Phase I Study of Docetaxel, Cisplatin and S-1 in Patients with Advanced Gastric Cancer

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Objective: S-1 plus cisplatin is standard treatment for advanced gastric cancer in Japan. Triplet therapy with docetaxel, cisplatin and fluoropyrimidine showed a survival benefit over doublet therapy, but was associated with substantial toxicities. We investigated the maximum tolerated dose of combination chemotherapy with divided-dose docetaxel added to standard-dose S-1 plus cisplatin in advanced gastric cancer patients.

Methods: Patients with advanced gastric cancer, naive to chemotherapy or not refractory to fluoropyrimidine, were enrolled. Fixed doses of S-1 (40 mg/m^2 twice daily for 3 weeks) and cisplatin (60 mg/m^2 on day 1) were administered with increasing docetaxel dose levels of 20 mg/m^2 (dose level 1), 25 mg/m^2 (dose level 2) and 30 mg/m^2 (dose level 3) on days 1, 8 and 15, or 40 mg/m^2 (dose level 4) on days 1 and 15 of a 5-week cycle. Treatment cycles were repeated until disease progression, patient’s refusal or unacceptable toxicity occurred.

Results: Fifteen patients were enrolled. During the first cycle, no dose-limiting toxicity was observed at dose levels 1 and 2. At dose level 3, grade 3 febrile neutropenia was seen in one patient. At dose level 4, grade 3 infection and grade 3 abdominal pain were observed. Thus, dose level 4 was determined to be the maximum tolerated dose. The response rate was 54% (7/13), and median progression-free survival and overall survival were 243 and 383 days, respectively.

Conclusions: The recommended dose of docetaxel added to standard-dose S-1 (80 mg/m^2 days 1–21) plus cisplatin (60 mg/m^2 day 1) was 40 mg/m^2 on days 1 and 15 of a 5-week cycle.

Key words: docetaxel – cisplatin – s-1 – DCS – gastric cancer

INTRODUCTION

Gastric cancer is more prevalent in Eastern Asia, Eastern Europe and Central and South America than in other regions. In Japan, gastric cancer is the second most frequent cause of cancer mortality, accounting for 50,597 of the 336,468 cancers occurring in 2007 (1). Because of the vague and non-specific symptoms associated with gastric cancer, the disease is often advanced at the time of diagnosis. Despite the identification and development of several new types of anti-cancer agents, gastric cancer remains an aggressive malignancy with a median survival of 9–13 months in patients with metastatic or recurrent disease (2–5).

There is no global consensus on a standard regimen for gastric cancer; however, a combination of 5-fluorouracil (5-FU) plus cisplatin is the most commonly used treatment worldwide. In Japan, 5-FU alone was used as the control.
arm in clinical trials based on the results of the JCOG9205 trial (6). The subsequent trial, JCOG9912, was started in 1999 and compared 5-FU alone with CPT-11 plus cisplatin or S-1 alone. The results showed that S-1 was not inferior to 5-FU alone, although CPT-11 plus cisplatin did not show superiority (4). Subsequently, the SPIRITS trial comparing S-1 alone with S-1 plus cisplatin showed the superiority of S-1 plus cisplatin to S-1 alone (5). From the results of these randomized trials, S-1 plus cisplatin was recognized as the new standard of care for advanced gastric cancer in Japan.

Docetaxel monotherapy used to treat advanced gastric cancer yielded response rates of 17–24% in phase II trials (7–9). Recently, several results of randomized trials with docetaxel in combination with fluorouracil plus cisplatin were reported. The V325 study demonstrated the superiority of docetaxel (75 mg/m², thrice weekly) in combination with 5-FU plus cisplatin (DCF) to S-1 plus cisplatin (CF) in the time to progression, overall survival and response rate (2). However, the toxicity of DCF caused a higher incidence of severe neutropenia than CF, and the authors emphasized the need for vigilant patient selection and education, monitoring and active management. Roth et al. (10) reported on a randomized phase II study comparing three chemotherapy regimens; TCF (docetaxel, 85 mg/m² at initiation then a dose reduction to 75 mg/m², thrice weekly, with cisplatin and fluorouracil), TC (docetaxel and cisplatin) and ECF (epirubicin, cisplatin and fluorouracil). Although the efficacy of TCF was more promising than that of TC, docetaxel-containing regimens were associated with more severe haematological toxicity than ECF. From the results of these two studies, it was thought that adding thrice-weekly docetaxel (75 mg/m²) to cisplatin and 5-FU is highly effective in advanced gastric cancer, although it is associated with a high incidence of haematological toxicity. However, the triplet regimen including thrice-weekly docetaxel has not been generally accepted as a new standard of treatment because of its substantial toxicity.

