Jpn J Clin Oncol 2003;33(3)136–140

Irinotecan (CPT11) Plus High-dose 5-Fluorouracil (5-FU) and Leucovorin (LV) as Salvage Therapy for Metastatic Colorectal Cancer (MCRC) after Failed Oxaliplatin Plus 5-FU and LV: a Pilot Study in Taiwan

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Received July 2, 2002; accepted November 26, 2002

Background: Irinotecan (CPT11) has established activity against advanced colorectal cancer without cross-resistance with 5-fluorouracil + leucovorin-based therapy. We conducted this pilot study to evaluate the efficacy and tolerance of combination treatment with irinotecan and 5-fluorouracil (5-FU) for patients in whom combination treatment with oxaliplatin with 5-FU + leucovorin has failed.

Methods: Patients were enrolled in this study after oxaliplatin treatment had failed. The treatment protocol consisted of CPT11 (180 mg/m^2 for 90 min) on day 1 and a 2 h infusion of 200 mg/m^2 leucovorin followed by 400 mg/m^2 5-FU as an intravenous bolus injection plus a 22 h continuous infusion of 600 mg/m^2 5-FU. This regimen was repeated for two consecutive days every 2 weeks.

Results: A total of 18 patients were eligible for this study and in total 144 cycles of therapy (median eight cycles) were given to these patients. Four patients (22.2%; 95% CI: 8–36.4%) achieved an objective response of partial remission (PR) and an additional seven obtained stable disease (SD) status or minor response. The median duration of response was 8 months and 14 patients were alive at the end of the study. Hematological toxicity (neutropenia) was the most common serious side effect (29.2%), followed by gastrointestinal effects (diarrhea, 28.5%). Grade II–III diarrhea was experienced for at least one cycle by each patient.

Conclusions: The results of treatment for patients after oxaliplatin failure are encouraging and this treatment protocol is also well tolerated by previously heavily treated patients.

Key words: irinotecan – oxaliplatin – metastatic colorectal cancer – chemotherapy

INTRODUCTION

Colorectal cancer is among the leading causes of cancer-related morbidity and mortality in Taiwan. Resection of the primary tumor is the main treatment for patients in early stages with localized disease and may offer a chance of cure, but for metastatic disease, cure is rarely achieved. Chemotherapy is currently the main treatment for metastatic disease (1). Since it was introduced some 40 years ago, 5-fluorouracil (5-FU) has remained the most effective single-agent treatment for advanced colorectal cancer (2). 5-FU has been administered with many schedules, dosages and routes to increase its antitumor activity, but the optimum schedule for administration is still not clear. Recently, an apparent consensus has emerged on the superiority of 5-FU plus leucovorin (LV) in terms of objective response, but no definitive agreement exists in terms of extension of survival (3).

Current therapeutic strategies for colorectal malignancies are based on 5-FU, which can produce response rates of ~11% as a single agent (4). Strategies aimed at enhancing the therapeutic efficacy of 5-FU have involved changes in its administration schedule and also its use in combination with other anticancer or biochemical modulating agents to produce a better treatment response (5). In recent years, the results of innovative research and a measure of good fortune have produced several promising new agents, among which are the novel inhibitor of the DNA enzyme topoisomerase I, irinotecan (CPT11), and oxali-

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Table 1. Characteristics of patients

Characteristic	No.
No. of patients	18
Courses of treatment	
Total	144
Median	8
Range	4–15
Age (years)	
Average	61.9
Range	36–74
Performance status	
0	14
1	2
2	2
Time to progression (months)	
Average	7.5
Range	4–13
Primary tumor	
Colon	12
Rectum	6
Prior resection of primary tumor	
Yes	15
No	3
Previous adjuvant chemotherapy	
Yes	15
No	3
Site of metastases	
Liver	12
Lung	5
Liver and lung	2
Urinary bladder	1
Pancreas	1
Terminal ileum	1
Adrenal gland	1
Ovary	1

platin (6). Oxaliplatin, a platinum-based chemotherapeutic agent, when combined with 5-FU and leucovorin, exhibits response rates of 25–40% as first-line treatment and ~10% for second-line treatment (7–9). Furthermore, utilizing oxaliplatin for continuous treatment is frequently limited by oxaliplatin-induced neurotoxicity, hand–foot syndrome and hematological toxicities (10). Despite the advances, there is evidence that incorporating new anticancer agents with conventional high-dose 5-FU plus leucovorin can improve treatment response and survival (11). In the past year, the health authorities in Taiwan have approved both oxaliplatin and irinotecan as first-line chemotherapeutic agents for MCRC; nonetheless, there is little published literature regarding the combination treatment of irinotecan or oxaliplatin with 5-FU and LV on Taiwanese patients.

