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ORIGINAL ARTICLE

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Preliminary study of fortnightly irinotecan hydrochloride plus cisplatin therapy in patients with advanced gastric and colorectal cancer

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Abstract *Purpose*: Irinotecan hydrochloride shows a strong activity against gastric cancer and colorectal cancer, while combined therapy with irinotecan and cisplatin is useful for gastric cancer. However, myelosuppression and diarrhea are still dose-limiting factors. To reduce such toxicities to enable therapy to be performed on an outpatient basis, we tested the effect of divided administration of cisplatin. *Methods*: Irinotecan (60 mg/m^2) plus cisplatin (30 mg/m^2) were administered on days 1 and 15 every 4 weeks to 13 patients with advanced gastric cancer and 13 with advanced colorectal cancer. Treatment was continued if a leukocyte count ≥3000/mm^3, a platelet count ≥100,000/mm^3, and grade 0 diarrhea were confirmed. Doses were reduced if grade 3–4 hematological toxicity and grade 2 or higher nonhematological toxicity occurred. *Results*: The major toxicity was leukopenia (neutropenia), but grade 3–4 nonhematological toxicity was not observed. The response rate was 41.7% for gastric cancer (5/12 evaluable patients) and 36.7% for colorectal cancer (4/11 evaluable patients). The median survival time was 313 days (range 29–920 days) for gastric cancer patients and 490 days (range 83–1184+ days) for colorectal cancer patients. *Conclusion*: Fortnightly administration of irinotecan and cisplatin (with a divided cisplatin dose) seems to be a useful regimen for gastrointestinal cancer. It reduces toxicity while maintaining a good antitumor effect.

Key words Irinotecan · Cisplatin · Gastric cancer · Colorectal cancer · Fortnightly administration

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Introduction

In patients with unresectable gastric and colorectal cancer, the response rate to chemotherapy has improved with advances in multidrug therapy. However, the duration of response and the survival time are not yet satisfactory, so that new treatment regimens are needed to improve the prognosis. For patients with a limited survival, it is also very important to reduce the time required for treatment and to reduce the toxicity of therapy.

Irinotecan hydrochloride (irinotecan) is a chemotherapy agent with a novel mechanism of action, that is topoisomerase I inhibition. In Japan, the late phase II multicenter study of irinotecan was performed in patients with gastrointestinal cancers, and its efficacy was confirmed. Currently, studies of combined chemotherapy with irinotecan and other agents are being performed in an attempt to intensify its antitumor effect [1, 2]. The preclinical study showed that SN-38, an active metabolite of irinotecan, inhibits DNA remodeling of cancer cells injured by platinum derivatives [3]. Therefore, cisplatin possesses a potentially synergistic effect with irinotecan, and it is thought that the greatest response can be obtained by concurrent administration of these two drugs [4]. Clinically, it has been confirmed that a good response can be obtained by the combined use of irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1) in patients with unresectable advanced gastric cancer [5]. However, it often becomes difficult to continue this regimen because of myelosuppression and gastrointestinal symptoms such as diarrhea, and these toxicities are considered to be dose-limiting factors. Therefore, it would be clinically useful to develop a new regimen for irinotecan plus cisplatin therapy with reduced the toxicity and which would allow administration on an outpatient basis while maintaining a good antitumor effect.

Cisplatin has a cytocidal effect that is dependent on the area under the concentration vs time curve and is

maintained even when the drug is given in divided doses [6, 7]. Therefore, it may be possible to reduce the toxicity of cisplatin and maintain its antitumor effect by administering divided doses. Kobayashi et al. have reported that the response rate to the combination of irinotecan and cisplatin therapy can be maintained without grade 3–4 toxicity by concurrent weekly administration of the two drugs (irinotecan at 60 mg/m^2 and cisplatin at 33 mg/m^2 for 3 weeks, followed by 1 week off therapy) [8]. We have also treated patients with advanced gastrointestinal cancer using this schedule, but have encountered severe toxicity (including grade 4 diarrhea and grade 3 leukopenia). Therefore, we considered that it was difficult to use this regimen on an outpatient basis and modified it to fortnightly administration (on days 1 and 15). We then performed a preliminary study of this new regimen in patients with advanced gastric or colorectal cancer.