For advanced non-small cell lung cancer, several randomized phase II or III trials of weekly docetaxel compared with thrice-weekly docetaxel in the second-line setting were reported (11–16). A meta-analysis of these randomized studies demonstrated that grade 3 neutropenia was significantly less with weekly docetaxel than with thrice-weekly docetaxel, while overall survival did not significantly differ between the two schedules (relative risk was 1.01) (17).

From these results, it is speculated that divided doses of docetaxel can reduce the toxicity while preserving its activity. In order to reduce the severe haematological toxicity of a triplet regimen, we conducted a phase I study of divided-dose docetaxel in combination with the standard treatment schedule of S-1 plus cisplatin for advanced gastric cancer. The primary endpoint was to determine the maximum tolerated dose (MTD) of this regimen in patients with advanced gastric cancer. Secondary endpoints were toxicity and the response rate.

PATIENTS AND METHODS

PATIENT ELIGIBILITY

This study was conducted at Shizuoka Cancer Center, Shizuoka, Japan, and Aichi Cancer Center, Aichi, Japan. To be eligible, patients had to meet the following eligibility criteria: (i) have histologically proven metastatic or recurrent gastric cancer, (ii) be between the ages of 20–75 years, (iii) have a performance status of 1 or less according to the Eastern Clinical Oncology Group (ECOG) scale, (iv) an estimated life expectancy of >8 weeks, (v) no prior chemotherapy or no evidence of resistance to fluoropyrimidines (more than 6 months after the last administration if a patient had received monotherapy with fluoropyrimidine in the adjuvant or neo-adjuvant setting), (vi) adequate bone marrow function (a white blood cell count >4000 and <12 000/mm³, neutrophil count >2000/mm³, platelet count >100 000/mm³), (vii) adequate hepatic function [a serum total bilirubin level ≤1.2 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤100IU/l], (viii) adequate renal function (a serum creatinine level of ≤1.2 mg/dl, creatinine clearance by Cockcroft–Gault Equation >60 ml/minute), (ix) an assessable lesion [measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.0 (18) was not mandatory] and (x) provide written informed consent.

The exclusion criteria were as follows: (i) patients with an active infection, (ii) severe peritoneal dissemination with subileus or massive ascites, (iii) marked pleural effusion, (iv) metastasis to the central nervous system, (v) mental disorder, (vi) watery diarrhoea, (vii) interstitial pneumonia, (viii) severe comorbidities such as heart disease or renal disease, (ix) active concomitant malignancy or were (x) pregnant or lactating women or women of childbearing age, unless they were practising effective contraception.

ADMINISTRATION AND DOSE ESCALATION

S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) was given orally twice daily for the first 3 weeks of a 5-week cycle. The dose of S-1 administered each time was determined according to the patient’s body surface area as follows: <1.25 m², 40 mg; 1.25–1.50 m², 50 mg and >1.5 m², 60 mg. Docetaxel (Sanofi-aventis K.K., Tokyo, Japan) was given as a 1-hour intravenous infusion followed by cisplatin (Bristol-Myers Squibb Company, Tokyo, Japan) 60 mg/m² given as a 2-hour intravenous infusion on day 1 of each cycle.

Initially, this study was started with three dose levels of weekly docetaxel given on days 1, 8 and 15 every 5 weeks at dose levels of 20 mg/m² (DL1), 25 mg/m² (DL2) and 30 mg/m² (DL3). Three patients were initially enrolled at each DL. If none experienced a DLT during the first cycle, the next cohort of patients was treated at the subsequent DL. If one or two of the three patients at each DL experienced any DLT, an additional three patients were enrolled at the same DL, and
then if less than two of six patients experienced any DLT, the next cohort was started at the next higher DL.

