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Phase II Study of Docetaxel Plus Cisplatin as a Second-line Combined Therapy in Patients with Advanced Gastric Carcinoma

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Abstract. *Background: We conducted a pilot phase II study to evaluate the efficacy and safety of docetaxel and cisplatin as a combination second-line therapy for advanced gastric cancer. Patients and Methods: Between 2000 and 2003, 30 patients were enrolled into this study. Chemotherapy consisted of 60 mg/m^2 of docetaxel followed by 60 mg/m^2 of cisplatin. This regimen was repeated at least three times at 3-week intervals. Results: The overall response rate was 26.7%. The median time to disease progression was 4.5 months. The median survival time was 13 months from the start of the first-line therapy and 6 months from the second-line therapy. With respect to toxicity, the major adverse effect was leukopenia, which reached grades 3-4 in 26.7%. Non-hematological toxicities were usually moderate, and no deaths were attributable to the adverse effects of the drugs. Conclusion: This combination therapy was effective as a second-line treatment for advanced gastric cancer with acceptable toxic side-effects.*

Although the incidence of gastric cancer has declined over recent decades in industrialized countries, it remains the second most common cause of cancer-related death worldwide. Even after curative resection, advanced gastric cancer frequently recurs as peritoneal metastases (1, 2). Therefore, the treatment for advanced gastric cancer, in addition to surgery, needs to be optimized. Although many different regimens have been tested, a standard chemotherapeutic agent has not yet been established (3-7).

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Recently, S-1, which is a new oral fluoropyrimidine that inhibits dihydropyrimidine dehydrogenase, has been widely adopted in many institutes in Japan as the front-line therapy for advanced gastric cancer (8, 9) that is unresectable, resected but not cured, or recurrent. S-1 has produced response rates ranging from 30 to 40%, which is astonishingly high for an oral drug and makes S-1 one of the most effective chemotherapeutic agents for gastric cancer. Unfortunately, some gastric cancers do not respond to this agent. Therefore, when S-1 therapy has failed, we have administered a second-line regimen, using docetaxel and cisplatin as a combined therapy. We adopted this approach because the drugs used in these two regimens showed no cross-resistance and had completely different side-effect profiles (10). In addition, previous combination chemotherapy regimens have failed to improve survival rates compared to chemotherapy using a single drug (11, 12). Few drugs have produced response rates of 20% or more as second-line chemotherapeutic agents for highly advanced gastric cancer (13). In this study, we evaluated docetaxel and cisplatin as a combination therapy for advanced gastric cancer, measuring the objective response rate, the time to progression, the overall survival and the safety profile for use as a second-line chemotherapeutic regimen.

Patients and Methods

Patient eligibility. A series of 30 patients were enrolled in this study between November 2000 and December 2003. To be eligible for inclusion, patients had to have histologically or cytologically confirmed gastric adenocarcinoma that had measurable lesions and was unresectable (16), palliatively resected (8) or recurrent (6). The patients must have already received first-line chemotherapy, to which they had failed to respond, and shown disease progression, as evaluated radiographically. First-line therapies had been administered as follows: 20 patients, who could be treated with oral chemotherapeutic agents as outpatients, were given 80-120 mg S-1

(Taiho, Tokyo, Japan) daily for two 4-week periods, separated by a 2-week interval, and 10 patients, who could not take orally-administered drugs, in most cases due to malignant pyloric stenosis, were admitted to hospital and treated with fluorouracil and cisplatin (FP; 500 mg/m^2 5-fluorouracil plus 5 mg/m^2 cisplatin by intravenous infusion on days 1-5, 8-12, 15-19 and 22-26). Patients were also required to have the following: a Karnofsky performance score of ≥50; a life expectancy of ≥3 months; and an adequate hematological status (defined as a total leukocyte count ≥3,500/μl, a neutrophil count ≥1,500/μl, a platelet count >100,000/μl, serum creatinine <1.5 mg/dl, total serum bilirubin <1.5 mg/dl and an aspartate aminotransferase (AST) level less than 2.5 times the upper limit of the normal range). Patients were excluded from the study if they had any other current or prior malignancies, active uncontrolled infections or other diseases or a neurological or mental disease that prevented adequate comprehension of the information sheet. Pretreatment evaluation consisted of a complete history and physical examination, blood count, serum biochemistry, chest X-ray and computed tomography (CT) of the thorax and abdomen. In some cases, patients also underwent bone scintigraphy, aspiration cytology and aspiration or incisional biopsy. All patients gave informed consent before the initiation of second-line treatment.