Our study was designed to characterize the antitumor activity and toxicity of CPT11 (180 mg/m^2 for 90 min) in combination with bolus 5-FU, followed by a continuous infusion of 5-FU and high-dose leucovorin given every 2 weeks to patients for whom oxaliplatin treatment had failed (12,13).

PATIENTS AND METHODS

Characteristics of Patients

Between February 2000 and January 2001, a total of 18 patients with metastatic colorectal cancers were enrolled in this study. All patients eligible for the study had to fulfil all of the following criteria: histological proof of locally advanced or metastatic colorectal adenocarcinoma; one or more measurable lesions, unless subsequent progression was documented; age >18 and <75 years; and a life expectancy of >12 weeks. All patients had to have had prior salvage chemotherapy with oxaliplatin and were all in a progressive disease status (Table 1). Adjuvant treatment using 5-FU and LV was allowed but patients had to be free from treatment with irinotecan.

All patients were required to have a WHO performance status of ≤2 and have adequate hematopoietic function as evidenced by a leukocyte count of >4000/μl and a platelet count of >100 000/μl. A liver panel that included serum alkaline phosphatase, albumin, globulin, total and direct bilirubin, lactic dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium and creatinine, was obtained for all patients before chemotherapy was initiated. Those patients with serum creatinine >2 mg/dl were rejected. Liver dysfunction was defined as serum aminotransferase levels above the upper level of normal (ULN) and elevated bilirubin of >3 mg/dl. The liver panel was also obtained 2 weeks after completion of each chemotherapy cycle and every 4 weeks during treatment. If clinically indicated, AST, ALT, PT and bilirubin levels were also determined at other times during the chemotherapy cycles. No concurrent chemotherapy was allowed during this study. The protocol was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital and all patients gave written informed consent to participate in this study.

Treatment

This regimen utilized CPT11 180 mg/m^2 for 90 min on day 1 and a 2 h infusion of 200 mg/m^2 leucovorin followed by 400 mg/m^2 5-FU as an intravenous bolus injection plus a 22 h continuous infusion of 600 mg/m^2 5-FU. This regimen was repeated for two consecutive days every 2 weeks. Each patient was monitored through the Outpatient Department after discharge. A total of 18 patients with prior exposure to oxaliplatin plus 5-FU were enrolled in this study. In instances of grade 3 leukopenia, mucositis or diarrhea, the dose of irinotecan was reduced by 25% and delayed for at least 1 week until there was

complete disappearance of the toxic side effects. If grade 2 leukopenia, mucositis or diarrhea appeared, the dose of irinotecan was not modified but treatment was delayed for at least 1 week until complete disappearance of all signs of toxicity.

Response Criteria

Response was evaluated using the Eastern Cooperative Oncology Group (ECOG) criteria. Complete response (CR) was defined as the complete disappearance of all known lesions documented by two separate observations at least 4 weeks apart and without the appearance of any new lesions. Partial response (PR) required at least a 50% reduction in the cross-sectional area of the indicator lesion (or sum of areas if there was more than one indicator lesion), again documented by two separate observations at least 4 weeks apart, with no individual lesion growing or no new lesion appearing. Stable disease (SD) was defined as a <50% reduction or a <25% increase in the sum of cross-sectional areas of all measurable lesions, with no appearance of new lesions for at least 4 weeks. Patients were considered to have progressive disease (PD) when any lesion grew >25% in cross-sectional area or when any new lesion appeared.