However, the protocol was amended after DLT evaluation to DL2, because two of six patients (one at DL1 and another at DL2) refused treatment due to severe fatigue after the second cycle. We believe the severe fatigue was caused by the weekly schedule of docetaxel (19). Thus, the protocol was amended and DL4 of docetaxel (40 mg/m²) was administered on days 1 and 15 every 5 weeks with a fixed dose of S-1 plus cisplatin. Actually the dose intensity of docetaxel at DL4 (16 mg/m²/week) was less than DL3 (18 mg/m²/week). Simultaneously, in the protocol amendment, if less than two of the initial three patients at DL3 experienced any DLT, the subsequent patients were enrolled at DL4 because of the lower dose intensity at DL4 than at DL3. The recommended dose (RD) for the next trial was defined as the DL at which less than two of six patients experienced DLT. No intra-subject dose escalation was performed.

If patients had counts of leukocytes <2000/mm³, platelets <50 000/mm³, total bilirubin of >1.5 mg/dl, serum creatinine of >1.5 mg/dl or non-haematological toxicity (nausea, vomiting, diarrhoea, stomatitis and fatigue) of grade 3, S-1 was stopped until recovery. If patients had counts of leukocytes <2000/mm³, platelets <50 000/mm³, total bilirubin >1.5 mg/dl, AST or ALT levels >100 IU/L or non-haematological toxicity (nausea, vomiting, diarrhoea, stomatitis and fatigue) of grade 3, docetaxel was stopped until recovery; however, if these toxicities lasted for more than 14 days, docetaxel was skipped. To receive a subsequent cycle of chemotherapy, patients had to have leukocyte counts >3000/mm³, neutrophil counts >1500/mm³, platelets >100 000/mm³ and serum creatinine <1.2 mg/dl, and the recovery of any treatment-related non-haematological toxicity to grade <1 (except alopecia and neuropathy). Treatment was repeated until disease progression, patient refusal, a serious adverse event occurred or completion of the protocol-designated treatment of eight cycles.

**Dose-Limiting Toxicity**

A DLT was defined as any of following events observed before the second course: (i) grade 4 neutropenia lasting for >3 days, even with granulocyte colony stimulating factor; (ii) grade 3 febrile neutropenia; (iii) grade 4 thrombocytopenia; (iv) grade 3 or 4 non-haematological toxicity (excluding nausea, vomiting, constipation, allergic reaction and electrolyte abnormalities); (v) grade 3 diarrhoea persisting despite adequate anti-diarrhoeal medication; (vi) a delay of starting the second course over 2 weeks; (vii) skipping docetaxel administration (day 8 or 15) or (viii) the interruption of S-1 medication >7 days.

**Toxicity and Response Evaluation**

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0. Patients’ symptoms and general condition were observed periodically, and physical examinations, complete blood counts with differential counts, and serum chemical laboratory and urine tests were checked at least once a week during the DLT evaluation period. Tumour response was evaluated according to RECIST version 1.0 (18) every 2 months until tumour progression. Progression-free survival was defined as the time from the date of starting treatment to the date of the first documentation of disease progression (by imaging methods or clinical judgment) or death. Patients with progression-free status were censored at the last date verifying survival. Overall survival was defined as the time from the date of starting treatment to the date of death. Surviving patients were censored at the last confirmation date of survival.

This phase I study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at Shizuoka Cancer Center and Aichi Cancer Center, including the protocol amendment. An independent data and safety monitoring committee monitored this study. The study was registered with UMIN-CTR, number UMIN00000978.

**RESULTS**

Fifteen patients were enrolled in this study between September 2007 and March 2009 at Shizuoka Cancer Center and Aichi Cancer Center. Toxicity was assessable in all patients, and objective response was assessable in 13 patients with target lesions. The patient characteristics are shown in Table 1. The patients’ median age was 65 (range, 52–72) years; three patients (20%) had prior gastrectomy, and three (20%) and two patients (13%) had prior chemotherapy in the neo-adjuvant and adjuvant settings, respectively. A total of 67 cycles of chemotherapy were administered with a median of 4 cycles. One patient was lost to follow-up because of moving to another hospital after discontinuation of treatment.

