ANTICANCER RESEARCH *25*: 1297-1302 (2005)

A Phase II Multicentric Trial of S-1 Combined with 24 h-infusion of Cisplatin in Patients with Advanced Gastric Cancer*

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Abstract. *Background: The aim of this multicentric trial was to determine the clinical toxicities and antitumor effects of a chemotherapy regimen of S-1 combined with cisplatin in patients with inoperable locally or metastatic advanced gastric cancer. Patients and Methods: Forty-two patients were entered into the study. S-1 (80 mg/m^2) was administered orally daily for 14 consecutive days and 24-h infusion of cisplatin (70 mg/m^2) was administered on day 8 of every 28-day cycle. Results: The overall response rate was 50% and complete response rate was 5%. The most common adverse event was leucopenia, which occurred with grade 3 in 7 patients (16.6%) and grade 4 in 2 patients (4.8%). Non-hematological adverse events were generally mild. The median survival time was 342 days. The 2-year survival rate was 22.9%. Conclusion: This combination chemotherapy is active, convenient and well tolerated in patients with high-grade advanced gastric cancer.*

Synthesized by Duschinsky *et al.* in 1957, 5-fluorouracil ¦(5-FU) (1, 2) has been used widely for the treatment of various types of solid tumors. Since this drug has a short plasma half-life, many schedules for 5-FU administration have been investigated: continuous venous infusion (CVI) has shown the best antitumor effect (3). However, CVI of 5-FU restricts the quality of life of patients as it requires venous access and the use of a portable infusion pump. The dose administered is also limited by high incidences of mucositis, hand-foot syndrome and diarrhea (3, 4).

Oral treatment is an attractive modality, since it is easy to administer and can be given in outpatient clinics. S-1 is a novel oral fluoropyrimidine anticancer agent designed to enhance anticancer activity and reduce gastrointestinal toxicity, by which a prodrug of 5-FU, tegafur (FT), has been combined with two modulating substances, gimestat (CDHP: a 5-chloro-2,4-dihydroxy-pyrimidine) and a potassium oxonate (Oxo) (5). The reported response rate for gastric cancer in S-1 was higher and the incidence of adverse reactions was lower compared to that for CVI of 5-FU (6-8). Combined therapy with S-1 and other chemotherapeutic agents might yield an enhanced therapeutic benefit. We reported a dose-escalation study of S-1 combined with cisplatin for advanced gastric cancer and established a recommended protocol based on acceptable toxicity levels (9). In the present study, we conducted a phase II multicentric trial of S-1 in combination with cisplatin for high-grade advanced gastric cancer. The primary end-point was to determine the antitumor effect and clinical toxicities. The secondary end-point was overall survival.

Patients and Methods

Patient enrollment. Patients with histologically verified gastric carcinomas, that were inoperable locally, advanced or metastatic, were eligible for enrollment in the study. Patients had to be under 75 years of age and also have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less. Other eligibility criteria included: no chemotherapy within 4 weeks before entry; adequate bone marrow (WBC≥4,000/μl and platelet count≥100,000/μl); adequate liver function (serum bilirubin level≤1.5 mg/dL and serum transaminase concentrations no more than three times the normal upper limit); adequate renal function (serum creatine≤1.5 mg/dL and blood urea nitrogen ≤25 mg/dL);

*The institutions participating in this phase II multicentric trial are listed in the Appendix.

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Kew Words: Phase II, multicentric trial, S-1, cisplatin, gastric cancer.

Table I. *Patient characteristics.*

Characteristics	No. of Patients
Total	42
Male	31
Female	11
Age (years)	
Median	68
Range	39-74
Performance status (WHO)	
0-1	39
2	3
Locally advanced ca.	14
Metastatic ca.	28
Site of metastasis	
Abdominal lymph nodes	21
Liver	14
Peritonitis carcinomatosa (ascites)	8
Others	6
Lung	1
Bone	1

Table II. *Toxicity in combination S-1 and 24-h infusion of cisplatin chemotherapy.*

	CR	PR	SD	PD	Response rate (%)
Overall	2 (5)	19 (45)	15 (36)	6 (14)	21 (50)
Primary lesion	3 (7)	18 (43)	15 (36)	6 (14)	21 (50)
Abdominal lymph node	4 (19)	8 (38)	6 (29)	3 (14)	9 (57)
Liver	0	9 (64)	5 (36)	0	9 (64)
Lung	0	0	1 (100)	0	0
Bone	0	0	1 (100)	0	0
Ascites	3 (38)	2 (25)	1 (13)	2 (25)	5 (63)
Others	1 (17)	2 (33)	2 (33)	1 (17)	3 (50)

