorin	14 (36%)
UFT/leucovorin	6 (16%)
Others	10 (26%)
CEA level	
Normal	5 (13%)
Elevated	33 (84%)
Unknown	1 (3%)

characteristics are listed in Table 1. The median age of the patients was 57 yr (range, 33-75). About 60% of the patients were male, and 41% had a Karnofsky performance scale of 90 or 100. Most patients had multiple sites of metastases involving two or more organ systems. The predominant sites of metastases were the liver in 92% of the patients, the lung in 49%, and peritoneum in 10%. Nine patients had tumor recurrence after adjuvant therapy with 5-FU/leucovorin, and all others progressed while receiving or after discontinuing palliative fluoropyrimidine-based chemotherapy. Two thirds of the patients received two or more regimens of prior chemotherapy. Prior chemotherapy regimens were intravenous bolus 5-FU plus leucovorin in 89%, oral doxifluridine plus leucovorin in 36%, and oral UFT plus leucovorin in 16%.

A total of 244 courses were administered to the patients. The median number of courses per patient was six (range, 1-13). The median follow-up duration of alive patients at the time of this analysis was 177 days (range, 40-321).

Toxicities

Toxicities associated with treatment are listed in Table 2. There was no treatment-related death documented. Hematologic toxicities were common, but they were generally mild to moderate in degree and fully reversible. Six patients required dose reduction of 5-FU due to grade III or IV cytopenia. Non-hematologic toxicities were mild (≤grade II) except grade III stomatitis in one patient. Nausea/vomiting (70%) was the most common acute toxic effect and peripheral neuropathy (61%) was the second. Peripheral neuropathy was sensory type in all cases and was typically aggravated at cold exposure. No dose modification or discontinuation of chemotherapeutic drugs was made for neurotoxicity.

Antitumor efficacy and survival

Overall objective response rate among 31 assessable patients was 42.0% including 3 CR (9.7%) and 10 PR (32.3%) (Table 3). Seven patients (22.5%) showed sta-

Table 2. Highest grade of treatment toxicity per patient (n=33)

	WHO grade				
	0	1	2	3	4
Leukopenia	16 (49%)	6 (18%)	9 (27%)	2 (6%)	0 (0%)
Neutropenia	16 (49%)	5 (15%)	8 (24%)	3 (9%)	1 (3%)
Thrombocytopenia	24 (73%)	3 (9%)	5 (15%)	1 (3%)	0 (0%)
Anemia	19 (58%)	7 (21%)	5 (15%)	2 (6%)	0 (0%)
Nausea/vomiting	10 (30%)	12 (37%)	11 (33%)	0 (0%)	0 (0%)
Stomatitis	26 (79%)	0 (0%)	6 (18%)	1 (3%)	0 (0%)
Diarrhea	27 (82%)	4 (12%)	2 (6%)	0 (0%)	0 (0%)
Alopecia	29 (88%)	1 (3%)	3 (9%)	0 (0%)	0 (0%)
Peripheral neuropathy	13 (39%)	15 (46%)	5 (15%)	0 (0%)	0 (0%)

Table 3. Objective response

	No. of patients
No. of patients assessable for response	31 (100.0%)
Complete response	3 (9.7%)
Partial response	10 (32.3%)
Stable disease	7 (22.5%)
Progressive disease	11 (35.5%)
Total objective response	13 (42.0%)

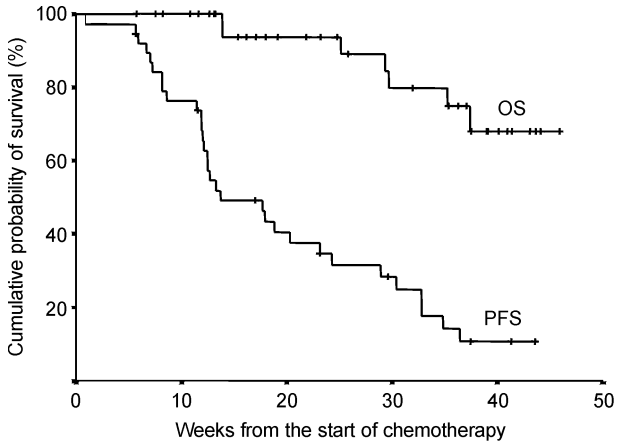

Fig. 1. Progression-free survival (PFS) and overall survival (OS) curves.

bilized disease following 12 weeks' treatment and 11 (35.5%) had progressive disease in the course of the treatment. The median duration of response was 91 days (range, 28-224+). Two of three patients who achieved CR were alive in continuous CR states at 173 days and 224 days from the onset of documented response, respectively.