**Toxicity**

Major adverse events occurring during the first cycle at each DL are shown in Table 2. There was no DLT at DL1 and DL2. Grade 3 febrile neutropenia occurred in one of the three patients at DL3. At DL4, two DLTs, grade 3 infection in one patient with a normal absolute neutrophil count (blood) and grade 3 pain (abdomen-NOS) in another patient were observed. In the former patient, who had peritoneal metastasis, fever (40°C) was observed on day 3 after initiation of chemotherapy, and antibiotics were administered after performing the blood culture. Thereafter, his body temperature was reduced on day 5. The result of a blood culture showed gram-negative bacillus, and we defined this adverse event as a DLT, because it is very difficult to deny the relation between this event and the protocol treatment.
In the latter case, grade 3 abdominal pain occurred on day 13 after the initiation of chemotherapy, after which the administration of S-1 was discontinued and patient was taken off food, with the administration of pentazocine hydrochloride if necessary. The patient recovered from pain on day 17, and this adverse event was thought to be enteritis related to S-1.

From these results, we determined that the MTD of this triplet regimen was DL4.

Toxicities in all treatment cycles are shown in Table 3. As anticipated, myelosuppression was the major toxicity of this regimen. However, there was no episode of febrile neutropenia, although one patient with a normal neutrophil count experienced infection. As for the non-haematological toxicities, grade 3 fatigue was seen in one patient each at DL1, DL2 and DL3, and anorexia in one patient at DL2 and DL3, which led to a protocol amendment. Among the six patients at DL4, grade 4 haematological toxicity did not occur, grade 3 nausea occurred in one patient, grade 3 anorexia in two patients and grade 3 hyponatremia in one patient.

One patient at DL1 died within 30 days after the last administration of the treatment according to protocol. This patient received gastro-jejunostomy for impaired gastric passage because of progressive disease on day 32 in the sixth cycle of the protocol treatment, and then experienced sepsis and multiple organ dysfunction.

**Efficacy**

Response was evaluated in 13 patients who had target lesions. Objective tumour responses at each DL are shown in Table 4. Of the 13 patients with target lesions, seven patients (two at DL1; three at DL2; one at DL3; one at DL4) achieved partial responses yielding an overall response rate of 54% [95% confidence interval (CI), 27–81%]. Median progression-free survival was 243 days, and median overall survival was 383 days with a median follow-up period of 290 days.
In October 2009, protocol treatment was continued in three patients. The reasons for discontinuation of the protocol treatment were progressive disease in seven (47%), patient refusal due to toxicities in three (20%, severe fatigue in two and abdominal pain in one) and completion of eight cycles of protocol treatment in two (13%) patients. One patient, who had only para-aortic lymph node metastasis, had completed eight cycles of treatment and had a partial response. Thereafter, he received gastrectomy and lymphadenectomy with curative intent. The pathological findings showed only 1 of 36 dissected lymph nodes with small nests of metastasis, and no residual tumour was detected in the primary site.

### DISCUSSION

Several reports showed the superiority of triplet chemotherapy containing a taxane compared with doublet chemotherapy with fluorouracil plus cisplatin for head and neck cancer (20,21) and gastric cancer (2). However, high incidences of severe neutropenia and febrile neutropenia are serious problems associated with these treatment regimens. Recently, triplet regimens with divided-dose docetaxel have been investigated. Tebbutt et al. (22) reported a randomized phase II trial (AGITG ATTAX). In this study, the schedule of this triplet (weekly TCF) regimen included weekly administration of docetaxel as follows: docetaxel 30 mg/m² on days 1 and 8, cisplatin 60 mg/m² on day 1 and fluorouracil 200 mg/m² continuously every three weeks. The incidence of febrile neutropenia was 4%. Another phase II study of a triplet regimen with a bi-weekly dose of docetaxel was the GASTRO-TAX-1 trial (23). The schedule of the T-PLF regimen was docetaxel 50 mg/m² and cisplatin 50 mg/m² on days 1, 15 and 29, and fluorouracil 2000 mg/m² plus leucovorin 500 mg/m² on days 1, 8, 15, 22, 29 and 36 every 8 weeks. The incidence of febrile neutropenia was also as low as 5%. In this study of DCS with divided-dose docetaxel, none of the 15 patients experienced febrile neutropenia, although some haematological toxicity occurred. Thus, divided-dose docetaxel added to a cisplatin plus fluorouracil regimen is associated with lower grade haematological toxicities than triplet chemotherapy based on thrice-weekly docetaxel.

