Docetaxel and S-1 as a First-line Treatment in Patients with Advanced or Recurrent Gastric Cancer

YASUHIRO TSUTANI, MASAHIRO OHARA, TAKAHISA SUZUKI, KAZUHITO MINAMI, EIJI MIYAHARA, AKIRA KAMEDA and YOSHIHIRO NOSO

Department of Surgery, Saiseikai Hiroshima Hospital, 2-3-10, Kitashinchi, Saka-cho, Aki-gun, Hiroshima, 731-4311, Japan

Abstract. *Background: The safety and efficacy of docetaxel plus S-1 combination chemotherapy as a first-line treatment in patients with advanced or recurrent gastric cancer was verified retrospectively. Patients and Methods: Eighteen patients with advanced or recurrent gastric cancer were enrolled. The regimen used was intravenous docetaxel, 40 mg/m^2, on day 1 and oral S-1, 80 mg/m^2/day, on days 1-14 every three weeks. Results: In total 101 cycles were administered. One and 11 patients achieved complete and partial responses, while six and zero patients showed stable and progressive disease, respectively. The median time to progression (TTP) and median overall survival were 7.0 and 14.3 months, respectively. Neutropenia was the most common grade 3/4 hematological toxicity. Nausea and stomatitis were the most common grade 3 nonhematological toxicities. No treatment-related death was observed. Conclusion: Docetaxel plus S-1 combination is an active and tolerable regimen as a first-line treatment in patients with advanced or recurrent gastric cancer.*

Gastric cancer is the second most common cause of cancer death worldwide (1). Patients with advanced gastric cancer have a poor prognosis, with a median survival time, if untreated, of 3-5 months (2-4). Patients with inoperable gastric cancer may benefit from palliative chemotherapy. Many regimens consisting of a single drug or a two or more drug combination have been employed, such as 5-fluorouracil, doxorubicin, and mitomycin (FAM) which showed a short-lived effect in 20-40% of patients (5), etoposide, doxorubicin, and cisplatin (EAP) (6), methotrexate, 5-fluorouracil and adriamycin (FAMTX) (7) and epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF) (8) which were developed as second-generation chemotherapeutic regimens for gastric cancer. However, response rates have not been as high as expected, and furthermore, severe adverse effects have been observed. Therefore, at present, no standard chemotherapy regimen has been generally accepted.

S-1 is an oral fluoropyrimidine, consisting of tegafur (a dihydropyrimidine dehydrogenase inhibitor), 5-chloro-2,4-dihydroxypyrimidine, and an orotate phosphoribosyl transferase inhibitor, potassium oxonate (9). In the phase II studies of advanced gastric cancer conducted in Japan, patients administered 80 mg/m^2/day of S-1 daily for four weeks, followed by a two-week rest, showed high response rates of 44-49% (9, 10). S-1 has become one of the leading drugs in Japan for first-line chemotherapy of advanced and recurrent gastric carcinomas. S-1 is also synergistic with several anticancer agents, including cisplatin, irinotecan and docetaxel. Docetaxel is a novel semi-synthetic taxoid that has demonstrated activity against human gastric cancer *in vitro* and *in vivo* (11). The use of this agent for the treatment of patients with advanced or metastatic gastric cancer has resulted in a response rate of 15-24% when it was administered as a first-line therapy (12-14) and 18-24% when administered as a second-line therapy (15, 16). In phase I/II studies, the use of a docetaxel plus S-1 combination as first-line chemotherapy for advanced and recurrent gastric carcinomas achieved response rates of 46.0-56.3% and a median survival time of 14.0-14.3 months (17, 18). The aim of this study was to evaluate retrospectively the safety and efficacy of docetaxel plus S-1 combination therapy as a first-line treatment in patients with advanced or recurrent gastric cancer treated at the Saiseikai Hiroshima hospital.