Patient Evaluation

Pretreatment evaluation included a detailed medical history, physical examination, complete blood and biochemical surveys, ECG, chest X-ray, bone scan, liver ultrasound and/or abdominal computed tomography (CT) scan. Complete blood count (CBC), blood biochemistry and carcinoembryonic antigen were repeated prior to each course of chemotherapy. However, patients underwent CBC between courses only in case of fever or severe mucositis.

Objective pretreatment tumor assessment was performed before the first course (baseline) but no more than 3 weeks prior to start of therapy, then was repeated every 12 weeks irrespective of the timing of treatment, unless objective disease progression was evident. Lesions were assessed using the same methods on each occasion. Antitumor response was assessed by giving a required abdominal sonography or CT scan to document measurable disease or after every cycle if clinical examination results were adequate for response evaluation. Pulmonary lesions could be assessed by chest X-ray or chest CT scan. Bone lesions had to be assessed using CT scan or X-ray but not by radioisotopic methods. All materials pertaining to assessment of tumor response and tumor progression were evaluated by one of the authors and one independent radiologist. Adverse effects were evaluated according to the ECOG criteria. Patients with CR, PR or SD remained in the protocol until progressive disease or unacceptable toxicity was documented.

Statistical Analysis

The primary endpoint of this study was the patient response rate to chemotherapy. The Simon optimum, two-stage, phase II clinical trial design was used. In the first stage, the study would have been halted if no response had been observed or the response was not satisfactory for the first 14 patients. This approach ensured that if the aim was to identify a drug with at least 20% response rate, the chance of rejecting it wrongly was 0.044 (<0.05). The confidence intervals for the response rate were based on the exact binomial distribution. Response duration was defined as the interval from the onset of a response to the time that evidence of disease progression was identified. This was the preliminary report of the first stage of this phase II study.

Table 2. Overall treatment-related toxicity in each cycle, graded according to ECOG criteria (n = 144)

Toxicity	Grade				Total cycles (%)
	1	2	3	4	
Leukopenia	5	26	9	2	42 (29.2)
Thrombocytopenia	6	0	0	0	6 (4.2)
Nausea	16	6	0	0	22 (15.3)
Vomiting	14	3	0	0	17 (11.8)
Hepatic	0	0	0	0	0 (0)
Renal	0	0	0	0	0 (0)
Cardiac	0	0	0	0	0 (0)
Hand–foot syndrome	2	16	1	0	19 (13.2)
Neurological	0	0	0	0	0 (0)
Diarrhea	3	26	12	0	41 (28.5)
Stomatitis	6	16	4	0	26 (18.1)

RESULTS

Response to Therapy and Survival

A total of 144 cycles of therapy (median eight cycles) were given to these 18 eligible patients. Four patients (22.2%; 95% CI: 8–36.4%) achieved an objective response of partial remission (PR) and an additional seven obtained stable disease status or minor response (MR). The median duration of response was 8 months. The median survival time was 7.5 months and at the end of this study there were 14 surviving patients.

Toxicity

Toxicities in this study are summarized in Table 2. Hematological toxicity (neutropenia) was the most common serious side effect (29.2%), but significant fever developed in only four patients. Gastrointestinal toxicities including diarrhea and stomatitis were the major side effects, but they were generally tolerable and were not life-threatening. Grade II–III diarrhea was experienced for at least one cycle by 10% of patients during treatment. Generally, toxicities were well tolerated in the majority of patients. There were no cardiac, renal or neuro-

logical complications. There were no drug-related deaths during the treatment period (Table 2).