Study design. All second-line treatment was administered to inpatients. Patients were premedicated with 8 mg dexamethasone and 10 mg DL-chlorpheniramine, diluted in 100 ml of saline and given intravenously. In addition, antiemetic prophylaxis with 4 mg ondansetron hydrochloride was always administered intravenously 30 minutes prior to treatment. Chemotherapy was administered by intravenous infusion and consisted of 60 mg/m^2 docetaxel (Taxotere; Aventis Pharma, Japan, Tokyo, Japan) given over 60 minutes followed by 60 mg/m^2 of cisplatin (Nihonkayaku, Tokyo, Japan) administered over 120 minutes. This regimen was repeated at least three times at 3-week intervals. A new cycle of the treatment could begin if the total leukocyte count was ≥3,500/μl, the neutrophil count was ≥1,500/μl, the platelet count was >100,000/μl, and all relevant non-hematological toxicities were grade 2 or lower.

If granulocyte counts fell below 1,000/mm^3 (grade 3) or tended to decrease below 1,000/mm^3, granulocyte-colony stimulating factor (G-CSF) (4 mg of ondansetron hydrochloride, Glaxo Smithkline, Japan) was subcutaneously administered until recovery of the granulocyte count.

The treatment was continued unless there was unacceptable toxicity or disease progression, or the patient chose to withdraw from the study. If the disease was judged to have progressed at the radiographic assessment carried out 2 weeks after the third treatment, another chemotherapeutic regimen (60 mg/m^2 irinotecan hydrochloride and 30 mg/m^2 cisplatin) was recommended as the third-line therapy.

Study evaluations. All responses were assessed by physical examination, direct visualization, examination of the upper gastrointestinal tract after a barium meal, gastrofibroscopy and CT. Tumor evaluation was carried out after three treatment cycles, according to the World Health Organization criteria, and responses were confirmed by radiography within 2 weeks. A complete response was defined as remission of all disease for a minimum of 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of the perpendicular diameters of the indicator lesions without the appearance of new lesions. Progressive disease (PD) was defined as an enlargement of >25% in an indicator lesion or the development of new lesions, and no change (NC) was defined as a failure to meet the criteria for either response or progression. All adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) at each treatment cycle. In the event of toxicity, chemotherapy was postponed until the symptoms had resolved.

Table I. *Characteristics of enrolled patients.*

Characteristics	Number of patients	(%)
Total number of patients	30	
Age (years)		
Median (range)	64.5 (50-75)	
Sex		
Male	28	93.3
Female	2	6.7
Karnofsky performance status		
80-100	16	53.3
50-70	14	46.7
Tumor characteristics		
Primary disease	16	53.3
Metastatic		
Peritoneal metastasis	8	26.7
Hematogenous metastasis	10	33.3
Lymph node metastasis	23	76.7
Histological type (Japanese classification)		
Differentiated	15	50.0
Undifferentiated	15	50.0
Primary treatment		
Curative gastrectomy	6	20.0
Palliative gastrectomy	8	26.7

Survival analysis. The length of survival and time to progression (TTP) were measured from the initiation of the treatment to death and progression, respectively. The duration of the response was measured from the time at which a response was documented to the detection of disease progression. The Kaplan-Meier method was used for calculating the survival rate. The difference between the curves was assessed using the log-rank test. Results with probability (p) values ≤0.05 were considered to be statistically significant.

Results

Patient characteristics. The demographic features of the 30 patients enrolled in this study are shown in Table I. All patients were assessed for response and toxicity. The median patient age was 64.5 years (range: 50-75 years); 28 patients were male (93.3%) and 2 were female (6.7%), with many patients being in good general condition (53.3% with a performance status of 80-100). However, the performance status of patients who received FP treatment was poor compared to that of patients with S-1 therapy (Karnofsky performance status, 80 ~ 100/50 ~ 70: 3/7 *vs.* 13/7). All patients had histologically confirmed adenocarcinoma, with 50% being differentiated and 50% undifferentiated. The median number

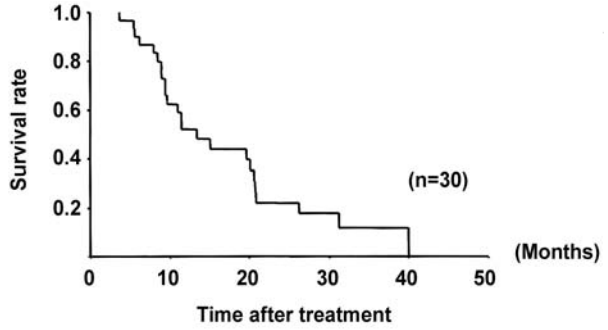

Figure 1. *Overall survival for all patients. The median survival time (MST) for patients over the whole course of their treatment was 13 months.*