Patients and Methods

Patients. Patients who satisfied all of the following requirements were eligible for this study: advanced or recurrent gastric cancer, which was histologically confirmed; no prior therapy, including adjuvant chemotherapy; adequate bone marrow, liver and kidney function; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 and life expectancy of three months or more. Written informed consent to the treatment was obtained from all the patients before the treatment.

Correspondence to: Yasuhiro Tsutani, Department of Surgical Oncology, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan. Tel: +81 822575869, Fax: +81 822567109, e-mail: yatsutani@msn.com

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Table I. *Patient characteristics*.

Characteristic	No. of patients N=18
Age (years)	
Median	70
Range	32-90
Gender (%)	
Male	13 (72.2)
Female	5 (27.8)
ECOG PS (%)	
0	10 (55.6)
1	6 (33.3)
2	2 (11.1)
Disease status (%)	
Advanced	16 (88.9)
Recurrent	2 (11.1)
Prior gastrectomy	
–	12 (66.7)
+	6 (33.3)
Metastatic sites (%)	
Liver	5 (27.8)
Lymph node	14 (77.8)
Peritoneum	6 (33.3)
Other	3 (16.7)
Histology (%)	
Well differentiated adenocarcinoma	2 (11.1)
Moderately differentiated adenocarcinoma	6 (33.3)
Poorly differentiated adenocarcinoma	10 (55.6)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Treatment regimen. S-1, 80 mg/m^2, was orally administered twice daily (within 30 min after morning and evening meals) for two weeks, followed by a drug-free interval of one week (one cycle). Docetaxel, 40 mg/m^2, was diluted in 250 ml of 0.9% saline and administered as a one-hour infusion on the morning of day 1 of each cycle (*i.e.* every three weeks). The regimen was referred to previously in the phase I and II studies of combination therapy with S-1 and docetaxel for advanced or recurrent gastric cancer that showed the safety and efficacy (17, 19). The docetaxel infusion was started simultaneously with the S-1 administration. Dexamethasone, 20 mg, and granisetron, 3 mg, were infused 30 min before docetaxel administration. The dose was reduced by 25% for all grade 3 and 4 events, except for nausea and vomiting. The treatment was repeated until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue treatment.

Adverse events. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) (20).

Evaluation of response. Response evaluation criteria in solid tumors (RECIST) was used to assess tumor response (21). Tumor size was measured by CT or MRI scan of all measurable lesions in the week preceding treatment. These imaging studies were repeated, and response was confirmed at least four weeks (for complete or partial response) or six weeks (for stable disease) after it was first documented. Response was not evaluated in the primary gastric tumors to avoid measurement bias of primary tumor diameter. For the evaluation of nonmeasurable lesions, gastrointestinal fiberscopy, ultrasonography, other radiographic examinations and cytology were performed if needed. Time to progression (TTP) was measured from the start of treatment until the first documentation of progression. Overall survival was measured from the start of treatment until the time of death. The median TTP and overall survival were estimated using the Kaplan–Meier method.

Table II. *Response*.

	No. of patients	%
CR	1	5.6
PR	11	61.1
SD	6	33.3
PD	0	0

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Results

Patient characteristics. From August 2005 to March 2007, 18 patients with advanced or recurrent gastric cancer were treated with docetaxel plus S-1 combination as first-line chemotherapy at our hospital. The patients' characteristics are listed in Table I. A prior gastrectomy had been performed in six patients, two with recurrence after curative resection and four with noncurative resection. The major sites of metastases were the liver, lymph nodes and peritoneum.

Treatment, response, and survival. A total of 101 cycles was administered. The median number of cycles per patient was four (range: 1-18). All 18 patients were assessable for response. The dose of S-1 was reduced to 60 mg/m^2 in two patients (11.1%) because of grade 4 neutropenia and grade 3 stomatitis in line with the dose reduction criteria. Treatment administration was delayed in 11 out of the 101 cycles (range, 7-14 days) because of grade 3 or 4 neutropenia. No docetaxel doses were omitted. The reasons for treatment discontinuation were tumor progression in all the patients.