The median duration of PFS was 132 days (range, 40-308). The median overall survival duration has not been reached yet at the time of this analysis. The probability of being alive at sixth month was 89% (Fig. 1).

DISCUSSION

Second-line chemotherapy after the failure of 5-FU treatment is a new challenge in advanced colorectal cancer. Our study showed the efficacy and safety of oxaliplatin when added to a 5-FU/leucovorin treatment for pretreated patients with metastatic colorectal cancer. All patients previously received fluoropyrimidine-based chemotherapy, mostly intravenous bolus 5-FU with leucovorin, and two thirds of the patients were treated with two or more regimens. A combination of oxaliplatin, 5-FU, and leucovorin was highly efficacious in these heavily pretreated patients. In many other phase II trials, oxaliplatin in combination with 5-FU/leucovorin has been extensively evaluated for previously treated metastatic colorectal cancer. De Gramont group has systematically studied the efficacy of the combinations (FOLFOX1 through FOLFOX7) of oxaliplatin and 5-FU/leucovorin administered as a constant-rate continuous infusion (4, 21-25). FOLFOX1 through FOLFOX6 regimens consisted of oxaliplatin 85-130 mg/m^2, 5-FU 2,000-4,000 mg/m^2, and leucovorin 400-1,000 mg/m^2 which were repeated every two weeks. They achieved 16-37% of response rates in previously treated colorectal cancer patients. A recently reported trial by the same de Gramont group employed the FOLFOX7 regimen (25), in which oxaliplatin was administered at 130 mg/m^2 in a two-hr infusion with a 400 mg/m^2 bolus of leucovorin, followed by a 400 mg/m^2 bolus of 5-FU and a further 2.4 g/m^2 of 5-FU over 46 hr every three weeks. The objective response rate in 29 5-FU-refractory patients was 52%, with a median PFS of 6.2 months. Our regimen was a modification of FOLFOX4 scheme. Considering the expense and reimbursement issues, we used low-dose leucovorin. High-dose leucovorin proved to be no better than low-dose leucovorin in the 5-FU/leucovorin treatment for colorectal cancer in a randomized trial (26). Forty-two percent of response rate in our study is comparable to that in FOLFOX regimens using high-dose leucovorin.

Although our study showed high response rate, the duration of response of the patients who achieved PR or CR was relatively short (median of 3 months). The median PFS of all patients was 132 days, which were similar to the results from the European compassionate-use program (27). Because the addition of oxaliplatin to 5-FU/leucovorin can induce high rate of response even in pretreated patients, it is reasonable to administer this regimen as a first-line treatment for the patients with advanced colorectal cancer. Three phase II trials have reported the effectiveness of this therapy in chemotherapy-naive patients (28). The objective response rates in these trials ranged from 59% to 69%. In two phase III studies, oxaliplatin added to 5-FU/leucovorin resulted in the consistent 4-month advantage in time to progression and the doubling to tripling of objective response rate (29, 30). However, significant difference in response rates did not translate into survival differences probably due to crossover effect.

Overall, the safety data on oxaliplatin confirm a toxicity profile that is clearly differentiated from those of other platinum agents (31). Oxaliplatin demonstrates a lack of nephrotoxicity, minimal ototoxicity, and minimal hematologic toxicity. Peripheral neuropathy is the most severe toxicity resulting from oxaliplatin therapy, but it is usually reversible. With our regimen of the combination of oxaliplatin and 5-FU/leucovorin, hematologic tox-

icities were common and six patients required dose reduction of 5-FU for these toxicities. Non-hematologic toxicities were generally mild, and nausea/vomiting (70%) and peripheral neuropathy (61%) were common acute toxic effects.

In conclusion, a combination of oxaliplatin, 5-FU, and leucovorin showed high response rate in fluoropyrimidine-pretreated patients with metastatic colorectal cancer, but the duration of response was relatively short. It may be worthwhile to explore its therapeutic potential in the first-line treatment setting.

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