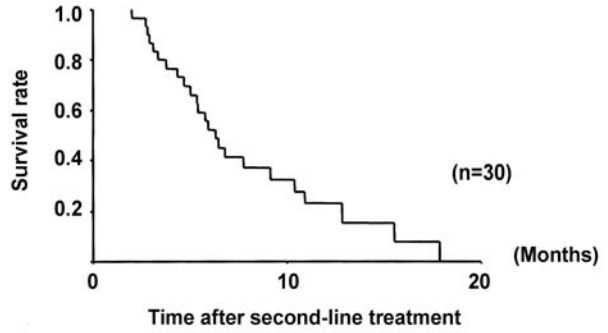

Figure 2. *Survival after second-line treatment for all patients. The MST after second-line chemotherapy was 6 months.*

of organs involved was 1.64±0.73 (range: 1-3). The most frequently observed sites of tumors were in the lymph nodes, with metastases in 23 patients, followed by the primary tumor site in 16 patients and hematogenous metastases in 10 patients (liver metastasis: 9, lung metastasis: 1).

Efficacy. The overall response rate was 26.7% (8 out of 30 patients) and in every case the response was partial: no patient achieved a complete response. In 19 patients (63.3%), the disease stabilized and in 3 patients (10.0%) the disease progressed. When analyzed by the organ affected, the response rates were 50.0% for patients with peritoneal disease, 30.0% for patients with hematogenous spread, 25.0% for patients with primary stomach cancer and 17.4% for patients with lymphatic metastasis. There was no correlation between responsiveness to the combined second-line therapy and the first treatment regimen used. None of the patients underwent subsequent surgery.

Survival. The median follow-up time was 15.1 months with a range of 3.7 to 40.0 months. The median time to progression was 4.5 months with a range of 2.6 to 11.4 months. The median survival time (MST) for patients over the whole

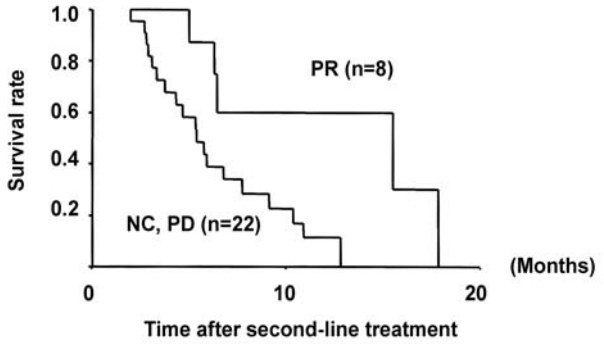

Figure 3. *Survival after second-line treatment for patients with (PR) or without (NC, PD) a response. The MSTs for the 8 patients who showed a response and the 22 patients who did not were 16 and 5 months, respectively. The difference in survival between these groups was significant ($p=0.0157$).*

course of their treatment was 13 months (Figure 1). The MST was 8 months for patients who received FP therapy and 20 months for patients who received S-1 therapy. The difference in survival between these two groups was significant ($p=0.0002$). The MST after second-line chemotherapy was 6 months (Figure 2). The MSTs for the 8 patients who showed a response and the 22 patients who did not were 16 and 5 months, respectively. The difference in survival between these groups was also significant ($p=0.0157$) (Figure 3).

Toxicity. The toxicities encountered during treatment are listed in Table II. Alopecia was the most common adverse event, affecting 93.3% of patients. The most frequent hematological side-effects were leukopenia and neutropenia, which both affected 73.3% of patients, with 26.7% affected severely at grades 3 or 4. Thrombocytopenia and anemia affected 60.0% and 50.0% of patients, respectively, but only 6.7% and 3.3% of patients, respectively, were severely affected (grades 3). In most patients, the leukocyte nadir was observed 7 days after the administration of chemotherapy. Eight patients (26.7%) with grade 3 or greater neutropenia received G-CSF for at least 3 consecutive days, or until the leukocytes or neutrophils reached the normal range. Febrile neutropenia was not observed during the treatment. Gastrointestinal toxicity was common and included nausea (66.7%), diarrhea (13.3%) and vomiting (10.0%). There were no signs of fluid retention or nephrotoxicity, and none of the patients were affected by neurotoxicity or ototoxicity.