The efficacy data are shown in Table II. One patient showed a complete response and 11 achieved a partial response. The overall response rate was 66.7%. There was no discrepancy between histological types in effectiveness including the response rate, TTP and overall survival.

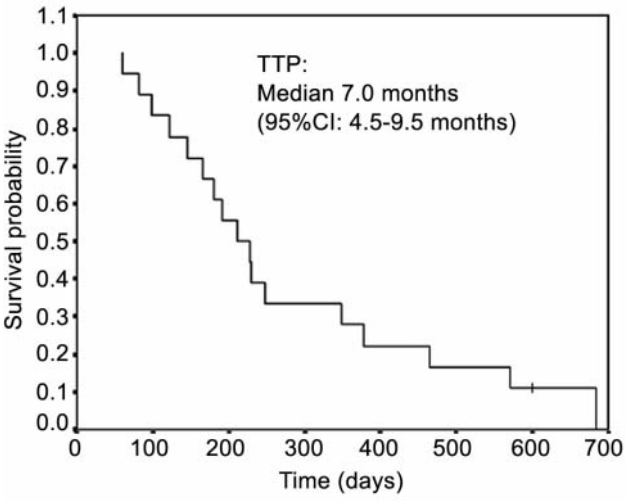

Figure 1. *Kaplan–Meier plot of time to progression (TTP).*

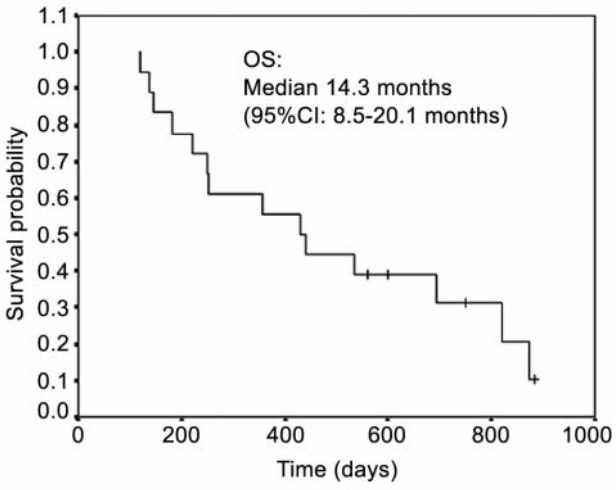

Figure 2. *Kaplan–Meier plot of overall survival (OS).*

At a median follow-up of 14.5 months (range: 4.0-29.5), the median TTP was 7.0 months (95% confidence interval [CI], range: 4.5-9.5 months). The median overall survival was 14.3 months (95% CI, 8.5-20.1 months). These data are shown in Figures 1 and 2.

Among the 12 of the patients with primary gastric carcinoma without prior gastrectomy, five underwent subsequent surgery. The indication for this surgery was not determined in this study. At the time of this analysis, two out of the five patients were still alive (25.0 and 18.7 months from the start of treatment). The five patients who underwent subsequent surgery received a median of six cycles of docetaxel plus S-1 combination therapy (range: 4-18). The histological responses of the primary lesions were two grade 1a, one grade 1b and two grade 2. Since all of the five patients underwent palliative surgery, the survival benefit of gastrectomy was limited.

Sixteen patients received second-line chemotherapy after failure of this regimen: S-1 alone in six patients; weekly paclitaxel in four patients; irinotecan plus S-1 in four patients and cisplatin plus S-1 in two patients.

Toxicity. The toxicity profile is summarized in Table III. Neutropenia was the most common grade 3/4 hematological toxicity (five patients, 27.8%). No febrile neutropenia was observed. No patient received granulocyte colony-stimulating factor (G-CSF). The nonhematological toxicities were generally mild in severity and no grade 4 toxicities were observed. The most common grade 3 nonhematological toxicities were nausea (one patient, 5.6%) and stomatitis (one patient, 5.6%). No treatment-related death was observed.

