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Original article

Long-term outcome of S-1 and cisplatin combination therapy in patients with advanced or recurrent gastric cancer

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Abstract

Background. **Although combination therapy of S-1 and cisplatin (CDDP) has excellent efficacy against gastric cancer, the effect of the treatment on survival has been unclear. The aim of this study was to evaluate the long-term outcome of this combination therapy.**

Methods. **Sixty-three patients with advanced or recurrent gastric cancer were treated with S-1, with or without CDDP, as first-line chemotherapy, and the clinical results were compared retrospectively. S-1 was administered orally at a standard dose of 80 mg/m^2. In the treatment of the S-1 group, S-1 was given for 28 consecutive days, followed by a 14-day rest. In the treatment of the S-1/CDDP group, S-1 was given for 21 consecutive days, followed by a 14-day rest, and CDDP, at 60 mg/m^2, was infused on day 8.**

Results. **The incidence of adverse reactions of more than grade 3 was 22.5% in the S-1 group and 43.5% in the S-1/CDDP group, and the treatment compliance was better in the S-1 group. The overall response rate was 25.9% in the S-1 group, and 36.8% in the S-1/CDDP group. The combination of S-1 with CDDP had better effects on the primary lesion and on differentiated-type carcinoma than S-1 alone. However, there was no difference in survival between the two patient groups. The median survival time after the initiation of treatment in the S-1 group was 322 days, and that in the S-1/CDDP group was 319 days.**

Conclusions. **Our results suggest that the combination of CDDP with S-1 does not improve the long-term outcome of S-1 therapy.**

Key words S-1 · Cisplatin · Gastric cancer

Introduction

Fluorouracil (5-FU) has been widely used as a key drug against gastrointestinal cancer for some decades, and chemotherapy regimens using biochemical modulation and/or combination therapies have improved the prognosis of patients with gastric cancer. S-1 is an oral anticancer agent that was developed based on the theory of the biochemical modulation of 5-FU. S-1 is composed of tegafur (FT, a prodrug of 5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo), at a molar ratio of 1:0.4:1 [1]. CDHP inhibits the biodegradation of 5-FU, and Oxo reduces 5-FU-induced gastrointestinal toxicities. In summary, S-1 not only increases the anticancer activity but also reduces the adverse reactions of 5-FU. In clinical studies, as a single agent, S-1 has demonstrated a higher response rate against gastric cancer compared to any other anticancer agent [2-4]. S-1 has become one of the drugs used in first-line chemotherapy for advanced or recurrent gastric cancer in Japan.

In an attempt to increase the efficacy of S-1, several combination chemotherapy regimens using S-1 have been examined, and cisplatin (CDDP) has received attention as a result of its remarkable activity. Koizumi et al. [5] performed a phase I/II study of S-1 plus CDDP for patients with advanced gastric cancer. S-1 was administered at a standard dose for 3 weeks, and the recommended dose of CDDP, infused on day 8, was 60 mg/m^2; this study revealed an overall response rate of 74%. Baba et al. [6] treated 12 patients using the same schedule, and showed a response rate of 66.7%. These results suggested the excellent therapeutic efficacy of the combination of S-1 and CDDP in the treatment of gastric cancer. However, the effect of the combination therapy on survival has been unclear.

The aim of the present study was to evaluate the long-term outcome of combination therapy of CDDP and S-1. We compared, retrospectively, the clinical results of treatment with S-1 alone and treatment with S-1 plus CDDP in patients with advanced or recurrent gastric cancer who were treated in our hospital.

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Patients and methods

Patients

Patients who satisfied all of the following requirements were eligible for this study: (1) advanced or recurrent gastric cancer, which was histologically confirmed; (2) no prior therapy, except for adjuvant chemotherapy; (3) adequate bone marrow, liver, and kidney function; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; and (5) life expectancy of 3 months or more. All patients provided informed consent, and agreed to be selected for either of the two regimens, by the patient's or doctor's choice.