Materials and methods

Subjects

Patients with metastatic gastric or colorectal cancer were enrolled from June 1996 to July 1998 in our clinic. All subjects enrolled in this study gave informed consent and satisfied the following criteria: (1) gastric or colorectal cancer confirmed histopathologically; (2) expected survival time at least 2 months; (3) age between 20 and 75 years; (4) performance status 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale; (5) function of major organs (including bone marrow, heart, lungs, kidneys) well maintained (WBC ≥3000/mm^3, platelet count ≥100,000/mm^3); (6) no diarrhea; (7) no infections; (8) no paralytic ileus; (9) no other serious complications; (10) no massive pleural effusion or ascites; and (11) no jaundice. Subjects were not screened with respect to their prior therapy.

Treatment protocol

Irinotecan and cisplatin were administered on days 1 and 15 every 4 weeks. Irinotecan (60 mg/m^2) was dissolved in 500 ml 5% glucose and was infused intravenously over 90 min, and cisplatin (30 mg/m^2) was dissolved in 500 ml saline and was infused intravenously over 90 min. To maintain hydration, a total of 1500–2000 ml intravenous fluid was administered. Vomiting was controlled with a $5HT_3$ antagonist and a steroid. Subsequent courses were only administered if examination on the day of (or day before) administration confirmed a leukocyte count ≥3000/mm^3, a platelet count ≥100,000/mm^3, and grade 0 diarrhea. When other toxicities were noted, administration was delayed or the dose was reduced. The dose was also reduced as necessary based on organ function, the clinical response, and patient request.

Evaluation

The tumor response was evaluated based on changes in the size of measurable lesions and assessment of evaluable lesions. Measurable lesions and evaluable lesions were defined and efficacy was evaluated in accordance with the Japanese Criteria for Evaluating the Efficacy of Chemotherapy and Radiation Therapy in the Treatment of Gastric Cancer [9].

In brief, complete remission was defined as the disappearance of all evidence of the tumor for at least 4 weeks. Partial remission was defined as 50% or more reduction in the sum of the products of perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions developing or the progression of any lesions. No change was defined as less than 50% reduction or less than 25% increase in the sum of the products of perpendicular diameters of all lesions for at least 4 weeks without any evidence of new lesions developing or the progression of any lesions. Progressive disease was defined as an increase of 25% or more in one or more lesions or the appearance of new lesions. Measurement of the lesions was performed every 4 weeks using computed tomography, plain chest radiography, upper gastrointestinal endoscopy, and ultrasonography. Primary tumors were classified into the following three categories based on radiographic and endoscopic findings: measurable, not measurable but evaluable, and diffusely infiltrating.

Adverse events were graded in accordance with the Adverse Drug Reaction Judgment Criteria of the Japanese Society of Cancer Treatment [10], and the worst grade during the entire treatment was used for evaluation. Monitoring of general signs and laboratory parameters (including hepatic and renal function tests) was performed once a week.

Results

Clinical profile

The patient characteristics are shown in Table 1. There were 13 patients with gastric cancer and 13 with colorectal cancer. There were 12 patients with evaluable lesions in the gastric cancer group and 11 patients with evaluable lesions in the colorectal cancer group. There were ten patients with gastric cancer and nine with colorectal cancer who had previously received chemotherapy, predominantly 5-fluorouracil combined with cisplatin and mitomycin C. Five patients each with gastric cancer and colorectal cancer had previously received one chemotherapy regimen, four patients each had received two chemotherapy regimens, and one patient with gastric cancer had received three chemotherapy regimens. The median period from their initial treatment to the start of the current regimen was 6.9 months in gastric cancer patients and 4.2 months in colorectal cancer patients, so the interval was quite long in most patients. None of the subjects had previously received radiation therapy.