Table III. *Toxicity.*

	No. of patients (%) N=18		
Toxicity	Grade 1-2	Grade 3	Grade 4
Hematological			
Leukopenia	3 (16.7)	3 (16.7)	0 (0)
Neutropenia	4 (22.2)	4 (22.2)	1 (5.6)
Anemia	6 (33.3)	0 (0)	0 (0)
Thrombocytopenia	0 (0)	0 (0)	0 (0)
Nonhematological			
Nausea	6 (33.3)	1 (5.6)	0 (0)
Vomiting	2 (11.1)	0 (0)	0 (0)
Stomatitis	4 (22.2)	1 (5.6)	0 (0)
Constipation	4 (22.2)	0 (0)	0 (0)
Diarrhea	3 (16.7)	0 (0)	0 (0)
Dysgeusia	3 (16.7)	0 (0)	0 (0)
Fatigue	2 (11.1)	0 (0)	0 (0)
Alopecia	10 (55.6)		
Hyperpigmentation	2 (11.1)	0 (0)	0 (0)
Neuropathy	1 (5.6)	0 (0)	0 (0)

Discussion

The rationale for the design of the combination therapy of docetaxel and S-1 was the significant laboratory and clinical antitumoral activity of both docetaxel and 5-fluorouracil in gastric cancer, their synergistic activity *in vivo*, and the relative lack of overlapping toxicities (22). Takahashi *et al*. reported increased antitumor activity in combination therapy with

docetaxel and S-1 using gastric cancer xenografts (23). Wada *et al*. reported that docetaxel and S-1 combination therapy showed synergistic effects by modulating the expression of the metabolic enzymes of 5-fluorouracil, including thymidylate synthase, dihydropyrimidine dehydrogenase, and orotate phosphoribosyl transferase in human gastric cell lines (24).

The present study showed that a docetaxel plus S-1 combination was highly active in advanced and recurrent gastric cancer and had an acceptable and manageable toxicity profile. The combination achieved promising results for overall response rate (66.7%), median TTP (7.0 months; 95% CI, 4.5-9.5 months), and median overall survival (14.3 months; 95% CI, 8.5-20.1 months). The nonhematological toxicities were generally mild and none was greater than grade 3. Nausea and stomatitis, the most common grade 3 nonhematological toxicities, were each observed in just 5.6% of the patients. The predominant toxicity was myelosuppression and grade 3/4 neutropenia, which occurred in 27.8% of the patients. However, both the hematological and nonhematological toxicities were generally manageable and in most cases, treatment could be continued in an outpatient setting.

In this study, five patients underwent subsequent surgery. Since the surgery was palliative for all five patients, the survival benefit of gastrectomy was limited in this study and the significance of subsequent surgery for cure was unknown.

At a median follow-up of 14.5 months, the median overall survival was estimated to be 14.3 months. The mature survival results reported in this study were consistent with the recently reported analysis of phase II studies of S-1 plus docetaxel combination therapy for patients with advanced gastric cancer (17, 18). In a few phase I/II trials, docetaxel plus S-1 combination therapy showed good efficacy and toxicity profiles. However, this regimen has not been generally accepted. The results of the present study support the safety and effectiveness of docetaxel plus S-1 combination therapy for advanced or recurrent gastric cancer in a general hospital. Based on the positive results of these studies, clinical phase III trials comparing S-1 with S-1 plus docetaxel and cisplatin plus 5-fluorouracil with S-1 plus docetaxel, for advanced and recurrent gastric cancer have been conducted in Japan, and the usefulness of the S-1 plus docetaxel combination should be evaluated in detail in future studies. Recently, the Japanese phase III trial (SPIRITS trial) showed that the overall survival was better in patients with advanced gastric cancer treated with S-1 plus cisplatin than with S-1 alone. S-1 plus cisplatin is one of the standard first-line treatments for patients with advanced gastric cancer in Japan at present (25). In conclusion, the S-1 plus docetaxel combination is highly active against advanced as well as recurrent gastric cancer and can be safely administered, provided the adverse events are properly managed. Although the number of cases is small, this regimen is one of the most powerful candidates for a standard first-line regimen for metastatic gastric cancer.

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