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Original article

Second-line chemotherapy with irinotecan plus cisplatin after the failure of S-1 monotherapy for advanced gastric cancer

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Abstract

Background. **For advanced gastric cancer (AGC), second-line chemotherapy after the failure of S-1 has not yet been established. The present study aimed to retrospectively evaluate the efficacy and safety of irinotecan plus cisplatin (IP) therapy after the failure of S-1 in patients with AGC.**

Methods. **The subjects included 87 patients with AGC who received IP therapy as second-line chemotherapy. Irinotecan (70 mg/m^2) was administered by intravenous infusion followed by an intravenous infusion of cisplatin (80 mg/m^2) on day 1. On day 15, irinotecan (70 mg/m^2) alone was administered. The treatment was repeated every 4 weeks until disease progression, patient refusal, or severe adverse events.**

Results. **The median patient age was 62 years (range, 39–75 years), and the median number of treatment cycles was 3 (range, 1–9). Out of the 87 patients, 70 were assessable for clinical response. There were 2 complete responses and 18 partial responses. The overall response rate was 28.6% (95% confidence interval [CI], 18.4%-40.6%) and the disease control ratio was 70.0%. The median time to progression and median survival time from the first day of IP therapy were 4.3 months and 9.4 months, respectively. The 1-year survival rate was 34.6%. Severe (grade 3/4) leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 34%, 40%, 28%, and 8% of patients, respectively. Grade 3/4 nonhematologic toxicities included anorexia (17%), febrile neutropenia (10%), diarrhea (6%), fatigue (5%), nausea (2%), and elevated creatinine (1%).**

Conclusions. **The combination of irinotecan plus cisplatin as second-line chemotherapy for AGC appears to be an effective and feasible treatment option after S-1 failure.**

Key words Irinotecan · Cisplatin · Gastric cancer · Second-line chemotherapy · S-1 failure

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Introduction

For the first-line treatment of advanced gastric cancer (AGC), the Japan Clinical Oncology Group (JCOG) reported the results of a three-arm phase III study comparing 5-fluorouracil (5-FU), irinotecan hydrochloride (CPT-11) plus cisplatin (CDDP) combination chemotherapy (IP), and S-1 [1]. The results showed that IP therapy did not demonstrate statistically significant superiority to 5-FU (median survival time [MST], 12.3 months vs 10.8 months; $P = 0.055$), although it was potentially promising.

In contrast, S-1 showed significant noninferiority to 5-FU (MST, 11.4 months vs 10.8 months; $P < 0.001$). Furthermore, Koizumi et al. [2] reported that in the S-1 plus CDDP versus S-1 in RCT in the treatment for stomach cancer (SPIRITS) trial, S1 plus CDDP established superiority over S-1 monotherapy (MST, 13.0 months vs 11.0 months, respectively; $P = 0.037$). However, another phase III study, comparing S-1 and S-1 plus CPT-11 (GC0301/TOP-002 trial), could not demonstrate a significant survival benefit for S1 plus CPT-11 [3].

According to these results, S-1 plus CDDP is suitable for first-line chemotherapy for AGC, and CPT-11-based regimens failed as first-line chemotherapy. Additionally, Sakuramoto et al. [4] have reported that S-1 is effective as adjuvant chemotherapy in patients who have undergone curative gastrectomy for locally advanced gastric cancer (adjuvent chemotherapy trial of TS-1 for gastric cancer; ACTS-GC-trial). Thus, S-1 is currently used for gastric cancer in both first-line and adjuvant settings. As such, it is expected that the number of S-1-refractory cases will increase in the near future, and therefore, establishing second-line chemotherapy for S-1-refractory AGC is very important.

However, there are few data for second-line IP therapy for AGC refractory to S-1. Therefore, we decided to retrospectively evaluate the efficacy and

safety of IP therapy in 87 patients who received IP therapy only after failure of S-1 monotherapy.