Toxicity

Toxicity was investigated in all patients (Table 2). The major toxicity was leukopenia and/or neutropenia. Grade 3 or 4 neutropenia occurred in 42.3% of the gastric and colorectal cancer patients, but grade 4 neutropenia was only seen in one patient with gastric cancer. All patients with leukopenia/neutropenia were able to continue treatment without any problem after postponing administration or reducing the dose. Only two gastric cancer patients and one colorectal cancer patient used G-CSF against leukopenia/neutropenia. Anemia and thrombocytopenia were the grade 3 or 4 hematological toxicities in gastric cancer patients. It was noteworthy

Table 1 Patient characteristics (*Fluoro* fluoropyrimidines)

	Gastric cancer	Colorectal cancer
No. of patients	13	13
Sex (male/female)	10/3	9/4
Age (years)		
Median	59	61
Range	25–74	41–74
Eligible and evaluable (yes/no)	12/1	11/2
Prior chemotherapy		
Yes/no	10/3	9/4
Fluoro alone	0	2
Fluoro/cisplatin	6	1
Fluoro/cisplatin/ mitomycin-C	3	1
Fluoro/mitomycin-C	3	2
Other	3	7
One regimen	5	5
Two regimen	4	4
Three regimen	1	0
Time from primary treatment to CPT-11 (days)		
Median	208	127
Range	0–807	0–522

that gastrointestinal toxicity was mild (grade 1 or 2) and transient in all cases. Prophylactic therapy was unnecessary and loperamide was not needed to control diarrhea. No patient was hospitalized due to side effects of therapy. Death was not related to treatment in any of the patients.

Tumor response

The tumor response was assessed in the 12 gastric cancer patients and 11 colorectal cancer patients with evaluable lesions (Table 3). The duration of response was determined in accordance with the WHO criteria [11]. A response was obtained in five patients with gastric cancer and the response rate was 41.7% (95% confidence interval 13.8–69.6%). Among the patients who had previously received chemotherapy, the response rate was 25.0%. The median duration of response was 141 days (range 56–182 days). Four patients with colorectal cancer showed a response and the response rate was 36.4% (95% confidence interval 7.9–64.8%). Among patients who had previously received chemotherapy, the tumor response rate was 22.2%. The median duration of response was 133 days (range 90–180 days).

There was a response in 50.0% of gastric cancer patients (three of six) with diffuse-type adenocarcinoma and 33.3% (two of six) of those with intestinal-type, indicating that this regimen was also effective for diffuse gastric cancer. The survival time was analyzed by the Kaplan-Meier method. The median survival time was 313 days (range 29–920 days) in gastric cancer patients and 490 days (range 83–1184+ days) in colorectal cancer patients.

Duration of treatment

The duration of treatment was investigated in all patients. It was defined as the period from the start of the present regimen until 14 days after the last dose or the period until the day before the start of subsequent therapy if this was commenced within 14 days after the last dose in the present regimen. The median duration of treatment was 83 days (range 14–493 days) in gastric cancer patients and 161 days (range 34–476 days) in colorectal cancer patients. The median number of doses was 5 (range 1–25) in gastric cancer patients and 10 (range 2–24) in colorectal cancer patients. Except for three gastric cancer patients who required intravenous alimentation because of inability to eat, all other patients were managed on an outpatient basis. To avoid hospital admission, the dose was reduced for grade 3 or 4 hematological toxicity as well as for grade 2 or worse nonhematological toxicity.

It was possible to start treatment with the standard dose in nine gastric cancer patients and nine colorectal cancer patients. The dose of irinotecan was reduced by 20–50% in the four patients from each group who started therapy at lower doses. Among these patients, the dose was subsequently increased in two from each group, with a response being obtained in both gastric cancer patients and one colorectal cancer patient. The dose was adjusted after the start of therapy in two gastric cancer patients and five colorectal cancer patients

Table 2 Toxicity in gastric and colorectal cancer patients ($n=26$). The numbers indicate the number of patients experiencing that grade of toxicity as the worst grade during any cycle

Toxicity	Grade				Grade ≥3 (% of patients)
	1	2	3	4	
Leukopenia	3	16	1	1	7.7
Neutropenia	4	5	10	1	42.3
Anemia	2	3	8	0	30.8
Thrombocytopenia	0	1	2	1	11.5
Diarrhea	5	1	0	0	0
Nausea	7	5	0	–	0
Anorexia	9	1	0	–	0
Abdominal pain	1	1	0	0	0
Asthenia	7	0	0	0	0
Constipation	7	1	0	0	0
Hot flashes	3	0	0	0	0
Alopecia	9	0	–	–	–

Table 3 Objective responses in gastric and colorectal cancer patients, excluding nonevaluable lesions (*PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable, *RR* response rate)