Table III. *Response rates in combination S-1 and 24-h infusion of cisplatin chemotherapy.*

Toxicity (n=42)	Grade, n (%)		
	2	3	4
Hematological toxicity			
Leucopenia	20 (48)	7 (17)	2 (5)
Thrombocytopenia	5 (12)	3 (7)	0
Anemia	6 (14)	3 (7)	0
Non-hematological toxicity			
Nausea	9 (21)	4 (10)	0
Vomiting	7 (17)	4 (10)	0
Diarrhea	3 (7)	2 (5)	0
Infection	2 (5)	1 (2)	0
GOT/GPT elevation	1 (2)	1 (2)	0
Creatinine	3 (7)	0	0
Skin rash	3 (7)	0	0
Peripheral neuropathy	2 (5)	0	0
Mucositis	2 (5)	0	0
Perforation of stomach	0	0	1 (2)

expected survival more than 3 months. All patients provided fully informed written consent prior to entry into the study.

Assessability, toxicity and response criteria. Before entry into the study, the extent of disease was determined in all patients by physical examination, chest and gastrointestinal radiography, endoscopic examination of the upper gastrointestinal tract and computed tomography (CT) of the abdomen. A complete blood cell count, liver function tests, renal function tests and urinalysis were performed weekly during treatment. National Cancer Institute – Common Toxicity Criteria (NCI-CTC) were used to evaluate therapeutic toxicity. Tumor response was evaluated by the Japanese Research Society for Gastric Cancer (10). The primary lesion was estimated by rentgenophotographic and endoscopic findings and, for metastatic lesions, CT scan was used. Complete response (CR) was defined as complete disappearance of all evidence of cancer. Partial response (PR) was defined as a greater than 50% reduction of tumor volume. A new lesion or enlargement exceeding the original tumor size by 25% was defined as progressive disease (PD). All other patients were categorized as having stable disease (SD).

Treatment plan. S-1 (80 mg/m^2) was administered orally daily for 14 consecutive days and 24-h infusion of cisplatin (70 mg/m^2) was administered on day 8 without 14 days drug of every 28-day cycle. Cisplatin was dissolved in 2800 ml of physiologic saline with 5% glucose solution and 20 mEq KCl. The cisplatin was then administered intravenously over a period of 24 hours to minimize the adverse effect. To prevent nephrotoxicity induced by cisplatin, hydration was provided and diuresis was induced before and after cisplatin administration using 2,500 mL of saline-glucose solution with added KCl plus 300 ml of 20% D-mannitol. A 5-hydroxytryptamine (5-HT) 3 serotonin receptor antagonist was given on the day of cisplatin administration and for the following 2 days. Patients showing responses continued to receive treatment until disappearance of tumor, appearance of progressive disease, or development of serious toxicity.

Statistical analysis. The required sample size for this study was calculated based on a target response rate of 40% and a minimum response rate of 20%, with an α error of 0.1 and a β error of 0.1. The required number of patients was estimated to be 40.

Overall survival was measured from the start of S-1 administration to the date of death, or that of the most recent follow-up examination if the patient was alive. The Kaplan-Meier method was used to plot the overall survival curve. The date of final evaluation of survival data was November 1, 2004.

Results

From November 1, 2001 to October 31, 2003, 42 patients with locally advanced or metastatic gastric cancer entered the study. The patient characteristics are listed in Table I. The

