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ORIGINAL ARTICLE

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Second-line chemotherapy with low-dose CPT-11 and cisplatin for colorectal cancer resistant to 5-FU-based chemotherapy

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Abstract *Purpose*: With the aim of reducing the toxicities of irinotecan (CPT-11) while maintaining its antitumor effect, we treated colorectal cancer patients resistant to chemotherapy based on 5-fluorouracil (5-FU) with low-dose CPT-11 and cisplatin (CDDP). *Methods*: CPT-11 (27 mg/m^2) and CDDP (6 mg/m^2) were administered on days 1, 8 and 15 every 4 weeks to 20 patients with recurrent or metastatic colorectal cancer. When toxicities were noted, administrations were delayed or the dose was reduced. *Results*: No severe toxicity (i.e. grade 3 or more) was observed in this study. Nausea was observed in 50% of patients (10/20) and fatigue in 30% (6/20). Only four patients developed leukopenia (three grade 1 and one grade 2). Although the overall response rate was 15% (three partial response, seven no change, and ten progressive disease), the median time to progression was 7.0 months and the median survival time was 18.0 months. The treatment was well tolerated as outpatient therapy. *Conclusion*: Low-dose CPT-11 and CDDP treatment should be considered as second-line chemotherapy for patients with recurrent or metastatic colorectal cancer resistant to 5-FU-based chemotherapy.

Keywords Colorectal cancer · Chemotherapy · Recurrence · Metastasis · CPT-11 · CDDP · 5-FU

Introduction

Chemotherapy based on 5-fluorouracil (5-FU) is a standard treatment for patients with advanced or metastatic colorectal cancer (CRC) [1, 2, 3, 4, 5, 6]. The efficacy of single-agent 5-FU versus 5-FU with leucovorin (LV) (5-FU/LV) has been investigated in randomized clinical trials using several different regimens [3, 4, 5, 6]. Significantly higher response rates and prolonged survival have been reported for 5-FU/LV regimens [3, 4, 5, 6]. However, patients with advanced CRC that is refractory to 5-FU-based chemotherapy have a very poor prognosis. Survival is short, and disease-related symptoms worsen rapidly. Irinotecan hydrochloride (CPT-11) is a water-soluble, semisynthetic derivative of camptothecin (CPT) that retains the antitumor activity of CPT but has lower toxicity [7, 8, 9]. However, single administrations in CRC, non-small-cell lung cancer (NSCLC), ovarian cancer and cervical cancer have been shown to induce grade 3/4 toxicity in 8 to 67% of patients [10, 11, 12, 13, 14, 15].

The principal dose-limiting toxicity observed for all dosing regimens is delayed diarrhea, with or without neutropenia [16, 17]. Decreased doses of CPT-11 should be used in order to reduce toxicity without losing the antitumor effect. Therefore, the combination of CPT-11 and CDDP was chosen since these drugs have been reported to act synergistically in vitro [18, 19, 20, 21, 22, 23, 24] and the combination has been shown to be clinically effective in gastric cancer, NSCLC and CRC [25, 26, 27, 28, 29, 30]. In the study reported here, although we used a lower dose of both CPT-11 and CDDP as compared to those previously reported to reduce toxicity, the antitumor effect was maintained and less toxicity was observed.

Materials and methods

Patients

Patients with metastatic or recurrent CRC were enrolled in this study from 1996 to 2001 in our hospital. All patients had received prior therapy with 5-FU-based chemotherapy (LV/5-FU, CDDP/LV/5-FU or CDDP/5-FU), but their tumors had been evaluated as progressive disease (PD). All patients had evaluable disease and

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their performance status (PS) was less than Eastern Cooperative Oncology Group (ECOG) PS of 2. Adequate hematologic function (total leukocyte count $>3000/\mu l$ and platelet count $>80{,}000/\mu l$), renal function (serum creatinine <1.5 mg/ml), and hepatobiliary function (total serum bilirubin <1.5 mg/ml) were also essential. Treatments were started within at least 2 weeks from prior therapy.