	Total no. of patients	PR	NC	PD	NE	RR (%)
Gastric cancer						
Overall	12	5	2	3	2	41.7
Previously untreated	4	3	1	0	0	75.0
Previously treated	8	2	1	3	2	25.0
Colorectal cancer						
Overall	11	4	7	0	0	36.4
Previously untreated	2	2	0	0	0	100
Previously treated	9	2	7	0	0	22.2

after a median of four doses (range three to nine). Among patients starting the therapy at the standard dose, the dose was reduced within four doses in four patients (three with colorectal cancer and one with gastric cancer), in two of whom the dose was reduced from the third dose and in two of whom it was reduced from the fourth dose. The dose was reduced due to neutropenia in three gastric cancer patients, due to anemia in two gastric cancer patients, and due to abdominal pain in two gastric cancer patients.

Discussion

The results of this study suggest the benefit of irinotecan plus cisplatin therapy using a regimen of a divided dose of cisplatin for the treatment of advanced gastric and colorectal cancer. This regimen was intended to decrease toxicity while maintaining the antitumor effect of irinotecan. The antitumor effect was augmented by coadministration of the two drugs, and the toxicities of both agents were reduced by administration with a 2-week interval between the first and second doses of each agent in the monthly course of therapy. Administration was performed over 6 h (including intravenous fluid infusion), so it was possible to manage the patients on an ambulatory basis.

In a multicenter study of irinotecan monotherapy in Japanese patients with gastrointestinal cancer, diarrhea and leukopenia were found to be the dose-limiting toxicities. Based on this study, the recommended dose of irinotecan was set at 100 mg/m^2 for weekly administration or 150 mg/m^2 for fortnightly administration, which are lower doses than those recommended in Europe and North America [12]. In the present study, the response rate was 18.4% in gastric cancer patients (one) and 27.0% in colorectal cancer patients (two), the incidence of grade 3 or 4 neutropenia was 30.9% and 62.1%, respectively, and the incidence of diarrhea was 12.9% and 22.4%, respectively. These results resemble those of a phase II clinical study of irinotecan performed in Caucasian patients with colorectal cancer [13, 14].

Boku et al. administered irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1) to patients with advanced gastric cancer, and observed a response rate of 48% and a median survival of 272 days. However, they also observed grade 4 neutropenia in 57% of the patients and diarrhea in 20% [5]. With the present schedule, hematological toxicity showed a similar overall incidence, but the incidence of grade 4 neutropenia was far lower at 3.8%. It is notable that grade 3 or worse nonhematological toxicity was not observed in any of our patients, and this facilitated their management on an outpatient basis. Thus, the present regimen achieved a similar response rate to that reported previously and caused less toxicity.

Rougler et al. performed a multicenter, randomized, phase III study of irinotecan monotherapy and optimal 5-fluorouracil-based combined chemotherapy in patients resistant to 5-fluorouracil alone. They confirmed the benefit of irinotecan for colorectal cancer resistant to 5-fluorouracil [15]. The combination of irinotecan with agents other than fluorouracil may also achieve good results. Irinotecan plus cisplatin has been reported to be effective against colorectal cancer in vitro [16], but there have been few clinical studies, so the present findings provide useful new clinical data.

The median survival time of the gastric cancer patients was 10.4 months and that of the colorectal cancer patients was 16.3 months. A previous randomized study of patients with advanced gastric cancer has shown a median survival of 3–4 months with supportive care and 6–12 months with chemotherapy [17, 18, 19]. Another randomized study in patients with advanced colorectal cancer has shown a median survival of 5 months with supportive care and 11 months with chemotherapy [20]. A similar median survival has been reported with 5-fluorouracil and leucovarin/5-fluorouracil therapy [21]. Direct comparison of the results of these studies is not possible, but our regimen seems worthy of further evaluation.

In conclusion, the fortnightly administration of irinotecan plus cisplatin was effective for gastric and colorectal cancer, and it also allowed management of patients on an ambulatory basis. However, the dose of irinotecan had to be reduced in 26.9% of the patients

and dose reduction was needed before the fourth dose in 15.4%. Therefore, it may be necessary to reconsider the dose of irinotecan. Although the number of subjects was small, because this was a preliminary study, the present regimen reduced toxicity while maintaining a good antitumor effect and could be administered on an ambulatory basis. Accordingly, it seems to be an attractive regimen for the treatment of gastric and colorectal cancer. A phase I/II study is currently in progress.

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