Abstract

Purpose: To evaluate the efficacy and toxicity of docetaxel in combination with a novel oral 5-fluorouracil analogue S-1 for patients with advanced or recurrent gastric cancer.

Experimental Design: Patients with advanced or recurrent adenocarcinoma of the stomach and up to one previous chemotherapy regimen were treated with i.v. docetaxel 40 mg/m² on day 1 and oral S-1 80 mg/m²/d on days 1 to 14 every 3 weeks.

Results: Forty-eight patients (median age, 65 years; range, 25-75 years) received a total of 272 treatment cycles (median, 4; range, 1-17). No complete responses and 27 partial responses were observed for an overall response rate of 56.3% [95% confidence interval (95% CI), 38-66%]. Eighteen patients (37.5%) had stable disease and three patients (6.3%) had progressive disease as best response. The tumor control rate (complete response + partial response + stable disease) was 93.8% (95% CI, 83-98%). Median overall survival was 14.3 months (95% CI, 10.7-20.3 months) and median time to tumor progression was 7.3 months (95% CI, 4.3-10.0 months). The most common grade 3 to 4 hematologic toxicities were neutropenia (58.3%), leukopenia (41.7%), febrile neutropenia (8.3%), and anemia (8.3%). The most common grade 3 nonhematologic toxicities included anorexia (14.6%), stomatitis (8.3%), and nausea (6.3%). No grade 4 nonhematologic toxicities were reported and all treatment-related toxicities were resolved.

Conclusion: Docetaxel/S-1 combination is highly active and well tolerated in advanced or recurrent gastric cancer. Further investigation in randomized studies is warranted.

The prognosis for patients with unresectable advanced or recurrent gastric cancer is extremely poor; indeed, gastric cancer is the second most frequent cause of cancer-related mortality worldwide, accounting for ~700,000 deaths annually (1). Several novel chemotherapeutic agents, including the taxanes (paclitaxel and docetaxel), irinotecan, and, more recently, oxaliplatin, S-1, and capecitabine, have shown activity in gastric cancer and offer hope for improving patient outcomes in this setting (2, 3). Response rates of up to 65% were reported in phase II studies of regimens, including taxanes, irinotecan, or oxaliplatin, and, consequently, several combinations have been investigated in randomized phase II/III studies (3).

Docetaxel has shown promising activity in gastric cancer, both as monotherapy (4, 5) and in combination with other agents (6-8). In the phase III TAX 325 study, triple-agent therapy with docetaxel-cisplatin-5-fluorouracil (5-FU; TCF) was superior to cisplatin-5-FU in terms of response rate (37% versus 25%; x², P = 0.0106), time to progression (TTP; 5.6 months versus 3.7 months; risk reduction 32%; log-rank P = 0.0004), and survival (risk reduction 23% after a median follow-up of 23 months; log-rank P = 0.0201) in patients with metastatic gastric cancer (7). However, grade 3 to 4 treatment-emergent adverse events (regardless of relationship to study medication) occurred in 81% and 75% of patients receiving TCF and cisplatin-5-FU, respectively (7). In a phase II study in patients with advanced gastric cancer without prior chemotherapy, docetaxel combined with a continuous infusion of 5-FU (TF) showed promising efficacy compared with epirubicin-cisplatin-5-FU; among patients treated with TF and epirubicin-cisplatin-5-FU, respectively, the overall response rate (confirmed complete response plus confirmed partial response) was 37.8% and 35.6%, respectively (8). In a phase II study in patients with advanced gastric cancer without prior chemotherapy, docetaxel combined with a continuous infusion of 5-FU (TF) showed promising efficacy compared with epirubicin-cisplatin-5-FU; among patients treated with TF and epirubicin-cisplatin-5-FU, respectively, the overall response rate (confirmed complete response plus confirmed partial response) was 37.8% and 35.6%, respectively (8). In a phase II study in patients with advanced gastric cancer without prior chemotherapy, docetaxel combined with a continuous infusion of 5-FU (TF) showed promising efficacy compared with epirubicin-cisplatin-5-FU; among patients treated with TF and epirubicin-cisplatin-5-FU, respectively, the overall response rate (confirmed complete response plus confirmed partial response) was 37.8% and 35.6%, respectively (8).
gastrectomy (6). The median overall survival time of 12
months was prolonged compared with the survival times
reported for TF (8) and similar to those reported for the other
new-generation combinations (2).