Treatment regimens

In the treatment regimen of S-1 alone (S-1 group), S-1 was orally administered for 28 consecutive days, followed by a 14-day rest. The dose of S-1 was based on the body surface area (BSA), as follows: 80 mg/day for patients with a BSA of less than 1.25 m^2, 100 mg/day for those with a BSA of 1.25–1.5 m^2, and 120 mg/day for those with a BSA of more than 1.5 m^2. This schedule was repeated every 6 weeks. In the treatment regimen of S-1 combined with CDDP (S-1/CDDP group), S-1 was given at the same dose as that in the S-1-alone regimen, for 21 consecutive days, followed by a 14-day rest. CDDP, at 60 mg/m^2, was infused over a 2-h period, with adequate hydration, on day 8. This schedule was repeated every 5 weeks. When adverse reactions appeared, the dose was reduced and/or treatment was interrupted according to the oncologist's considerations. Each treatment was repeated until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal.

Adverse reactions

Adverse reactions were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Evaluation of response

For the primary gastric lesions, the response was assessed by the criteria of the Japanese Research Society for Gastric Cancer, using gastrography or gastroscopy. The response of metastatic lesions was assessed by World Health Organization (WHO) criteria, using computed tomography or ultrasonography. The overall response was assessed according to the WHO criteria. The response rate was defined as: response rate (%) = (number of patients with complete response [CR] and partial response [PR] after treatment/number of patients evaluated) × 100. Survival time was calculated as the time from the date of the beginning of the first course of treatment to the date of death from any cause, or to the date of the last confirmation of survival. The overall survival was calculated using the Kaplan-Meier method.

Statistical analysis

The mean ages of the patients in the two groups were compared by Student's *t*-test. The frequency distributions of the patients' characteristics were compared by the χ^2 test. Differences between the survival curves were assessed using the log-rank test.

Results

Patient characteristics

From January 2000 to December 2003, 63 patients with advanced or recurrent gastric cancer were treated with S-1, with or without CDDP, as first-line chemotherapy at our hospital. Forty patients were treated with S-1 alone, and 23 patients were treated with S-1 combined with CDDP. Patients' clinical features are shown in Table 1. Advanced cancer was defined as inoperable or unresectable disease. Prior gastrectomy had been performed in 19 patients in the S-1 group — 13 with recurrence after curative resection and 6 with non-curative resection. In the S-1/CDDP group, 10 patients had received prior gastrectomy, as curative resection in 5 patients and noncurative resection in 5. In regard to definition of histological type, differentiated type included well- and moderately differentiated tubular adenocarcinoma, and undifferentiated type included poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma. The major sites of metastases were the liver, lymph nodes, and peritoneum. There were no differences between the two groups in terms of age, sex, PS, disease status, prior gastrectomy, metastatic sites, or histological types.

Compliance

Compliance with the regimens, and reasons for patients' discontinuation of treatment were compared between the two groups. The mean treatment duration with S-1 alone was 160 days, and that with S-1 plus CDDP was 127 days. Treatment for more than 6 months was completed in 15 of the 40 patients in the S-1 alone group (37.5%) and in 7 of the 23 in the combination group (30.4%). Treatment was discontinued because of toxicity, tumor progression, or the patient's refusal. Toxicity was the cause of the treatment discontinuance in 22.5%

Table 1. Patient characteristics

	S-1 (n = 40)	S-1/CDDP (n = 23)	P value
Age (years; mean ± SD)	67.7 ± 9.4	63.9 ± 10.2	0.1300
Sex			
Male	27	14	0.5951
Female	13	9	
ECOG PS			
0	21	12	0.9208
1	18	10	
2	1	1	
Disease status			
Advanced	27	18	0.3627
Recurrent	13	5	
Prior gastrectomy			
−	21	13	0.7578
+	19	10	
Metastasis site			
Liver	9	11	0.1949
Lymph node	22	9	
Peritoneum	18	8	
Others	5	5	
Histological type			
Differentiated	18	12	0.6468
Undifferentiated	22	11	

