Phase I Study of Biweekly Docetaxel and S-1 Combination Chemotherapy for Advanced Gastric Cancer

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Abstract. Background: Docetaxel and S-1 are novel antitumour chemotherapeutic agents with distinct toxicities. Here a phase I study of combined docetaxel and S-1 therapy for advanced gastric cancer is reported. Patients and Methods: The study group comprised 21 patients who received at least two courses of treatment. Intravenous docetaxel was administered with dose escalation from 20-45 mg/m² depending on the dose-limiting toxicity (DLT) on days 1 and 15, and oral S-1 (BSA <1.25 m², 80 mg/day; 1.25 ≤ BSA <1.50 m², 100 mg/day; 1.50 m² ≤BSA, 120 mg/day) was administered on days 1-7 and 15-21. Results: The maximum tolerated dose of docetaxel was 45 mg/m² and the DLT was defined as neutropenia. The recommended docetaxel dose was identified as 40 mg/m². The response rate (including partial responses) was 57.1%. Five cases showed no change and four showed progressive disease after two courses of treatment. The mean survival rate was 15 months. Conclusion: A phase II clinical trial is required to confirm these results.

Although the incidence of gastric cancer has been declining throughout the world, it is still a common cause of cancer-related death. In Japan, the incidence of early gastric cancer is high due to the prevalence of early-detection programmes (1, 2). However, most countries do not have mass-screening systems for gastric cancer and consequently have poor therapeutic outcomes for patients with advanced stage disease. Surgical resection is a promising treatment for gastric cancer. However, peritoneal metastasis, haematogenous metastasis and locally advanced tumours are frequently observed after curative resection in patients with advanced gastric cancer (3-5). Surgical resection has a limited ability to improve the survival time of patients with advanced gastric cancer. Chemotherapy thus has potential for the treatment of advanced gastric cancer and there is an urgent need to establish an effective chemotherapeutic regimen for such patients.

A 5-fluorouracil (5-FU) regimen has frequently been used for patients with advanced gastric cancer and provides acceptable survival benefits and improvements in quality of life compared with the best supportive care such as pain control and mental care (6, 7). However, the patient survival times on this regimen, administered either in combination with other drugs or as a monotherapy, have not been satisfactory for cases of advanced gastric cancer (8, 9). It is therefore important to establish a more effective regimen than 5-FU.

S-1 (TS-1; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) was developed by the biochemical modulation of tegafur (FT) in order to inhibit dihydropyrimidine dehydrogenase (DPD). S-1 contains FT, 5-chloro-2,4-dihydroxypyridine (gimeracil, CDHP) and potassium oxonate (oteracil, oxo) in a molar ratio of 1:0.4:1. Although 5-FU is degraded to α-fluoro-β-alanine by DPD, CDHP greatly inhibits DPD activity, leading to high serum levels of 5-FU. Moreover, oxo, which is distributed throughout the gastrointestinal tract, inhibits the phosphorylation of 5-FU and therefore decreases its gastrointestinal tract toxicity. S-1 is a well-designed oral...
anticancer drug with dual actions in reinforcing antitumour activity and reducing gastrointestinal toxicity (10). Recently, a randomized controlled study that compared therapeutic outcomes with and without S-1 adjuvant chemotherapy for patients with stage II or III gastric cancer showed that this treatment was effective (11). The therapeutic results of S-1 administered either alone or in combination with other chemotherapeutic agents in patients with advanced gastric cancer have also shown satisfactory outcomes (12-14).

Docetaxel (Taxotere; Sanofi-Aventis, Paris, France) is a semi-synthetic taxoid derived from the European yew tree, Taxus baccata. Docetaxel has been frequently used for the treatment of gastric cancer, as well as breast, oesophageal, and head and neck cancer. Docetaxel has shown acceptable outcomes both as a single agent and in combination with fluoropyrimidines or other agents, although it has adverse haematological toxicities (leucopenia and neutropenia) (15-18).

Based on the promising activities of S-1 and docetaxel as first-line treatments for gastric cancer patients, a phase I study of biweekly S-1 and docetaxel combination therapy was conducted in an outpatient clinic, in order to determine the maximum tolerated dose (MTD) and the recommended dose (RD) for a phase II study. There have been two previous reports on phase I studies of S-1 and docetaxel therapy for gastric cancer (19, 20), and there have only been two phase I/II studies (21, 22). Moreover, these studies involved relatively small mean numbers of treatment cycles. The current study was thus intended to establish a safe long-term regimen of docetaxel and S-1 in an outpatient setting.