S-1 is a novel, orally administered 5-FU analogue that contains
drug that contains three pharmacologic agents: tegafur, 5-chloro-2,4-dihydroxy-5-fluorouracil (a dihydropyrimidine dehydrogenase inhibitor), and potassium oxonate (which reduces the gastrointestinal toxicity of 5-FU; refs. 10–12). In a phase II study, S-1 monotherapy achieved an overall response rate of 44% in patients with advanced gastric cancer (11). S-1 is also synergistic with several
other anticancer agents, including cisplatin and irinotecan. In
one nonrandomized study, S-1 plus cisplatin achieved a 74% response rate and a median survival time of 12.5 months (13). However, in a subsequent study, the overall response rate for this
combination was 65% (14).

Docetaxel and S-1 have different mechanisms of antitumor
activity and are highly synergistic in gastric cancer xenografts (15). The combination was active and well tolerated in a phase
I study in patients with advanced and or recurrent gastric cancer (16). Hence, we initiated the present phase II study to further
assess the efficacy and toxicity profile of this regimen.

**Patients and Methods**

**Eligibility.** Patients were required to have pathologically proven inoperable or recurrent gastric cancer and to have at least one measurable lesion. Other main eligibility criteria were as follows: age 20 to 75 years; Eastern Cooperative Oncology Group performance status ≤2; estimated life expectancy ≥3 months; no prior chemotherapy or one adjuvant regimen that did not include a taxane or S-1 and that was completed ≥4 weeks before entry; adequate hepatic, cardiac, renal, and bone marrow function [i.e., WBC count ≥4,000 to 12,000/mm3, absolute neutrophil count ≥2,000/mm3, platelet count ≥100,000/mm3, hemoglobin ≥9.5 g/dL, serum bilirubin level ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase within twice the upper limit of normal (ULN) for the institution, blood urea nitrogen ≤25 mg/dL, serum creatinine within the ULN, and 24-hour creatinine clearance ≥50 mL/min]. Main exclusion criteria were as follows: symptomatic infectious disease, pulmonary fibrosis, interstitial pneumonia, hemorrhage/bleeding ≥grade 3 (National Cancer Institute Common Toxicity Criteria), symptomatic peripheral neuropathy or edema ≥grade 2, active secondary cancer, symptomatic pleural effusion or ascites, past history of allergic reaction to polysorbate 80, pregnancy or breast feeding, obstructive bowel disease, concomitant therapy with another anticancer drug or fluycytocine, and a past history of drug allergy. The study was approved by the institutional review board of the participating center and all patients provided written informed consent.

**Study design and treatment.** This was a nonrandomized, single-center (Hiroshima Cancer Treatment Development Organization), phase II study. The primary end point of this study was the objective response rate induced by treatment with docetaxel and S-1 in patients with unresectable advanced or recurrent gastric cancer. On the basis of the hypothesis of an expected response rate between 35% and 55%, the planned number of patients for inclusion was 48 according to the Fleming’s single-stage design. With null hypothesis 35% response rate and alternative hypothesis 55% response rate (worthy of further study) one-sided ≥ 0.05 and 85% power, a total of 44 evaluable patients were required. In consideration of 10% ineligible patients, we planned to enroll 48 patients. S-1 80 mg/m2 was given orally twice daily (within 30 minutes after the morning and evening meals) for 2 weeks, followed by a drug-free interval of 1 week (one cycle). Docetaxel 40 mg/m2 was diluted in 100 mL of 0.9% saline and administered as a 1-hour infusion on the morning of day 1 of each cycle (i.e., every 3 weeks). The docetaxel infusion was started simultaneously with S-1 administration. Dexamethasone 8 mg was infused 1 hour before docetaxel administration and a further 4 mg dose was taken orally 12 and 24 hours after the docetaxel administration to reduce the risk of hypersensitivity reaction. Additional treatment with corticosteroids was not permitted unless the patient’s condition was life threatening. Granulocyte colony-stimulating factor was permitted if a patient developed grade 4 neutropenia; primary prophylaxis was not allowed. Antiemetic (ondansetron) treatment and diuretic treatment for edema were allowed at the discretion of the treating physician. Treatment was continued until tumor progression, unacceptable toxicity, patient refusal, or the physician’s decision to stop treatment.