Chemotherapy regimen

CPT-11 and CDDP were administered on days 1, 8 and 15 every 4 weeks as one cycle. CPT-11 (27 mg/m^2) was dissolved in 500 ml 5% glucose and infused intravenously over 120 min. Subsequently, CDDP (6 mg/m^2) was dissolved in 100 ml saline and infused over 30 min. To avoid vomiting, ondansetron and dexamethasone were administered [31]. When adverse reactions were noted, administrations were delayed or the dose was reduced. If PD was detected by evaluation, patients were given the option of switching to third-line chemotherapy or best supportive care.

Evaluation

The tumor response was evaluated based on changes in the size of measurable lesions as assessed by CT scan and chest radiography. Tumor responses and toxicities were classified in accordance with World Health Organization criteria [32]. In brief, complete remission (CR) was defined as the disappearance of all evidence of tumor for a minimum of 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of perpendicular diameters of all measurable lesions for a minimum of 4 weeks without any evidence of new lesions or enlargement. PD was defined as an enlargement of an existing lesion by more than 25% or the development of one or more new lesions. Lesions that did not meet the criteria for response or progression were classified as showing no change (NC). The worst grade during the entire treatment was used for evaluation of toxicities.

Survival and time to progression were calculated from the initiation of low-dose cisplatin and CPT-11 using the Kaplan-Meier method.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Their median age was 62 years (30–82 years). All patients had been given 5-FU-based chemotherapy previously: 15 patients had received LV/5-FU, 1 had received CDDP/5-FU and 4 had received CDDP/LV/5-FU. The sites of metastasis were liver in ten patients (50%), local site in seven (35%), lung in six (30%), distant lymph node in five (25%), and peritoneum in three (15%). Six patients with liver metastasis had lung metastasis and the others had non-resectable liver metastasis ($>25\%$ replacement). The sites of local recurrence were the intrapelvic space after surgery for rectal cancer in six patients, and the site of anastomosis in the other patient. All three patients with peritoneal metastasis showed carcinomatosis.

Response

There were no CRs but three PRs, giving a response rate of 15% (3 of 20 patients). Although seven patients were evaluated as NC, the duration of NC was over 100 days in all of them (Table 2). Seven patients received high-dose LV/5-FU (LV 250 mg/m^2, 5-FU 600 mg/m^2) as third-line therapy. Five patients had only one cycle, and two patients received five and nine cycles as third-line therapy. Median survival time with third-line therapy was 9.0 months.

Table 1 Patient characteristics

	n
Total number of patients	20
Age (years)	
Median	62
Range	30–82
Gender (M:F)	15:5
Performance status	
0–1	16
2	4
Site of recurrence	
Liver	10
Local site	7
Lung	6
Lymph node	5
Peritoneum	3
Prior chemotherapy	
5-FU/LV	15
5-FU/CDDP	1
5-FU/LV/CDDP	4

Table 2 Overall response

Complete remission	Partial response	No change	Progressive disease	Response rate (%)
0	3	7	10	15

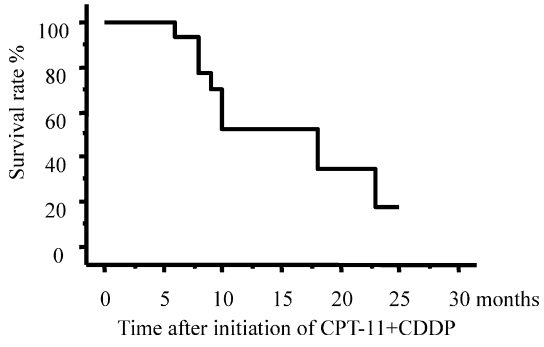

Fig. 1 Survival curve for all patients in this study. The median survival time of all patients was 18.0 months

Survival and time to progression

The survival curve for all patients is shown in Fig. 1. The median survival time for all patients was 18.0 months, and the median time to progression was 7.0 months.