Table 2. Adverse reactions of grade 3 or 4

	Incidence (%)	
Toxic effects	S-1 (n = 40)	S-1/CDDP (n = 23)
Leukopenia	0	1 (4.3%)
Neutropenia	3 (7.5%)	6 (26.1%)
Anemia	1 (2.5%)	2 (8.7%)
Thrombocytopenia	0	1 (4.3%)
Anorexia	2 (5.0%)	2 (8.7%)
Diarrhea	1 (2.5%)	1 (4.3%)
Eruption	2 (5.0%)	1 (4.3%)
Mucositis	1 (2.5%)	0
Total	9 (22.5%)	10 (43.5%)

of patients in the S-1 group and in 26.1% of the patients in the S-1/CDDP group.

Adverse reactions

Table 2 summarizes the adverse reactions of grade 3 or 4 that were observed during all treatment courses in the two groups. Bone marrow suppression, anorexia, diarrhea, eruption, and mucositis were observed. The incidence of adverse reactions of more than grade 3 was 22.5% in the S-1 group and 43.5% in the S-1/CDDP group. Bone marrow suppression was more severe in the combination treatment group, and grade 4 neutropenia was observed in two patients in this group. None of the patients treated with S-1 alone showed grade 4 toxicity. There were no toxicity-related deaths.

Table 3. Overall response to the treatments

	CR	PR	NC	PD	NE	RR (%)
S-1	0	7	9	9	2	25.9
S-1/CDDP	0	7	5	5	2	36.8

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

Treatment efficacy

Efficacy was evaluated in those patients who had received the treatment regimen for at least one course (33 patients in the S-1 group and 22 patients in the S-1/CDDP group). Tumor response was evaluated in the patients who had assessable lesions (27 patients in the S-1 group and 19 patients in the S-1/CDDP group). The overall response rate was 25.9% in the S-1 group, and 36.8% in the S-1/CDDP group (Table 3). The results of tumor response, assessed by target organ and histological type, are shown in Tables 4 and 5. In the S-1 group, response rates were 11.7% for the primary lesion, 40.0% for liver, and 28.5% for lymph nodes. In the S-1/CDDP group, these rates were 35.7%, 40.0%, and 28.5%, respectively. There were two CRs in the primary tumors treated by the combination therapy. The effect of the combination treatment on the primary tumors was better than that of S-1 alone. There was no difference between the groups in response rates for undifferentiated type carcinoma: 35.2% with S-1 alone and 37.5% with S-1 plus CDDP. For differentiated type carcinoma, however, the combination therapy increased the rate to 36.3%, compared with that of 10.0% with S-1 alone.

Figure 1 shows the survival of the patients in the two treatment groups; there was no difference between the groups. The median survival time (MST) after the initiation of treatment in the S-1 group was 322 days, and that in the S-1/CDDP group was 319 days. The 1-year survival rates were 48% and 40%, respectively.

Discussion

Chemotherapy has contributed to an improvement of treatment outcome in gastric cancer [7]. It has been demonstrated that chemotherapy provides a significant advantage over best supportive care in patients with advanced or recurrent gastric cancer [8,9]. Several second-generation regimens, such as FAMTX (5-FU, doxorubicin, methotrexate) and FP (5-FU, CDDP), have demonstrated relatively high response rates [10–13], but none of these has had a satisfactory impact on survival. S-1, even when used alone, is comparable in efficacy to the above combination therapies. Several clinical trials have revealed that S-1 alone showed high response rates, of up to approximately 50%, and favorable survival rates [3,4]. A post-marketing survey of S-1 in Japan revealed a response rate of 43% and an MST of 337 days [14]. Indeed, S-1 has become a key drug in the treatment of advanced and recurrent gastric cancer in Japan.