Toxicity was graded at each cycle according to the National Cancer Institute Common Toxicity Criteria version 2. The dose of S-1 alone was to be reduced to 50 mg/m2 in the event of any of the following toxicities during the previous treatment cycle: grade 4 leukopenia or neutropenia; thrombocytopenia ≥grade 3; and nonhematologic toxicity ≥grade 3 except anorexia, nausea, and vomiting. There were no dose reductions for docetaxel. Treatment with both S-1 and docetaxel was delayed for up to 2 weeks if patients had insufficient hepatic, cardiac, renal, or bone marrow function (i.e., WBC ≤3,000/mm3, neutrophils ≤1,500/mm3, platelets ≤100,000/mm3, fever ≥38°C with grade 3 to 4 neutropenia, or nonhematologic toxicity ≥grade 3). Treatment with both agents was discontinued if recovery did not occur within 14 days.

**Response and toxicity assessment.** At the time of enrollment, all patients had a medical history assessment and physical examination, including evaluation of performance status, complete blood cell count, serum chemistry profile, creatinine clearance, urinalysis, electrocardiogram, chest X-ray and computed tomography, and/or magnetic resonance imaging scan. Upper gastrointestinal series, gastrointestinal fibercopy, and barium enema were done if necessary. Biological analysis (complete blood count, serum chemistry profile, and urinalysis) and physical examination, including determination of weight and performance status, were assessed at the time of enrollment and once weekly during the treatment period. Tumor markers, including carcinoembryonic antigen and CA19-9, were monitored once monthly.

Response Evaluation Criteria In Solid Tumors criteria were used to assess tumor response (17). Tumor size was measured by computed tomography scan or magnetic resonance imaging scan of all measurable lesions in the week preceding treatment. These imaging studies were repeated, and response was confirmed at least 4 weeks (for complete or partial response) or 6 weeks (for stable disease) after it was first documented. Response was not evaluated in the primary gastric tumor to avoid measurement bias of the diameter of the primary tumor. For the evaluation of nonmeasurable lesions, gastrointestinal fibercopy, ultrasonography, other radiographic examinations, and cytology were done if needed. All responses were reviewed by two external review panels. The duration of a complete response or partial response was defined as the time from the first day that measurement criteria were met for complete response or partial response until the first documentation of progressive disease or recurrence (taking as reference the smallest measurements recorded since the treatment started). TTP was measured from the start of treatment until the first documentation of progression, date of last contact, or start of subsequent antitumor therapy, including chemotherapy, radiotherapy, or surgery. Overall survival was measured from the start of treatment until the time of death; overall survival was estimated using the Kaplan-Meier product-limit method and the 95% confidence interval (95% CI) for median survival was estimated by the Brookmeyer-Crowley method.

**Results**

**Patient characteristics.** Between June 2002 and July 2004, 51 patients were enrolled. In total, 48 patients with advanced or
recurrent, unresectable, histologically confirmed gastric or gastroesophageal junction adenocarcinoma were eligible for the current analysis (two patients were ineligible owing to lack of objective measurable lesions by Response Evaluation Criteria In Solid Tumors and one patient refused to start treatment). Eight of the 12 patients with recurrent disease had received prior chemotherapy. Baseline characteristics of the 48 patients are summarized in Table 1.

