Original article

Combination chemotherapy of irinotecan plus cisplatin for advanced gastric cancer: efficacy and feasibility in clinical practice

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Abstract

Background. A previous phase II study showed that a combination of irinotecan (CPT-11) with cisplatin (CDDP) was effective for advanced gastric cancers, but was associated with substantial neutropenia and diarrhea. The aim of this retrospective study was to evaluate the efficacy and feasibility of the combination in clinical practice.

Methods. The subjects comprised 65 patients with advanced gastric cancer treated with CPT-11 (70 mg/m², day 1, day 15) and CDDP (80 mg/m², day 1) as first-line chemotherapy between April 1993 and March 1999. Patient backgrounds, response rates, response durations, times to progression, and survival rates were investigated retrospectively.

Results. The overall response rate and the response rates for measurable metastatic lesions and primary sites were 43% (28/65), 48% (31/64), and 24% (10/42). Leucopenia of grade 4 and diarrhea of grade 3 or 4 were observed in 6 (9%) and 5 (8%) patients, respectively. Among the 19 patients with peritoneal metastasis, leucopenia of grade 4 and diarrhea of grade 3 or 4 were observed in only 1 of the 18 patients who received sufficient oral intake (6%). There were no treatment-related or early deaths within 30 days from the last treatment day. The median survival times of all patients, patients with an intestinal type of adenocarcinoma, and patients with a diffuse type were 365, 472, and 291 days, respectively. Multivariate analysis showed that the histological type of cancer was a significant independent prognostic factor ($P = 0.0169$).

Conclusion. This retrospective study confirmed the efficacy and feasibility of this combination therapy in clinical practice.

Key words Irinotecan · Cisplatin · Gastric cancer · Peritoneal dissemination · Intestinal type of adenocarcinoma.

Introduction

Cisplatin (CDDP) is an active agent against gastric cancer,¹ and some combination regimens that include this agent have been reported to show high response rates.^{2–5} However, none of the combination regimens have yet demonstrated a prolongation of survival as compared with 5-fluorouracil alone;^{6–8} accordingly new active chemotherapy regimens are needed. Irinotecan hydrochloride (CPT-11) is a water-soluble, semisynthetic derivative of camptothecin (CPT) that retains the original antitumor activity of CPT, but has lower toxicity.⁹ Its antitumor effects are due to the inhibition of DNA topoisomerase,^{10,11} and a response rate of 18% for gastric cancer patients has been reported in a phase II study, regardless of prior chemotherapy.¹² Combination chemotherapy of CPT-11 with CDDP was reported to be effective for metastatic gastric cancers, with a response rate of 48% (21/44) for all patients and 59% (17/29) for chemotherapy-naïve patients in a phase II study.¹³

However, this regimen has been reported to cause substantial toxicity, particularly neutropenia and diarrhea.¹⁴ These side effects are especially critical for patients with bowel obstruction, because SN-38, an active metabolite of CPT-11, is excreted to the duodenum via the bile duct and accumulates beyond the tolerable limit in such patients with bowel obstruction. Clinically, about half of the patients with gastric cancer have peritoneal dissemination. Moreover, antitumor effects may be assessed only in the primary tumor in most of them.¹⁵ A previous phase II study of CPT-11 in combination with CDDP provided insufficient information with respect to responses in primary sites in patients with peritoneal dissemination, because the number of chemotherapy-naïve patients was too small.

The aim of this retrospective study was to evaluate the efficacy and feasibility of this therapy in clinical practice and to identify the best candidates for receiving

Offprint requests to: M. Yoshida

Received: April 16, 2001 / Accepted: July 27, 2001

this combination among patients with advanced gastric cancer.