Because the efficacy of S-1 was shown to be outstanding, it was expected that combination therapy using S-1 would give further benefit. Among several drugs considered, CDDP attracted attention as an agent for the combination, because the clinical effects of 5-FU are enhanced by combination with CDDP [15]. Koizumi et al. conducted a phase I/II study of a combination of S-1 and CDDP, and reported a significantly high response rate [5]. Therefore, it seemed appropriate to evaluate the clinical outcome of combined treatment with CDDP and S-1 in patients with advanced or recurrent gastric cancer.

We studied, retrospectively, the clinical effects of treatment of S-1 with or without CDDP. The results showed that survival was not improved by CDDP, compared to that with S-1 alone. One of the reasons why CDDP did not contribute to the long-term outcome may have been poor compliance with the treatment regimen. The treatment was interrupted because of toxicity in about one of four patients in the S-1/CDDP group, and the treatment duration was shorter

Table 4. Tumor response in the S-1 group

	CR	PR	NC	PD	NE	RR (%)
Site of disease						
Primary tumor	0	2	6	2	7	11.7
Liver	0	2	1	2	0	40.0
Lymph node	0	4	4	5	1	28.5
Histological type						
Differentiated	0	1	4	4	1	10.0
Undifferentiated	0	6	5	5	1	35.2

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

Table 5. Tumor response in the S-1/CDDP group

	CR	PR	NC	PD	NE	RR (%)
Site of disease						
Primary tumor	2	3	2	0	7	35.7
Liver	0	4	2	4	0	40.0
Lymph node	0	2	2	2	1	28.5
Histological type						
Differentiated	0	4	3	3	1	36.3
Undifferentiated	0	3	2	2	1	37.5

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

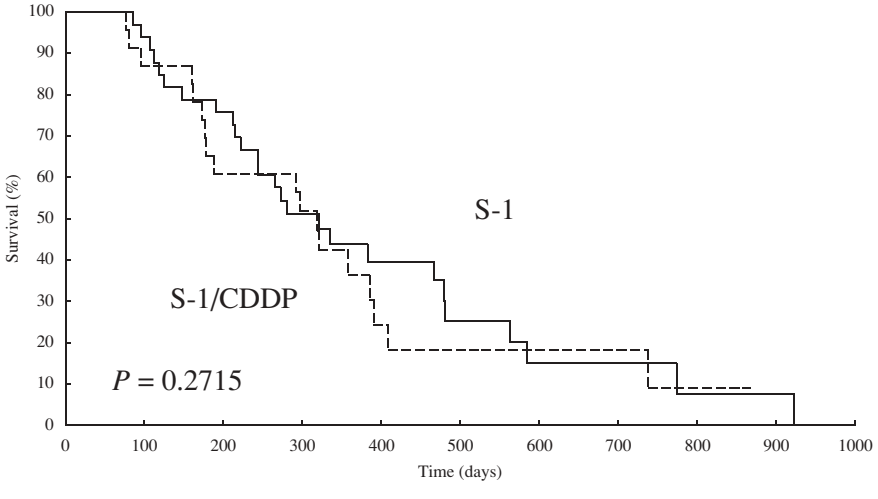

Fig. 1. Survival of the patients in the *S-1* group and the *S-1*/cisplatin (*CDDP*) group. *Continuous line*, S-1; *dashed line*, S-1/CDDP; *S-1*, tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate

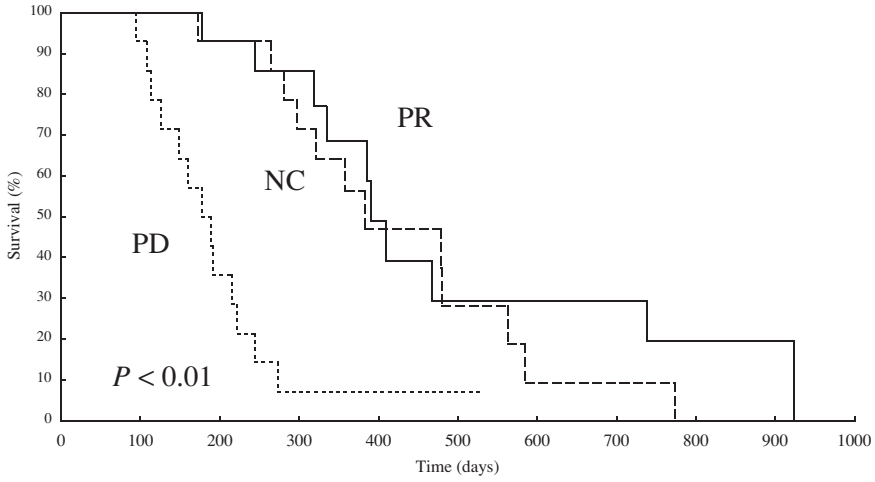

Fig. 2. Survival of the patients according to response to the treatments. *Continuous line*, partial response (*PR*); *long-dash line*, no change (*NC*); *short-dash line*, progressive disease (*PD*)

than that in the S-1 group. The combination with CDDP reduced the compliance of the S-1 regimen. For improving prognosis, it is important to treat patients for a long period with a treatment regimen that has good compliance and high efficacy. Another reason for the discrepancy between the tumor response by the combined regimen and its lack of effect on survival may be the fact that tumor reduction does not always produce prolonged survival. Figure 2 shows the survival of the two groups of patients in our study, stratified according to the response to the treatment. The prognosis of the patients with progressive disease (PD) was worse compared to the prognosis of those with no change (NC) or PR, but there was no difference between the survival of the patients with NC and that of the patients with PR. For improving the survival time, tumor reduction may not always be necessary, and inhibition of tumor growth may be sufficient. Our data on tumor response showed similar disease control rates (rates of patients with CR, PR, and NC) in the two treatment groups: 64.0% in the S-1 group and 70.6% in the S-1/CDDP group. In summary, the disease control rate rather than the response rate seems to correlate with the effect of treatment on survival.

Because our study was not a randomized control trial, the usefulness of CDDP in prolonging long-term outcome remains unclear, and its efficacy should be evaluated in a prospective randomized study. A clinical phase III trial comparing S-1 and S-1 plus CDDP, (with the same treatment schedule of S-1 in both arms) for advanced and recurrent gastric cancer has been conducted in Japan, and the usefulness of the combination with CDDP will be evaluated appropriately in the near future.

Even if CDDP is not useful for prolonging long-term outcome in combination with S-1, this combination regimen appears to be promising for neoadjuvant chemotherapy (NAC) against advanced gastric cancer. A regimen for NAC is required to produce a high response rate, to increase the resectability of tumor, and not to induce severe toxicity that may delay surgery. Our data showed that the combination of S-1 and CDDP produced satisfactory responses to both the primary lesion and metastatic lesions, with tolerable adverse reactions. A response to NAC was reported to be able to predict prognosis in patients with advanced gastric cancer [16]; therefore, an effective neoadjuvant regimen may lead to further improvement of the prognosis. For establishing a standard regimen for NAC in patients with advanced or recurrent gastric cancer, further study to determine the optimal regimens, including the study of S-1/CDDP, is necessary.

Modification of CDDP administration in combination with S-1 has also been investigated. It was reported that middle-dose-weekly and low-dose-daily regimens also produced high response rates in phase I and II studies [17–19]. Furthermore, several trials have been conducted using taxanes (docetaxel and paclitaxel) or irinotecan in combination with S-1. These studies are expected to demonstrate further improvement in both tumor response and patient survival.

It is clarified that S-1 has powerful potential and impact in the treatment of gastric cancer, and combination therapy appears to be hopeful. Therefore, establishment of a treatment regimen in which S-1 can be administered for a long period may contribute to the achievement of a favorable survival period.

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