### Treatment administered
Patients received a median of four cycles of docetaxel-S-1 (range, 1-17). The dose of S-1 was reduced to 50 mg/m² in six patients (12.5%), in line with the dose reduction criteria [five patients had grade 4 leukopenia and/or neutropenia and one patient had grade 3 nonhematologic toxicity (interstitial pneumonia) during the previous treatment cycle]. Treatment administration was delayed for a median of 7 days (range, 1-14 days) in 56 of 272 cycles; the major causes of the delayed administrations were insufficient bone marrow function (50 cycles with WBC <3,000/mm³ or neutrophils <1,500/mm³) and grade 3 nonhematologic toxicity (four cycles with stomatitis, one cycle with fever in the absence of neutropenia, and one cycle with asthenia). The reasons for treatment discontinuations were tumor progression (20 patients, 41.7%), adverse event without recovery within 14 days (14 patients, 29.2%), and further surgery with curative or tumor reductive intent (12 patients, 25.0%). There were no deaths leading to study discontinuation.

### Response and survival
Response and survival data were updated in May 2005. Forty-eight patients were assessable for tumor response and survival. There were 27 partial responses and no complete responses; hence, the overall response rate (partial response + complete response) was 56.3% (95% CI, 38-66%). Eighteen patients (37.5%) had stable disease; hence, the overall tumor control rate (complete response + partial response + stable disease) was 93.8% (95% CI, 83-98%). The median duration of partial response was 5.1 months (95% CI, 2.4-10.1 months). Three patients (6.3%) had progressive disease as the best response.

The highest overall response rates among the metastatic sites were observed for liver (64.7%), locoregional lymph node (60.0%), and peritoneum (60.0%); a complete response was observed for two liver, two locoregional lymph node, two distal lymph node, and one peritoneal metastases. There was no evidence that tumor response was affected by the number of organs involved; the observed partial response rates were 50.0%, 64.7%, and 52.2% for patients with one, two, and three or more organs involved, respectively. The histologic type also did not affect tumor response; the partial response rates were 62.1%, 50.0%, and 60.0% for poorly, moderately, and well-differentiated adenocarcinoma, respectively.

Among the 37 patients with tumors within the stomach (36 primary and 1 recurrent in gastric remnant), 12 underwent further surgery, with 4 patients achieving complete resection of residual tumor. These four patients had a median survival of 13.2 months (range, 7.6-16.8 months) and, at the time of this analysis, two of the four patients were still alive (15.5 and 16.8 months from the start of treatment); one of these patients (initial diagnosis of type 3 gastric cancer with esophageal invasion) became histologically cancer-free (fibrosis alone) after two cycles of treatment and is still free from recurrence. The 12 patients who underwent further surgery received a median of four cycles of docetaxel-S-1 (range, 3-10).

After a median follow-up of 20.1 months (range, 8.4-35.2 months), 17 of 48 patients (35.4%) were alive. The median survival time was 14.3 months (95% CI, 10.7-20.3 months) and the median TTP was 7.3 months (95% CI, 4.3-10.0 months; Figs. 1 and 2).

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (n = 48)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
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<tr>
<td>Median</td>
<td>65</td>
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<tr>
<td>Range</td>
<td>25-75</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>35 (72.9)</td>
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<tr>
<td>Female</td>
<td>13 (27.1)</td>
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<td>ECOG PS, n (%)</td>
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<td>0</td>
<td>33 (68.8)</td>
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<tr>
<td>1</td>
<td>13 (27.1)</td>
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<td>2</td>
<td>2 (4.2)</td>
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<tr>
<td>Disease status, n (%)</td>
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<tr>
<td>Newly diagnosed</td>
<td>36 (75.0)</td>
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<tr>
<td>Recurrent</td>
<td>12 (25.0)</td>
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<tr>
<td>Locally advanced disease</td>
<td>5 (10.4)</td>
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<td>Metastatic disease</td>
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<tr>
<td>Histology, n (%)</td>
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<tr>
<td>Adenocarcinoma, poorly differentiated</td>
<td>29 (60.4)</td>
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<tr>
<td>Adenocarcinoma, moderately differentiated</td>
<td>14 (29.2)</td>
</tr>
<tr>
<td>Adenocarcinoma, well differentiated</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>36 (75.0)</td>
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<tr>
<td>Gastroesophageal junction tumor</td>
<td>3 (6.3)</td>
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<tr>
<td>Other tumor</td>
<td>33 (68.8)</td>
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<tr>
<td>None (recurrent after curative resection)</td>
<td>12 (25.0)</td>
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<tr>
<td>Metastatic sites, n (%)</td>
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<tr>
<td>Lymph node</td>
<td>33 (68.8)</td>
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<tr>
<td>Locoregional</td>
<td>25 (52.1)</td>
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<tr>
<td>Distant</td>
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<tr>
<td>Recurrent in remnant stomach</td>
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<tr>
<td>Liver</td>
<td>14 (29.2)</td>
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<tr>
<td>Peritoneum</td>
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<tr>
<td>Other</td>
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<tr>
<td>No. organs involved, n (%)</td>
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<tr>
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<td>8 (16.7)</td>
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<tr>
<td>2</td>
<td>17 (35.4)</td>
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<tr>
<td>≥3</td>
<td>23 (47.9)</td>
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<td>Prior therapy, n (%)</td>
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<tr>
<td>Surgery only</td>
<td>15 (31.3)</td>
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<tr>
<td>Surgery + adjuvant chemotherapy</td>
<td>8 (16.7)</td>
</tr>
<tr>
<td>None</td>
<td>25 (52.1)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