Patients, materials, and methods

Patient information

The subjects in this retrospective study included 87 patients with primary AGC who received IP therapy as second-line chemotherapy for unresectable or recurrent tumors at the National Cancer Center Hospital (Tokyo, Japan) between March 2001 and January 2007. The following inclusion criteria were used: (1) histologically proven adenocarcinoma of the stomach; (2) age 75 years or younger; (3) performance status (Eastern Cooperative Oncology Group) 0 to 2; (4) refractory to or unable to tolerate prior chemotherapy with S-1 monotherapy (given in 6-week cycles; 4 weeks of S-1 administration and 2 weeks' rest); (5) adequate organ function; (6) lack of massive ascites; and (7) written informed consent.

Treatment schedule

On day 1, CPT-11 (70 mg/m^2) was administered by intravenous infusion for 90 min, followed by intravenous infusion of CDDP (80 mg/m^2) for 120 min with adequate hydration. On day 15, CPT-11 (70 mg/m^2) alone was administered. The treatment was repeated every 4 weeks until disease progression, patient refusal to receive further treatment, or the occurrence of severe adverse event(s). Administration of CPT-11 on day 15 was delayed in the case of leukopenia or thrombocytopenia of grade 2 or more, diarrhea of grade 1 or more, or infection, until recovery from these adverse reactions. If the adverse reaction continued beyond day 22, CPT-11 was not given. If grade 4 leukopenia or thrombocytopenia or any grade 3/4 nonhematologic adverse reaction occurred, the doses of CPT-11 and CDDP were reduced to 60 mg/m^2 and 70 mg/m^2, respectively. If one of these severe adverse reactions occurred a second time, treatment was stopped. And if severe renal dysfunction (serum creatinine >2.0 mg/dl) developed, CDDP administration was halted, and CPT-11 monotherapy was continued until progression.

Clinical evaluation

Clinical response in measurable lesions was evaluated every 8 weeks by computed tomography (CT) using the Response Evaluation Criteria in Solid Tumors. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. We defined overall survival (OS) as the number of days between the date of initial chemotherapy and the date of death or last follow-up visit. Time to progression was also measured from the beginning of treatment to the date of disease progression, which was evaluated by each physician. Survival analysis was performed using the Kaplan-Meier method, and differences between curves were analyzed using the log-rank test. The time to an event was calculated beginning with the start of treatment. All analyses were performed using the statistical software package StatView, version 5.0 (SAS Institute, Cary, NC, USA).

Results

Clinicopathological features

Patient clinicopathological characteristics are listed in Table 1. Between May 2000 and October 2006, 427 patients with AGC received first-line S-1 monotherapy. After failure, 298 patients subsequently received second-line chemotherapy. Of these, 96 patients received IP therapy, and we evaluated 87 patients who fulfilled the inclusion criteria (the excluded patients consisted of 7 patients aged >75 years and 2 who did not have adenocarcinoma). The primary reasons for discontinuation of S-1 therapy were progressive disease (n = 80 [92%]); followed by adverse events (n = 6 [7%]), including acneiform eruption (n = 3), anorexia (n = 2), edema (n = 1), and diarrhea (n = 1); and patient refusal (n = 1 [1%]). The median number of prior S-1 courses administered was 3 (range, 1–16). The median follow-up was 5.0 years (range, 2.4–8.2 years). The median number of IP cycles administered after S-1 failure was 3 (range, 1–9 cycles; total, 300 cycles).

Table 1. Patient characteristics (n = 87)

Factor	No. of patients	Percentage
Age		
Median (years)	62 (39–75)	
Sex		
Male	65	75
Female	22	25
ECOG performance status		
0/1/2	29/53/5	
Histological type		
Intestinal	46	53
Diffuse	41	47
Metastatic site		
Lymph node	53	61
Liver	44	51
Peritoneum	20	23
Lung	7	8
Bone	1	1
Discontinuation of S-1 therapy		
PD	80	92
Adverse event	6	7
Patient refusal	1	1

ECOG, Eastern Cooperative Oncology Group; PD, progressive disease

Table 2. Overall response ($n = 70$)

CR	PR	SD	PD	RR	DCR
2	18	29	21	28.6%[a]	70.0%[b]

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; DCR, disease control ratio (CR+PR+SD/all)
[a] 95% confidence interval (CI): 18.4–40.6
[b] 95% CI: 57.9–80.4