DISCUSSION

Heidelberger et al. discovered 5-FU some 40 years ago; it remains the most extensively studied drug and is considered to be the standard treatment in metastatic colorectal cancer (2). However, the optimum dose scheduling of 5-FU is still controversial and it is generally accepted that an intravenous bolus injection of 5-FU will produce an unfavorable objective response rate in metastatic colorectal cancer (MCRC), as described previously (5). These reports were disappointing and prompted us to explore different dose schedules for improving the response and survival rates. It has been demonstrated that 5-FU modulation, mainly with LV, improves on the results obtained with 5-FU alone. Promising results have been achieved by utilizing 5-FU with leucovorin, which is currently used as the standard first-line chemotherapy for colorectal cancer. This combination also achieves a response rate of between 15 and 20%, a median progression-free survival of between 6 and 8 months and a median survival time ranging from 10 to 15 months (14). A review of seven studies on 5-FU plus leucovorin in the past 12 years showed that administration following a bimonthly schedule (as in this study) with comparison with the NCCTG–Mayo Clinic standard schedule (leucovorin 20 mg/m^2/day followed by a 5-FU bolus 425 mg/m^2/day for 5 days every 4 weeks) produced superior results in terms of response and progression-free survival, although there were no differences in overall survival (13). Based on considerations of convenience, we adopted a bimonthly schedule as reported by de Gramont et al. (13) with irinotecan.

The introduction of oxaliplatin into the colorectal cancer setting represents a significant advancement in the treatment of MCRC (15). In the literature, combination chemotherapy of oxaliplatin with 5-FU + leucovorin was effective as both first- and second-line treatments for metastatic colorectal cancer patients (16). Nonetheless, if patients fail to respond to this treatment, there are very limited choices for further treatment. Irinotecan (CPT11), an alternative treatment choice for MCRC, is a water-soluble, semi-synthetic derivative of an antineoplastic agent (17). *In vivo*, CPT11 is converted by the liver to a metabolite, 7-ethyl-10-hydroxycamptothecin (SN38), which appears to contribute to the antitumor activity of CPT11 (18). CPT11 possesses a novel mechanism of action that is dependent on the inhibition of the eukaryotic enzyme DNA topoisomerase I (17). This leads to accumulation of a drug-stabilized cleavable complex and then to the arrest of DNA replication and cell death (19,20). Encouraging results have been obtained in phase I trials with a diversity of malignancies including colorectal cancer and the efficacy of CPT-11 given as a combination regimen with 5-FU + leucovrin has been evaluated in Europe, the USA and Japan as first- and second-line treatments for metastatic colorectal cancer in more than 300 patients, with a similar response rate to that of oxaliplatin, which ranges from 13 to 32% (21,22).

The regimens of irinotecan that have been recommended range from 70 mg/m^2 once per week to 350 mg/m^2 every 3 weeks (23,24). The current study used a moderate dosage of CPT11 at 180 mg/m^2 with combination of 5-FU + leucovorin. This protocol has been shown to provide a safe and effective treatment choice for heavily pretreated patients. We also confirmed the antitumor activity of this regimen in patients with MCRC who had failed to respond to oxaliplatin. In this study, the overall tumor control was 61% (four partial responses and an additional seven patients with stable disease). This result is consistent with the literature on CPT11 for first- or second-line treatment for MCRC. However, this is a pilot study with favorable results of using CPT11 as salvage therapy for MCRC patients for whom oxaliplatin treatment had failed.

Concerning adverse reactions resulting from irinotecan, neutropenia and diarrhea are the major toxicities resulting in dose limitations of CPT11 (21). Neutropenia is reversible and there is rapid recovery with a nadir on days 9–10 (25). Although unwanted CPT11-induced delayed-onset diarrhea is CPT11's most notorious side effect, it can be circumvented by the use of high doses of loperamide and acetorphan (26).

The sequential utilization of irinotecan followed by oxaliplatin or of oxaliplatin followed by irinotecan had attracted much attention. In 2001, Christophe et al. (27) reported a phase III study at the American Society of Clinical Oncology and described their experience with the therapeutic sequence on MCRC patients. They enrolled previously untreated MCRC patients and found that both regimens produced a satisfactory response rate and a prolonged progression-free survival (27).

It is very important to determine the therapeutic sequence for MCRC in a clinical setting. In our study, we found that CPT-11 in combination with 5-FU + leucovorin was still able to achieve favorable results in MCRC patients for whom oxaliplatin treatment had failed, and this regimen produces tolerable adverse effects. However, to define clearly therapeutic efficacy in this setting might require a larger sample size and, for those patients who were refractory to sequential treatment with oxaliplatin and irinotecan plus 5FU + leucovorin or vice versa, further treatment modalities need to be investigated.

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