*Lung: 1; ovary: 1; bone: 1.
neutropenia occurred in a total of 12 cycles for 11 patients (22.9%; three, two, two, four, and one patients in the first, second, third, fourth, and eighth cycles, respectively); all cases were manageable with granulocyte colony-stimulating factor administration. One of these patients (1 of 48; 2.1%) received empirical antibiotic therapy. For most patients, the neutrophil nadirs occurred 5 to 7 days after the start of a treatment cycle and the neutrophil count was recovered by day 21. Among the patients who experienced grade 4 neutropenia, three discontinued treatment due to adverse event without recovery within 14 days and two discontinued treatment because of tumor progression.

Nonhematologic toxicities were generally mild in severity and no grade 4 cases were observed. The most common grade 3 nonhematologic toxicities were anorexia (14.6%), stomatitis (8.3%), nausea (6.3%), diarrhea (4.2%), constipation (4.2%), and vomiting (2.1%). All treatment-related toxicities resolved with appropriate care. There were no deaths during the study or within 30 days of the last infusion.

**Discussion**

This phase II study showed that a combination of docetaxel and S-1 is highly active in advanced and recurrent gastric cancer and has an acceptable and manageable toxicity profile. The combination achieved promising results for overall response rate (56.3%; 95% CI, 38-66%), median TTP (7.3 months; 95% CI, 4.3-10.0 months), and median overall survival (14.3 months; 95% CI, 10.7-20.3 months). Nonhematologic toxicities were generally mild and none was greater than grade 3. Stomatitis, the most common grade 3 nonhematologic toxicity, was observed in just 8.3% of patients. The predominant toxicity was myelosuppression and grade 3 to 4 neutropenia occurred in 58.3% of patients. However, both hematologic and
nonhematologic toxicities were generally manageable and, in most cases, treatment could be continued in the outpatient setting.

A variety of combination treatment regimens have been developed for advanced or metastatic gastric cancer (2, 3) and there has been a steady improvement in reported response rates. The overall response rate achieved in the present study (56.3%) was within the range reported for other regimens, such as fluorouracil-doxorubicin-methotrexate; etoposide-leucovorin-S-FU; etoposide-doxorubicin-cisplatin; epirubicin-cisplatin-S-FU; and recent taxane-, irinotecan-, oxaliplatin-, or S1-based regimens (2, 3, 6–8, 18–27). A particularly high response rate (74%) was reported for cisplatin-S-FU (13). However, the high response rates achieved by cisplatin-S-FU and various other combination regimens have failed to translate into major benefit survival and the reported median survival times remain approximately ≤1 year.