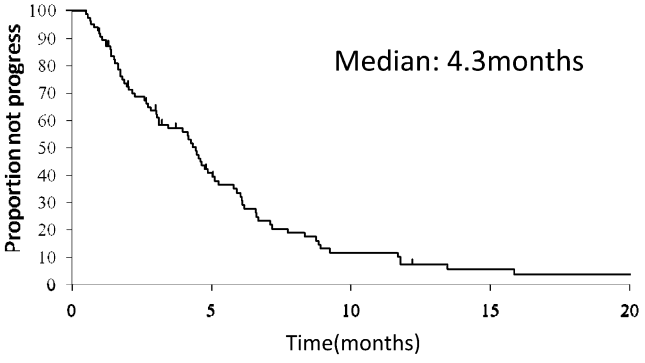

Fig. 1. Time to progression

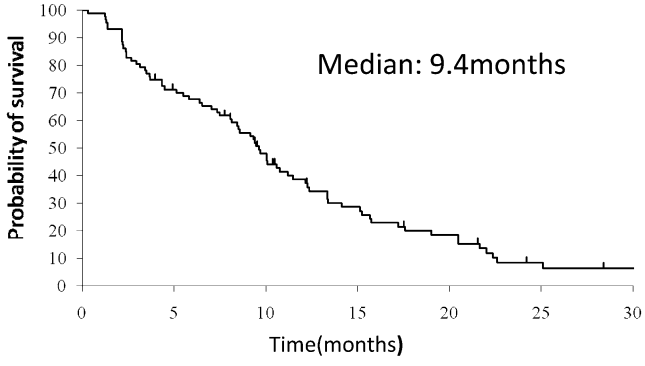

Fig. 2. Overall survival

Response and survival

A total of 70 patients had measurable lesions and were assessable for clinical response. There were 2 complete responses (CRs) and 18 partial responses (PRs). The overall response rate (ORR) was 28.6% (95% CI, 18.4–40.6%), and the disease control ratio was 70.0% (Table 2). The median time to progression (TTP) and MST from the first day of IP therapy were 4.3 months and 9.4 months, respectively (Figs. 1, 2). In addition, the MST from the first day of first-line S-1 was 14.3 months. The 1-year survival rate was 34.6%.

Toxicities

Toxicities experienced by patients treated with IP therapy are summarized in Table 3. Severe (grade 3/4) leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 34%, 40%, 28%, and 8% of patients, respectively. Grade 3/4 nonhematologic toxicities included anorexia (17%), febrile neutropenia (10%), diarrhea (6%), fatigue (5%), nausea (2%), and elevated creatinine (1%).

Table 3. Adverse events ($n = 87$)

Grade	0/1	2	3	4	Grade ≥3 (%)
Leukopenia	38	19	24	6	34
Neutropenia	44	8	11	24	40
Anemia	42	21	18	6	28
Thrombocytopenia	73	7	5	2	8
Anorexia	52	20	15	0	17
Nausea	75	10	2	0	2
Diarrhea	76	6	5	0	6
Neutropenic fever	—	—	8	1	10
Fatigue	60	23	4	0	5
Creatinine	76	10	1	0	1

There were four patients (5%) who died less than 30 days from the initiation of therapy; one death was due to febrile neutropenia and infection, while the three other deaths were assumed to have been due to rapidly progressive disease.

Reasons for discontinuation and additional chemotherapy administered

The primary reasons for discontinuation of IP therapy were progressive disease ($n = 73$ [84%]), followed by adverse events ($n = 9$ [10%]), including renal dysfunction ($n = 4$), neutropenia ($n = 1$), anorexia ($n = 1$), liver dysfunction ($n = 1$), acneiform eruption ($n = 1$), anaphylactic shock ($n = 1$), patient refusal ($n = 4$ [5%]), and discontinuation because of CR ($n = 1$ [1%]).

A total of 46 (53%) patients received additional chemotherapy. The most commonly used regimens were paclitaxel monotherapy ($n = 37$ [80%]), docetaxel monotherapy ($n = 6$ [13%]), and mitomycin C (MMC)-based therapy ($n = 3$ [7%]).