Discussion

This study has demonstrated that patients with advanced gastric cancer can obtain therapeutic benefit from docetaxel plus cisplatin combination chemotherapy as a second-line regimen, with acceptable toxicity. Until now, most agents

Table II. *Toxicity.*

	Grade				
	1	2	3	4	(%)
Leukopenia	13.3	33.3	23.3	3.3	73.3
Neutropenia	13.3	33.3	23.3	3.3	73.3
Anemia	33.3	13.3	3.3	0	50.0
Thrombocytopenia	26.7	26.7	6.7	0	60.0
Diarrhea	10.0	3.3	0	0	13.3
Nausea	26.7	30.0	10.0	0	66.7
Vomiting	6.7	3.3	0	0	10.0
Alopecia	26.7	66.7	0	0	93.3

used as second-line chemotherapeutics have failed to give satisfactory response rates for metastatic gastric cancer (14, 15); this includes docetaxel as a single agent, which produced response rates of only 5-20% in several trials. By contrast, the authors have found docetaxel to be an effective agent for highly advanced gastric cancer, with acceptable adverse effects. Another clinician reported the results of using docetaxel plus epirubicin as a combination second-line therapy: the mean progression-free survival was 16 weeks and the overall survival was 29 weeks (16). These results were similar to the survival rates observed here.

Many clinicians reported that docetaxel-based combination chemotherapy gave satisfactory response rates and MSTs in advanced gastric cancer when used as a first-line treatment (17, 18). Among these, the use of docetaxel combined with cisplatin resulted in response rates of 36-56%, with median times to progression of 6.1-8.3 months and overall survival times of 8.6-11.0 months. However, increasing doses of chemotherapeutic agents produced increasing rates of unacceptable toxic side-effects, without a clear improvement in survival. Few trials looked at docetaxel plus cisplatin as second-line chemotherapeutics. On the basis of these reports and the results presented here, we are encouraged to use docetaxel plus cisplatin combination chemotherapy as a second-line treatment for highly advanced gastric cancer. Recently, a study with this combination therapy as a second-line treatment showed similar results in patients with metastatic recurrent advanced gastric cancer (19). They used 5-fluorouracil-based conventional regimens as first-line chemotherapy, whereas we principally used S-1, except for patients who could not take orally-administered drugs. S-1 is a novel oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) based on a biochemical modulation of 5-fluorouracil (5-FU); S-1 contains tegafur (FT) and two types of enzyme inhibitor, 5-chloro-2,4- dihydroxypyrimidine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1 (20, 21). Approximately 80～90% of 5-FU is degraded by liver DPD and thereby the antitumor activity of 5-FU is diminished. CDHP, a reversible competitive inhibitor of DPD, is a pyrimidine derivative with inhibitory activity. Accordingly, the concentration of 5-FU can be retained in the plasma, tumor and peritoneal lining by combining CDHP and 5-FU (22). Moreover, Oxo reduces the gastrointestinal toxicity of 5-FU by inhibiting the phosphorylation of 5-FU within the gastrointestinal mucosal cells. Therefore, S-1 may be one of the most useful anticancer drugs for gastric cancer with augmented effects and reduced adverse effects. It is notable that docetaxel plus cisplatin combination chemotherapy has favorable outcomes in patients in whom such effective chemotherapeutic agents failed.

The patients enrolled in the current study had received either 5-fluorouracil plus cisplatin combination therapy or S-1 alone as front-line agents. When the antitumor effects of docetaxel and conventional chemotherapeutic agents (5-fluorouracil, S-1, cisplatin and mitomycin C) were compared using a novel MTT assay, no cross-resistance and distinct spectra of antitumor activity were observed (10). The unique inhibitory effect of docetaxel on the microtubule/tubulin system might contribute to these results. On the basis of this distinct mechanism of action, it is therefore reasonable to apply docetaxel after other conventional chemotherapeutic agents. The success of the combination therapy in terms of survival times was significantly better in patients who received S-1 as a first-line therapy compared to patients who were originally treated with FP. This might be attributable to the greater effectiveness of S-1 itself, as described above, or it might reflect the difference in background of the two patient groups, since the S-1-treated patients showed a better performance status than those in the FP-treated group.

It is of particular interest that the predominant toxic effects observed were severe leukopenia and neutropenia. These adverse effects clearly limited the use of this regimen, being reported in 70% of the patient population, with severe toxic effects (grades 3-4) in 26.7% of the patients. This level of toxicity was in the same range as that reported for other chemotherapeutic regimens (17, 18). However, the administration of G-CSF to patients suffering neutropenia supported their recovery and resulted in no infectious complications. None of the patients in this study died as a result of any adverse effects of the drugs used. Alopecia was frequently observed in this study and affected most of the male patients.

In conclusion, docetaxel-based combined chemotherapy (docetaxel and cisplatin) was relatively effective and tolerated by patients with advanced gastric cancer at the dose used in this study. Adverse hematological effects were severe and non-hematological toxic effects, including nausea/vomiting and alopecia, were moderate. This regimen should be studied further in order to confirm its utility for the treatment of advanced disease through a phase III trial.

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