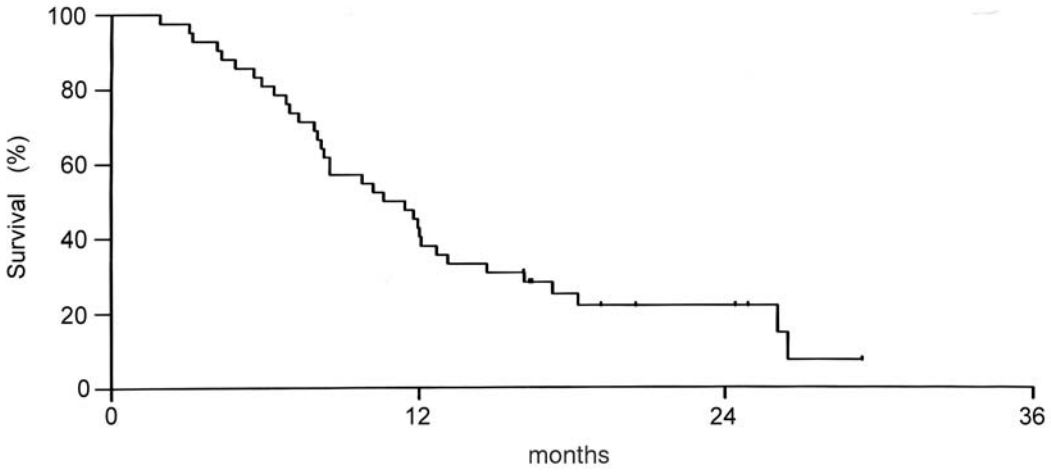

Figure 1. *Survival curve of all patients treated with combination S-1 and cisplatin.*

median age of the patients was 68. PS was 0 in 21 patients, 1 in 18 patients, and 2 in 3 patients. Twenty-eight patients had measurable metastatic lesions and 14 patients had locally advanced gastric carcinomas: 4 invaded the pancreas, 2 invaded the colon and 8 had disseminations within the peritoneal cavity with ascites. Liver metastasis was seen in 14 patients, abdominal lymph node metastasis in 21, lung metastasis in 1 patient and bone metastasis in 1 patient. Six patients had more than 2 different metastatic diseases.

Responses. All patients completed at least one cycle and were evaluated for antitumor effect. Responses for the primary lesion, metastases and overall tumor are shown in Table II.

The overall response rate was 50% (95% CI: 32-66%). CR was observed in 2 (CR rate: 5% (95% CI: 1-16%)) and PR was observed in 19 patients (PR rate: 45% (95% CI: 30-61%)). For the primary lesion, response rates and CR rates were 50% (95% CI: 32-66%) and 7% (95% CI: 2-20%). For abdominal lymph node metastases, response rates and CR rates were 57% (95% CI: 34-78%) and 19% (95% CI: 5-42%). For liver metastasis, the response rate was 64% (95%CI: 35- 87%). Ascites disappeared in 38% and decreased by over 50% in 25%. After this chemotherapy, radical operations became possible in 3 patients with locally advanced gastric cancer; 1 achieved CR (both primary lesion and ascites) after 4 courses, and 2 were PR (primary lesions PR, abdominal lymph nodes CR) after 3 courses and 8 courses, respectively.

Toxicity. A total of 163 treatment cycles (median 4, range 1-10) were administered. The toxicities are summarized in Table III. The most common hematological toxicity was leucopenia. Grade 3 thrombocytopenia and anemia were seen in 3 patients (7%), respectively, but grade 4 was not seen. Non-hematological toxicities generally were mild. Grade 3 nausea and vomiting were observed in 4 patients (10%), respectively. Grade 3 or more mucositis, hand-foot syndrome and renal abnormality were not observed. One patient, who had perforation of the stomach during the second course, recovered after emergency palliative surgery. Microscopic examination of the resected gastric specimen revealed scattered degenerated cancer cells at the perforation site.

Survival. The survival curve for all patients is shown in Figure 1: the median survival time (MST) was 344 days. The 1-year survival rate was 44% (95% CI: 29- 60%) and the 2-year survival rate was 23% (95% CI: 9- 36%). Surgery was performed in 3 patients with locally advanced gastric cancer in whom downstaging was achieved and in whom resection became inducted. They are all alive without recurrence, 16 months, 18 months and 25 months, respectively, after initiating treatment.

Discussion

In Japan, oral administration of anticancer drugs for gastric cancer has been used to enable more convenient and less toxic chemotherapy and to enhance compliance. Various 5-FU derivatives can be given orally, such as tegafur (11); uracil in combination with FT (UFT) (12); and 5'- deoxy –5–fluorouridine (5'DFUR) (13). These derivatives have been used together with other anticancer drugs to enhance the effectiveness for advanced gastric cancer (14-16). From 1987, we have used combination chemotherapy consisting of