Table 3 Adverse reactions

	Grade		
	1	2	3/4
Leukopenia	3	1	0
Nausea	6	4	0
Fatigue	2	4	0
Diarrhea	2	2	0
Alopecia	1	1	0
Stomatitis	1	0	0

Adverse reactions

The adverse reactions to this regimen are summarized in Table 3. Some adverse reactions were seen in 13 patients (13/20, 65%). There were no hematogenic toxicities, and no febrile neutropenia was seen. The most frequent adverse reaction was nausea: grade 1 nausea was observed in six patients, grade 2 in four patients. Grade 1/2 fatigue was observed in six patients. Diarrhea was observed in only four patients. No patient experienced grade 3/4 of any adverse reaction during the course of treatment. In addition, three patients with PS 2 prior to treatment showed an improvement in their PS.

Discussion

Several lines of evidence suggest that treatment with a combination of new antitumor drugs is effective in 5-FU-resistant CRC patients [10, 11, 12, 13, 33, 34]. The benefit of second-line chemotherapy with a single administration of irinotecan for CRC has been demonstrated by Cunningham and Glimelius [11]. In this phase III trial patients treated with irinotecan experienced significantly longer survival than those receiving best supportive care alone. However, 22% of patients experienced grade 3/4 neutropenia, and patients also showed grade 3/4 diarrhea and there was a 14% incidence of grade 3/4 vomiting. Similar adverse reaction rates were seen in studies involving a single administration of irinotecan for NSCLC, ovarian cancer and cervical cancer [14, 15].

Currently, studies of combined chemotherapy with CPT-11 and CDDP are being performed in an attempt to intensify the antitumor effect [25, 26, 27, 28, 29, 30]. Grade 3/4 adverse effects of CPT-11 plus CDDP are still frequently observed in patients with NSCLC or gastric cancer [25, 26, 27, 28, 29, 30]. Recently, it has been demonstrated that the in vitro topoisomerase I inhibitory effect of CPT-11 in NSCLC and CRC cell lines is enhanced approximately tenfold in the presence of CDDP at very low concentrations [23, 24]. This synergistic antitumor effect is thought to result from CDDP enhancing the inhibition of topoisomerase I caused by CPT-11 [23, 24]. We used a very low dose of CDDP as a modulator for CPT-11. So the dose of CPT-11 could be decreased to less than half the recommended dose to reduce the rate of adverse effects while maintaining the antitumor effect of the second-line chemotherapy to at least maintain tumor dormancy [35]. Accordingly, a regimen consisting of low doses of both CPT-11 and CDDP therapy was developed as a second-line chemotherapy for 5-FU-resistant CRC.

Even a very low dose of CPT-11 (27 mg/m^2) plus CDDP (6 mg/m^2) resulted in PR in three patients. Additionally, NC was seen in seven patients, and this status was prolonged in all seven. Since no grade 3/4 adverse effects were seen, this therapy can be considered safe and acceptable for outpatient therapy. In Japan, two studies have shown that the combination of CDDP and CPT-11 as a second-line therapy for CRC shows quite good responses and outcomes [25, 30]: a 36.7% response rate and 16.3 months median survival time were obtained following treatment with CPT-11 60 mg/m^2 and CDDP 30 mg/m^2. However, 42.3% of patients still showed grade 3/4 leukopenia [25]. A similar response rate has been observed in patients following treatment with CPT-11 60 mg/m^2 and CDDP 6 mg/m^2 [30]. Considering the adverse effects alone, the rates and grades were similar to those seen in our study. Otherwise, the median survival time with our regimen was better than that with the regimen used in the above study, even though a lower response rate was seen. This evidence suggests that a decrease in the dose of CPT-11 might induce tumor dormancy without drug resistance.

In conclusion, we report acceptable results of treatment with low doses of both CPT-11 and CDDP in patients with 5-FU-resistant CRC. Based on its low adverse effect rate and effectiveness in terms of survival, this regimen might be recommended to use as second-line chemotherapy for patients with even a low-grade PS.

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