Patients and methods

Patients

Between April 1993 and March 1999, 500 patients with unresectable or recurrent gastric cancer were treated with chemotherapy at the National Cancer Center Hospital East. Of the 286 patients receiving first-line chemotherapy, 91 (32%) were treated with a combination of CPT-11 and CDDP. The subjects of this study were selected from these 91 patients, using eligibility criteria similar to those of the previous phase II study: (1) histologically proven gastric cancer with measurable or assessable lesions; (2) performance status (PS), on the Eastern Cooperative Oncology Group (ECOG) scale, of 2 or less; (3) age 75 years or younger; (4) adequate organ function, including bone marrow (white blood cells, $\geq 4000/\mu\text{l}$ and platelets, $\geq 100000/\mu\text{l}$), liver (serum bilirubin level, $\leq 1.5\text{ mg/dl}$; serum transaminase levels, $\leq$ three times the upper limit of the normal range), and renal (serum creatinine level, $\leq 1.5\text{ mg/dl}$; blood urea nitrogen, $\leq 25\text{ mg/dl}$; and creatinine clearance, $\geq 50\text{ ml/min}$); (5) normal electrocardiogram; (6) no serious complications; and (7) no other active malignancies. After the application of these criteria, 65 patients were the final subjects of this study.

Treatment schedule

The treatment schedule was the same as that used in the previous phase II study. On day 1, CPT-11, at 70 mg/m^2 , was administered by intravenous infusion for 90 min, followed by a 2-h infusion of CDDP, at 80 mg/m^2 , with adequate hydration, with a 2-h interval between CPT-11 and CDDP administration. The same dose of CPT-11 alone was administered on day 15. This schedule was repeated every 4 weeks until disease progression occurred, the patient refused further treatment, or unacceptable toxicity developed. If leucopenia or thrombocytopenia was grade 2 or higher, diarrhea was grade 1 or higher, or there was an episode of infection on day 15, the second administration of CPT-11 was postponed until recovery from these adverse events. The second dose of CPT-11 was not administered when the above adverse events continued beyond day 22. If any grade 4 hematological toxicity or grade 3 or 4 diarrhea occurred during the first 15 days, the second CPT-11 dose was skipped and the subsequent dose of CPT-11 was reduced to 60 mg/m^2 . After six courses of this regimen, the administration of CDDP was discontinued, and CPT-11 alone was administered every 2 weeks thereafter.

Granisetron was used routinely before the administration of CPT-11. Granulocyte colony-stimulating factor (G-CSF) was administered when necessary.

Evaluation of responses and adverse reactions

Objective responses to chemotherapy were evaluated according to the standard World Health Organization criteria for measurable metastatic lesions.¹⁶ For primary lesions, the responses were evaluated according to the criteria proposed by the Japanese Research Society for Gastric Cancer,¹⁷ using either gastroscopy or barium gastrography. These examinations were performed at least once for every two courses of treatment. Patients were followed every 2 weeks to assess any toxic side effects, and the Japan Clinical Oncology Group (JCOG) common toxicity criteria were adopted to evaluate the adverse reactions.¹⁸

Statistics

Survival time was calculated, by the Kaplan-Meier method, from the date of initiation of the first course of chemotherapy to the date of death from any cause, or to the last confirmation of survival. Time to progression (TTP) was measured from the date of initiation of treatment to the date of confirmation of progressive disease, first by image diagnosis and secondly by clinical diagnosis. Response duration was measured from the first date that a partial remission was achieved to the date of progression of the disease. Response rates, survival, TTP, and response durations were compared between patients with intestinal and diffuse types of gastric cancer, using χ^2 and log-rank tests. Multivariate analysis of prognostic factors was performed by the Cox proportional hazard method, with the variables of age (>60 , ≤ 60 years), sex (male, female), PS (0, 1, or 2), macroscopic type (expansive, infiltrative), histological type (intestinal, diffuse), history of gastrectomy (+, -) and presence or absence of organ metastasis.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 59 years, ranging from 26 to 74 years. Sixty-three (97%) patients had a performance status of 0 or 1. Histologically, 33 patients (51%) had intestinal types of adenocarcinomas, and 32 (49%) had diffuse types. Forty-two patients (65%) had no prior history of gastrectomy. Sixty-four patients (98%) had multiple measurable metastatic lesions. The sites of metastasis were lymph nodes in 54 patients (83%), the liver in 39 (60%), and the peritoneum in 19 (29%). Peritoneal

dissemination was diagnosed by the presence of ascites in 9 patients, by laparotomy in 6 patients, by barium enemas in 3 patients, and by the diagnosis of a peritoneal tumor by computed tomography scan in 1 patient. Although 64 patients had sufficient oral intake, 1 patient, with incomplete bowel obstruction caused by peritoneal metastasis, had insufficient oral intake. Twenty-eight of the 33 patients with intestinal type cancers (85%) showed a performance status of 0, compared with 20 of the 32 (63%) with diffuse types ($P = 0.0404$; Table 2). Second-line chemotherapy was administered to 25 patients (76%) with intestinal-type cancers and to 24 (75%) with diffuse types after failure of this treatment.