UFT and cisplatin (16), which have different modes of action against DNA synthesis and a synergistic effect (17). Response by the primary gastric lesion was achieved in 14 patients (50%) in an early phase II study and this combination was considered to be moderately effective in advanced gastric cancer (16). However, since no patients with far-advanced disease showed a CR or long survival, refinement of the UFT and cisplatin chemotherapy is an important goal. Recently, a novel oral anticancer agent (S-1) that inhibits dihydropyrimidine dehydrogenase (DPD), an enzyme for 5-FU degradation, was developed. The DPD inhibitor (CDHP) used in S-1 is about 200-fold more potent than the uracil in UFT (18) and the antitumor activity of S-1 was shown to be more marked (6-8). Therefore, considering that better therapeutic benefit might be obtained if S-1 is combined with cisplatin instead of UFT, we tried a dose-escalation pilot study of S-1 combined with cisplatin (9). In the present study, we conducted a multicentric phase II trial of S-1 in combination with cisplatin using the schedule recommended in the dose-escalation study, to determine the clinical toxicities, antitumor effects and survival for advanced gastric cancer. The response rate was 50%; CR rate was 5%, resulting in a median overall survival of 344 days. This regimen was effective for both primary lesion and metastasis. Furthermore, it was noted that, after this treatment, radical operations became possible in 3 patients with locally advanced gastric cancer, who are all alive without recurrence. This treatment might be suitable for neoadjuvant treatment.

Toxicities were manageable. Leucopenia was the most common toxicity, but there was no treatment-related death. In the dose-escalation study (9), leucopenia increased with increasing duration of S-1 administration and was the only DLT in the regimen. The 24-h infusion of cisplatin would often induce mild nausea and vomiting, but was less than the severe toxicity associated with bolus injection of cisplatin (19). Administration of S-1 for 14 days, plus a 24-h injection of cisplatin on day 8, followed by 14 days without drugs, did not produce fatal toxicities. One patient had gastric perforation during the second course. Perforation might have been related to the antitumor effect of chemotherapy, in the light of the microscopic examination findings of degenerated cancer cells in the resected gastric specimen.

In recent years, a number of phase II combination studies with new drugs, such as topoisomerase I inhibitors, taxanes, oxaliplatin and oral fluoropyrimidines, have been reported to achieve of an effective treatment approach for high-grade advanced gastric cancer. The irinotecan/cisplatin regimen was reported to achieve a response rate of 59% and median survival of 322 days, but severe diarrhea was observed in 20% of the patients and significant neutropenia in 57% (20). Paclitaxel, 5-FU, folinic acid and cisplatin chemotherapy demonstrated encouraging efficacy, with a CR rate of 14% and MST of 11 months (21). Al-Batran *et al.* reported that bi-weekly fluorouracil, folinic acid and oxaliplatin are active and well-tolerated. The response rate was 43%, and MST was 9.6 months for advanced gastric cancer (22). Capecitabine plus cisplatin chemotherapy gave a response rate of 54.8% and MST of 10.1 months (23). These new regimens seem to be effective and well tolerated, however, few regimens obtained median survival exceeding 11 months and 2-year survival rate over 10% (24).

Koizumi *et al.* reported a phase I/II study of S-1 combined with cisplatin for advanced gastric cancer (25). The response rate were 74%, but with 0% CR. The MST was 383 days. The incidence of severe (grade 3-4) hematological and non-hematological toxicities was 15.8% and 26.3%. In that treatment, S-1 was given for 21 consecutive days and 2-h infusion of cisplatin (60 mg/m^2) was administered on day 8 of every 35-day cycle. The duration of the S-1 dose and the administration time of cisplatin in the courses was different from our study. Toxicities seemed to be milder in our regimen. A further phase III randomized study is needed for definitive evaluation and comparison.

In conclusion, this combination of S-1 for 14 days followed by 14 days without drugs, plus a 24-h infusion of CDDP (70 mg/m^2) on day 8 of every 28-day cycle is active, well tolerated and yielded good results in patients with high-grade advanced gastric cancer.

Acknowledgements

The author is indebted to Professor J. Patrick Barron of the Internal Medical Communications Center of Tokyo Medical University, Japan, for reviewing this manuscript.

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Appendix

This study was supported by the following institutions participating in the study:
1) Department of Gastroenterology, Nagoya Medical Hospital,
2) Department of Gastroenterology, Aichi Saiseikai Hospital,
3) Department of Gastroenterology, Ogaki Municipal Hospital,
4) Department of Gastroenterology, Japanese Red Cross Nagoya Hospital,
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9) Department of Gastroenterology, Hekinan Municipal Hospital,
10) Department of Gastroenterology, Toyota Memorial Hospital,
11) Department of Gastroenterology, Aich Medical University and
12) Department of Gastroenterology, Tohno Kousei Hospital.

Received November 15, 2004
Accepted February 21, 2005