**Patients and Methods**

*Eligibility.* Patients who had histologically proven advanced gastric cancer (inoperable or recurrent) were enrolled in this study. The inclusion criteria in terms of the disease characteristics were as follows: 20-75 years of age; Eastern Cooperative Oncology Group (ECOG) performance status <2; estimated life expectancy ≥3 months; adequate liver function (total serum bilirubin <1.5 mg/dl and transaminase ≤2 times the normal upper limit for our institution); adequate renal function (serum creatinine within the normal upper limit for our institution, blood urea nitrogen ≤25 mg/dl and 24 h creatinine clearance >50 ml/min); adequate haematopoietic function (4,000/mm³ ≤ WBC count ≤12,000/mm³; absolute neutrophil count >2,000/mm³; platelet count ≥10x10⁴/mm³ and haemoglobin level ≥9.5 g/dl); adequate cardiac function; adequate pulmonary function; written informed consent provided by the patient. The major exclusion criteria were as follows: brain metastasis, symptomatic infectious disease, past history of drug allergy, symptomatic peripheral neuropathy or oedema, other active malignancies, pregnancy or breast feeding, uncontrolled diabetes mellitus, uncontrolled mental illness and gastrointestinal haemorrhage. This study was approved by the Institutional Review Board of our institution.

**Study design and treatment.** S-1 of fixed dose was administered orally twice daily for one week according to the body surface area (BSA) as follows: BSA <1.25 m², 80 mg/day; 1.25 ≤ BSA <1.50 m², 100 mg/day; 1.50 ≤ BSA, 120 mg/day. This was followed by a drug-free interval of one week. A variable dose of docetaxel was administered intravenously on days 1 and 15. Docetaxel was diluted in 100 ml normal saline and infused for 1 h. Dexamethasone (8 mg) was infused 1 h prior to the administration of docetaxel, and a further 4 mg dexamethasone was administered orally for two days to reduce the risk of a hypersensitivity reaction. Each course lasted for one month. The dose-limiting toxicity (DLT) was assessed over two courses. The treatment was continued until either disease progression (PD) or DLT was observed (Figure 1).

The use of granulocyte colony-stimulating factor (G-CSF) was permitted if a patient developed grade 4 neutropenia. Antiemetic treatment was also permitted under the direction of the physician.

The initial dose of docetaxel was 20 mg/m² (dose level 1), and this was increased up to a maximum of 50 mg/m² in 5 mg/m² steps. If unacceptable toxicity was observed at dose level 1, the effect of docetaxel at 15 mg/m² (dose level 0) would be explored.

Toxicity was graded for each cycle according to the National Cancer Institute Common Toxicity Criteria (Version 3). DLT was defined as follows: grade 4 leu kopenia or neutropenia; grade 3 neutropenia with a fever (>38.0°C); grade 4 thrombocytopenia or grade 3 thrombocytopenia with a bleeding tendency; grade 3-4 non-haematological toxicity with the exceptions of nausea, vomiting and alopecia. Treatment was discontinued if recovery of the symptoms did not occur within days.

At least three patients were tested at each dose level. The dose-escalation schedule was as follows. If DLT was not observed in any of the three cases, the dose was increased to the next level. If DLT was observed in one of the three cases, an additional three patients were treated at the same dose level. If only one case showed DLT among these six cases, the dose was increased to the next level. If two or more of the six cases showed DLT, the dose level was defined as the MTD. The dose escalation was continued until the MTD was reached, and the level one step below was set as the RD for further evaluation in a phase II study.

The tumour response was assessed based on the Response Evaluation Criteria in Solid Tumours (RECIST) after two courses of treatment. The response status of measurable lesions during the treatment was evaluated by a barium meal study, endoscopy, ultrasonography, computed tomography or magnetic resonance imaging. These evaluations were repeated after one course if there was a partial response (PR). Cytology or diagnostic laparoscopy was additionally employed to assess non-measurable lesions, such as ascites. The mean follow-up period (mean±SD) was 10.4±0.5 months.

**Results**

**Patient characteristics.** The patient characteristics are listed in Table I. In total, 21 patients were enrolled in the study between April 2006 and December 2007. All of the patients had resectable primary gastric cancer. The ECOG performance status was 0 in 19 of the patients, and the mean
age was 65.6 years. In total, 105 courses were performed, and the mean number of courses for each patient (mean±SD) was 4.8±2.2 (range=2-11 courses). The evaluable lesions are listed in Table I.

Toxicity. The haematological toxicity profiles are shown in Table II. None of the patients developed haematological DLT at dose levels 1-4. However, one of the six patients showed grade 4 leukopenia during the first and second course of treatment at dose level 5. Moreover, all three of the patients developed DLT at dose level 6: one showed grade 4 neutropenia, while the other two showed grade 3 prolonged neutropenia. The non-haematological toxicities are summarized in Table III. At dose level 1, only grade 1 non-haematological toxicities were observed. At dose level 2, grade 1 or 2 anorexia and alopecia were noted. At dose level 3, grade 3 liver dysfunction with fever (DLT) was observed in one patient, in addition to grade 1 or 2 anorexia, general fatigue and alopecia. At dose levels 4-6, all of the non-haematological toxicities were grade 1 or 2.