Adverse reactions

The median number of courses of treatment administered was four, ranging from one to seven. Table 3

Table 1. Patient characteristics

Characteristic	<i>n</i> = 65
Age (years); median (range)	59 (26–74)
Sex	
Male	47
Female	18
PS	
0	48
1	15
2	2
History of gastrectomy (+/–)	23/42
Metastatic site	
Peritoneum	19
Liver	39
Lymph node	54

PS, Performance status (Eastern Cooperative Oncology Group (ECOG) scale)

summarizes the adverse reactions observed during the courses of combination chemotherapy. Grade 4 leucopenia was observed in six patients (9%). Five patients (8%) suffered from grade 3 or 4 diarrhea. There were no treatment-related or early deaths within 30 days of the last treatment day. Among the 19 patients with peritoneal metastasis, grade 4 leucopenia and grade 3 or 4 diarrhea were observed in only 1 of the 18 patients with sufficient oral intake (6%), and both critical adverse reactions were observed in the patient with incomplete bowel obstruction.

Response

Of the 65 patients in this study, 2 had complete responses (3%) and 26 had partial responses (40%), giving an overall response rate of 43% (28/65). The response rate for measurable metastatic lesions was 48% (31/64), and that for primary sites was 24% (10/42) (Table 4). The response rates of the patients with intestinal type and diffuse type were almost equal, at 42% (14/33) and 44% (14/32), respectively (Table 5). The median response duration of the 28 responders was 194 days (range, 63–512 days), and the median response durations of the 14 patients with intestinal and the 14 with diffuse types of adenocarcinoma were 175 days

Table 3. Adverse reactions of grade 3 or 4

Adverse reaction (grade 3/4)	<i>n</i> = 65	Percentage
Leucopenia	23/6	45
Thrombocytopenia	4/1	8
Nausea/Vomiting	7/0	11
Diarrhea	4/1	8
Stomatitis	0/0	0
Renal dysfunction	0/0	0
Treatment-related death	0	0

Table 2. Patient characteristics and histology

Characteristic	Intestinal type <i>n</i> = 33	Diffuse type <i>n</i> = 32	<i>P</i> value
Age (years); median (range)	58 (26–71)	60 (26–74)	
Sex			
Male	24	23	
Female	9	9	0.9388
PS			
0	28	20	
1	4	11	0.0404
2	1	1	
History of gastrectomy (+/–)	12/21	11/21	>0.9999
Metastatic site			
Peritoneum	7	12	
Liver	21	18	0.4447
Lymph node	28	26	

Table 4. Response

	CR	PR	NC	PD	NE	RR
Overall	2	26	22	15	0	43% (28/65)
Primary	0	10	22	5	5	24% (10/42)
Metastatic site	5	26	21	12	0	48% (31/64)
Liver	3	16	13	6	0	49% (19/39)
Lymph node	5	17	26	7	0	43% (23/54)

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; RR, response rate

Table 5. Response and histology

	Histology	
	Intestinal	Diffuse
Overall	42% (14/33)	44% (14/32)
Primary	24% (5/21)	24% (5/21)
Metastatic site	53% (17/32)	44% (14/32)

Intestinal, Intestinal type of adenocarcinoma; diffuse, diffuse type of adenocarcinoma

(range, 63–456 days) and 195 days (range, 70–512 days), respectively. Response rates to the second-line chemotherapy in the 25 patients with intestinal type cancers and in the 24 with diffuse type were 1/25 (4%) and 1/24 (4%), respectively.

Survival and time to progression

With a median follow-up period in survivors of 21 months, the median survival time (MST) of all patients was 365 days (Fig. 1). Figure 2 shows the survival curves of the 33 patients with intestinal types of adenocarcinoma and the 32 patients with diffuse types of adenocarcinoma (MSTs were 472 and 291 days, $P = 0.0115$; 1-year survival rates were 57% and 44%; 2-year survival rates were 16% and 4%). The TTP of all subjects was 176 days, and those of the patients with intestinal and diffuse types were 182 and 142 days ($P = 0.6933$), respectively.