A weekly schedule of docetaxel has been investigated in several cancers such as lung, breast and prostate cancer. A review of randomized studies (19), which compared weekly versus thrice-weekly administration of docetaxel, reported that the efficacy appeared to be similar between the two schedules in all diseases. However, severe fatigue and asthenia were the most common non-haematological toxicities in patients treated with a weekly schedule of docetaxel. In our study, two patients refused protocol treatment because of severe fatigue, causing us to amend the protocol to add DL4, which included a bi-weekly schedule of docetaxel. The results of this study show that fatigue greater than grade 3 was observed at all DLs (DL1, DL2 and DL3) with a weekly schedule of docetaxel; however, severe fatigue was not seen at DL4 with bi-weekly docetaxel. Although the follow-up period was shorter in the DL4 cohort than at the other DLs, bi-weekly docetaxel seemed to be better tolerated than docetaxel administered weekly.

### Table 3. Adverse events in all cycles

<table>
<thead>
<tr>
<th>Dose level 1</th>
<th>Dose level 2</th>
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<td>Grade 4</td>
<td>Grade 4</td>
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</table>

### Table 4. Response rate

<table>
<thead>
<tr>
<th>Dose level</th>
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<th>Total number of cycles administered</th>
<th>Overall response</th>
<th>RR (%)</th>
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<td></td>
<td>CR</td>
<td>PR</td>
</tr>
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<td>3</td>
<td>16</td>
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<td>67</td>
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<tr>
<td>2</td>
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<td>15</td>
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</tr>
<tr>
<td>3</td>
<td>3</td>
<td>13+</td>
<td>0  1  0  2  0  33</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>12+</td>
<td>0  1  0  2  1  25</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>56+</td>
<td>0  7  1  4  1  54</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; NE, not evaluated; RR, response rate.

### REASON OF PROTOCOL TREATMENT CESSION

In October 2009, protocol treatment was continued in three patients. The reasons for discontinuation of the protocol treatment were progressive disease in seven (47%), patient refusal due to toxicities in three (20%, severe fatigue in two and abdominal pain in one) and completion of eight cycles of protocol treatment in two (13%) patients. One patient, who had only para-aortic lymph node metastasis, had completed eight cycles of treatment and had a partial response. Thereafter, he received gastrectomy and lymphadenectomy with curative intent. The pathological findings showed only 1 of 36 dissected lymph nodes with small nests of metastasis, and no residual tumour was detected in the primary site.

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reported on a phase II study of the DCS regimen, which consisted of S-1 (40 mg/m²) and docetaxel (60 mg/m²) on day 1–14, intravenous cisplatin (60 mg/m²) and docetaxel (60 mg/m²) on day 8 every 3 weeks. The objective response rate was 87.1% with one complete response (3.2%); the median survival time and progression-free survival were 687 days and 226 days, respectively, and the regimen was associated with severe hematological toxicities. Nakayama et al. (25) reported on another phase II study of the DCS regimen, which consisted of docetaxel (40 mg/m²) and cisplatin (60–70 mg/m²) given intravenously on day 1, and S-1 given orally at a dose of 40 mg/m² twice daily from days 1 to 14 of a 28-day cycle. The overall response rate was 81.3% (48/59; 95% CI, 80.7–91.2), and the median survival time and progression-free survival had not been reached. From the results of these two phase II studies, the response rates of triplet regimens were estimated to be around 80%. These phase II studies suggested that triplet chemotherapy regimens using S-1 might be more active than those with S-FU.

In the future, DCS regimens are likely to have two indications: as palliative care and in the neo-adjuvant setting; and triplet regimens at higher dose intensities are anticipated to be suitable for maximizing tumour shrinkage in the neo-adjuvant setting. On the other hand, less toxic regimens seem to be preferred in the palliative setting. It is necessary to select the most suitable regimens in both the neo-adjuvant and palliative settings by comparing these triplet regimens from the comprehensive view of the response rate (water-fall plot), progression-free survival, time to treatment failure and adverse events. Because the sample size of this study was very small, the triplet regimen with bi-weekly doses of taxane, which can maintain high dose intensity, will require further investigation in a suitable treatment setting.

In conclusion, the RD of the DCS regimen is as follows: docetaxel 40 mg/m² on days 1 and 15, cisplatin 60 mg/m² on day 1, S-1 80 mg/m² on days 1–21 every 5 weeks. Divided-dose docetaxel could be added to a standard dose of S-1 plus cisplatin combination therapy for advanced gastric cancer.

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Conflict of interest statement

None declared.

References