Discussion

The clinical value of second-line chemotherapy for AGC remains controversial. However, in Japan, CPT-11 is widely used both as a single agent and as combined therapy with CDDP or MMC [5, 6]. Futatsuki et al. [7] reported that CPT-11 monotherapy (100 mg/m^2, weekly or 150 mg/m^2, biweekly) achieved ORRs of 20% (9/45) in previously treated gastric cancer patients, and 18.9% (7/37) in patients who were only pretreated with 5-FU. CPT-11 monotherapy therefore appears to be somewhat effective for 5-FU-refractory gastric cancer. In a more recent randomized phase III study, albeit of small

sample size (n = 40), Thuss-Patience et al. [8] reported that second-line CPT-11 monotherapy (250 to 350 mg/m^2, triweekly) significantly prolonged overall survival (OS) compared to best supportive care (BSC); the median survival in the CPT-11 arm was 123 days compared to 72.5 days for BSC; OS, hazard ratio [HR] = 2.85 (95% CI, 1.41–5.79); P = 0.0027. These results indicate that second-line chemotherapy using CPT-11 can now be considered as a treatment option in GC.

There have been two phase II studies evaluating IP therapy. Boku et al. [9] reported an ORR of 26.7% (4/15), and Ajani et al. [10] reported an ORR of 31% (9/29) and an MST of 5 months for AGC refractory to 5-FU therapy. In addition, in a retrospective study, Ueda et al. [11] reported a 28% (8/28) ORR, a progression-free survival (PFS) of 3.4 months, and an MST of 9.4 months.

Our present study had a selection bias, with comparatively few patients (23%) having peritoneal metastases, because such cases tend to be treated with taxanes; however, our results (28.6% ORR, TTP of 4.3 months, MST of 9.4 months, and 34.6% 1-year survival rate) indicate that second-line IP therapy for AGC appears to provide almost the same efficacy as that seen in other second-line trials, even for patients who have experienced S-1 failure.

We also demonstrated greater feasibility for IP therapy by using it in a second-line rather than first-line setting. In the first-line setting, IP therapy did not show statistically significant superiority to 5-FU because of its toxicity; more than 30% of patients receiving IP therapy discontinued for toxicity-related reasons, as opposed to fewer than 10% stopping for toxicity due to 5-FU and S-1 [1]. In the present study, grade 3/4 leukopenia or neutropenia were relatively mild, and only 10% of patients stopped treatment because of toxicity-related reasons. The reasons for these results may be that first, the duration of IP therapy is shorter in the second-line setting than in the first-line setting, and, second, in this study, dose reduction and discontinued treatment were carried out exactly according to protocol.

Another recent well-known IP regimen is biweekly CPT-11+CDDP. Koizumi et al. [12] reported on their phase I/II study using it as first-line therapy, where CPT-11 (60 mg/m^2) and CDDP (30 mg/m^2) were administered on days 1 and 15. In 2008, Nakae et al. [13] reported a phase II study of biweekly IP after S-1 failure. The ORR was 28.6%, and the median OS was 389 days. The most common grade 3/4 toxicities were: neutropenia (22.9%), anemia (11.4%), anorexia (14.3%), fatigue (8.6%), and diarrhea (2.9%). The efficacy and toxicity of this biweekly regimen were almost the same as those seen in our study. The biweekly regimen is available for outpatients; however, there are no phase III data on this regimen.

Currently, either CPT-11 (monotherapy or combined with CDDP) or taxanes [14–16] would be selected as second-line chemotherapy for AGC. However, it is not yet clear which of these regimens is most effective. Therefore, there are some currently ongoing clinical trials on the second-line treatment of AGC (after S-1 or S-1+CDDP failure), including phase III studies comparing CPT-11 and paclitaxel, CPT-11 alone and CPT-11+CDDP, CPT-11 alone and CPT-11+S-1, and so on. The results are anxiously awaited.

In conclusion, the combination of CPT-11 and CDDP as second-line chemotherapy for AGC appears to be effective and feasible, and should therefore be considered as a promising treatment option for patients who have experienced S-1 failure. Because CDDP has been widely used as first-line treatment for AGC patients, this regimen is suitable for patients who failed S-1 monotherapy used as adjuvant chemotherapy.

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