Multivariate analysis

Table 6 shows the result of multivariate analysis using a Cox proportional hazard model for survival time. Histological type (intestinal or diffuse) was a significant independent prognostic factor.

Discussion

About half of the patients receiving gastric cancer chemotherapy have bowel obstructions caused by peritoneal dissemination. Severe toxicity of CPT-11 is

Fig. 1. Overall survival curve of all patients **Fig. 2.** Survival curves of the 33 patients with intestinal types of adenocarcinoma (solid line) and the 32 patients with diffuse types of adenocarcinoma (dashed line)

reported in such patients. Therefore, in clinical practice at our institution, a combination of CPT-11 and CDDP was selected for the patients with measurable metastatic lesions, such as liver and/or lymph nodes. Patients with complete bowel obstruction were excluded from this regimen because of the risks of critical toxicity from CPT-11. Only one patient in our cohort was complicated with incomplete bowel obstruction. Neutropenia and diarrhea have been reported to be substantial toxicities of this regimen. Because this was a retrospective study, data on neutrophil counts were incomplete. The incidence of grade 4 leucopenia was 9% (6/65), which was similar to that noted in the previous phase II study. The incidences of grade 3 or 4 diarrhea were 8% (5/65) and 20% (9/44) in the present and previous phase II studies, respectively. Differences in the monitoring and in the evaluation of clinical symptoms seemed to cause

Table 6. Prognostic factors in multivariate analysis

Variables	P value
Sex	0.7507
Age	0.4737
PS	0.0753
Macroscopic type	0.2734
Histological type	0.0169
History of gastrectomy	0.2088
Tumor extent	0.2678

this discrepancy. Both grade 4 leucopenia and diarrhea were observed in the only patient with incomplete bowel obstruction in this study, and the toxicity in patients with peritoneal dissemination was acceptable in those who had sufficient oral intake. No treatment-related or early deaths were observed. The above results have confirmed the feasibility of this regimen in clinical practice, and we therefore consider that this combination chemotherapy may be feasible even in patients with peritoneal dissemination, as long as they are not complicated by bowel obstruction.

We have reported that a response in the primary site may be an indicator of long-term survival,¹⁹ although this relationship has been reported only in Japan. In the present study, the response rate for measurable metastatic lesions was 48% (31/64) and the response rate was 24% (10/42) in primary sites. The response rate in primary sites in this study was comparable to that reported for a combination of 5-fluorouracil and CDDP.⁵

The MST of all subjects in the present study was 365 days. These results recapitulated the favorable antitumor effects and survival outcomes reported in the previous phase II study (response rate, 17/29 [59%]; MST, 322 days).¹³ Considering that MSTs in other clinical trials of chemotherapy for advanced gastric cancer have ranged from 7 to 10 months,^{8,20–22} it appears that this regimen may yield favorable survival rates, even in clinical practice.

In the present study, patients with intestinal type cancers survived longer than those with diffuse types (MST, 472 and 291 days, respectively; $P = 0.0115$). Because there were no differences in response rate, PR duration, and TTP between these two groups, it is considered that the favorable survival in the patients intestinal-type cancers was probably not a result of differences in antitumor effects between these groups. In addition, it appeared that the survival impact of second-line chemotherapy was negligible, because the numbers of patients with each of the two types of cancers receiving the treatment, and the poor response rates, were similar for these two groups. A difference in the PS of the patients between the two groups, a result of this being a retrospective study, suggests that there may be a kind of

selection-based bias behind this favorable survival in the intestinal group. This factor should be investigated in the on-going phase III trial of the JCOG that is comparing continuous infusion of 5-fluorouracil, a combination of CPT-11 and CDDP, with 1M tegafur, 0.4M gimestat, and 1M otastat potassium (S-1).

In conclusion, this retrospective study recapitulated the results of the previous phase II study of a combination of CPT-11 and CDDP, with respect to efficacy and feasibility. This regimen is also a feasible treatment option for patients with peritoneal dissemination, provided they can have sufficient oral intake.

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