Treatment response. Of the 21 patients, 12 showed PR after two courses of the treatment, while five showed no change and four showed PD. The overall response rate was 57.1%. Among the 10 patients with haematogenous metastasis, PR was observed in four (40%). Among the nine patients with non-resectable primary tumour due to T4, PR was observed in eight (88.9%). Among the 10 patients with bulky N1, 2 or distant lymph node metastasis (N3), PR was observed in seven (70%). Among the five patients with peritoneal metastasis, PR was observed in two (40%). Among the 10 patients with a histologically undifferentiated-type tumour, PR was observed in four (40%). Eight out of the 11 patients (72.7%) with differentiated type tumours responded \(p=0.1301\). Out of the four patients who showed PD, three suffered from liver metastasis and one had peritoneal dissemination as confirmed by diagnostic laparoscopy. The response rate to the treatment did not differ between each dose level of docetaxel.
Survival. Out of these 21 patients, 15 patients remained alive at the end of the study, while six patients had died of gastric cancer. The 1-year survival rate was 80.4% and the mean survival time was 15 months (Figure 2).

### Discussion

The RD of docetaxel was identified as 40 mg/m$^2$ (days 1 and 15). Among the five patients who showed DLT, neutropenia was observed most frequently (three cases), along with leucopenia (one case) and liver dysfunction with fever (one patient). All of the toxicities were well controlled and the treatments were continued as initially planned.

In general, S-1 is administered orally for four consecutive weeks followed by a two-week interval. The effectiveness of S-1 has been demonstrated in an adjuvant setting for stage II and III gastric cancer (11). However, the continuous administration of S-1 for three weeks or more can result in unacceptable toxicities, particularly haematological toxicities. Therefore, an alternative treatment schedule (two-week administration followed by a one-week interval) is sometimes employed in order to allow continuation of the therapy. In a recent report, the therapeutic outcomes of combined treatment with S-1 and cisplatin were shown to be better than those of S-1 monotherapy for advanced gastric cancer (23). Therefore, S-1 should be used in adjuvant chemotherapy for stage II and III gastric cancer as a monotherapy, whereas combined therapy should be employed in the treatment of advanced gastric cancer (in cases that are non-resectable, recurrent or involve palliative gastrectomy).

In Europe, docetaxel, cisplatin and 5-FU (DCF) combination therapy has been commonly used for cases of advanced gastric cancer (18). In a previous study, we showed that docetaxel with cisplatin combined therapy had satisfactory outcomes as a second-line treatment for advanced gastric cancer (24). The principal toxicity of docetaxel is neutropenia, followed by leucopenia and alopecia. In general, neutropenia can be managed by G-CSF administration, which does not lead to life-threatening...
toxicities if administered in adequate doses and precisely managed. The use of docetaxel for advanced gastric cancer is therefore acceptable.

Previous phase I or II studies have reported acceptable toxicities and satisfactory outcomes of combination therapy with S-1 and docetaxel for advanced gastric cancer (19-22) (Figure 3). In these studies, the toxicities were assessed during the first course of treatment. By contrast, our current study assessed the toxicities during the first and second courses, and employed stricter criteria. In agreement with the previous studies, we found that the most common toxicity was neutropenia, which was both predictable and manageable. The dose intensities of S-1 and docetaxel employed in the previous studies were as follows: 280 mg/m$^2$/wk, 17.5 mg/m$^2$/wk (19); 373.3 mg/m$^2$/wk, 15.0 mg/m$^2$/wk (20); 373.3 mg/m$^2$/wk, 13.3 mg/m$^2$/wk (21) and 280 mg/m$^2$/wk, 10.0 mg/m$^2$/wk (22), respectively. By contrast in the current study, the dose intensities of S-1 and docetaxel were 280 mg/m$^2$/wk and 20.0 mg/m$^2$/wk, respectively. The dose intensity of docetaxel was thus notably higher than those in the previous studies. Moreover, the median or mean numbers of courses for each patient in each study were 1.7 (19), 2.3 (20), 7 (21) and 3 (22), while in the current study, it was 4.8. Therefore, it is hoped that the treatment schedule described may be adopted widely.

The two previous phase II studies using these regimens reported overall response rates and median overall survival rates of 56.3% (21) and 46.0% (22), and 14.3 months (21) and 14.0 months (22), respectively. The regimen in the current study provided equivalent therapeutic results, even though it was a phase I study. This regimen might therefore be satisfactory. Other regimens for advanced gastric cancer have previously demonstrated unfavourable outcomes. However, new chemotherapeutic agents, such as S-1, taxane derivatives, and CPT-11 (irinotecan) in combination with cisplatin have improved the therapeutic outcomes in patients with advanced gastric cancer. Docetaxel is thus a candidate for use in combination therapy with S-1, but to clarify which agent is most suitable for use with S-1 in advanced gastric cancer therapy, a well-designed phase III study is required.

The initial aim of this phase I study was to establish an effective, safe and long-term regimen for advanced gastric cancer in an outpatient setting. From this point of view, the regimen described in our study was acceptable, although more patients are necessary to confirm the results of this study.

Figure 3. Comparison of treatment schedules of combination therapy with docetaxel and S-1.
In conclusion, this phase I study showed the efficacy of biweekly docetaxel and S-1 combination chemotherapy for patients with advanced gastric cancer. A phase II clinical trial using this regimen in patients with advanced gastric cancer is required.

References