Various docetaxel-fluoropyrimidine-based combinations, such as TCF, TF, and docetaxel-capcitabine, are active in gastric cancer (6–8), but their potential is limited by treatment-associated toxicities. In the TAX 325 study, the most common grade 3 to 4 adverse events (regardless of relationship to study medication) were diarrhea and stomatitis, which occurred in 20% and 21% of patients, respectively, in the TCF arm and 8% and 27% of patients, respectively, in the cisplatin-S-FU arm. The rate of grade 3 to 4 neutropenia was higher in the TCF arm than in the cisplatin-S-FU arm, with 28.3% of patients in the TCF arm experiencing febrile neutropenia or neutropenic infection in the absence of prophylactic growth factor support (7). Although the incidence of severe toxicities differed in the two treatment arms, the major toxicities were hematologic and gastrointestinal in both treatment arms. Docetaxel (36 mg/m²) on days 1 and 8 in combination with capcitabine (1,000 mg/m² twice daily) on days 1 to 14 of a 3-week schedule was investigated in a phase II study in patients with metastatic gastric cancer; however, grade 3 diarrhea (10.9%) and stomatitis (25.5%) were observed despite the attenuated dose of capcitabine (6).

The promising median survival time observed in the present study (14.3 months) raises hope that the docetaxel-S-FU combination may improve survival outcomes for patients with advanced gastric cancer. The mature survival results reported in our study are consistent with recently reported preliminary analyses from a phase II study of a similar regimen for patients with advanced gastric cancer (28). The patient population disease status in this study was almost comparable with those in similar Western studies, except for the ratio of gastroesophageal junction tumor (3 of 48 cases, 6.3%). Forty-three of 48 eligible cases (89.6%) had highly advanced or recurrent disease with at least one M1 lesion. Although 12 patients underwent further surgery with four achieving complete resection of residual tumor in this study, patients with locally advanced disease, who could be potentially rendered free of primary tumor or disease by surgery, were not eligible for enrollment (29). The relatively low involvement of gastroesophageal junction tumor (3 of 48 cases, 6.3%) and the recently suggested difference in S1 pharmacokinetics caused by CYP2C6 polymorphic difference between Asians and Caucasians may require worldwide cooperative studies of this regimen (30). The tolerability of docetaxel-S-FU in the present study compares favorably with other docetaxel-fluoropyrimidine-based regimens (6–8). Although the toxicity profiles of docetaxel and S-1 partially overlap, only two cases (4.2%) of grade 3 diarrhea and four cases (8.3%) of stomatitis were observed in the present study. Moreover, all adverse effects that occurred during treatment resolved to baseline levels. Among patients receiving docetaxel-S-FU, the neutrophil nadir generally occurred 5 to 7 days after the start of a treatment cycle; however, the neutrophil count generally recovered by day 21. The rates of severe toxicities associated with docetaxel-S-FU were generally similar to those reported for TF (8), which is among the most well-tolerated, new-generation combination regimens. Asthenia and diarrhea were uncommon and the rate of stomatitis was lower than that previously reported for TF (8).

In a phase I study of docetaxel-S-1 (16), both efficacy and toxicity were improved when docetaxel was administered on day 1 compared with day 8. In the present study, the administration of S-1 for 2 weeks followed by 1 week off allowed the dose intensity to be maintained (although with reduced toxicity compared with the administration of S-1 for 4 weeks followed by 2 weeks off).

It is noteworthy that docetaxel-S-1 has shown activity against disseminated peritoneal metastases. S-1 is active in peritoneal dissemination in the mouse model (31) and it was previously shown that docetaxel is active in poorly differentiated gastric cancer (6–8), but their potential is limited by treatment-associated toxicities. In the TAX 325 study, the most common grade 3 to 4 adverse events (regardless of relationship to study medication) were diarrhea and stomatitis, which occurred in 20% and 21% of patients, respectively, in the TCF arm and 8% and 27% of patients, respectively, in the cisplatin-S-FU arm. The rate of grade 3 to 4 neutropenia was higher in the TCF arm than in the cisplatin-S-FU arm, with 28.3% of patients in the TCF arm experiencing febrile neutropenia or neutropenic infection in the absence of prophylactic growth factor support (7). Although the incidence of severe toxicities differed in the two treatment arms, the major toxicities were hematologic and gastrointestinal in both treatment arms. Docetaxel (36 mg/m²) on days 1 and 8 in combination with capcitabine (1,000 mg/m² twice daily) on days 1 to 14 of a 3-week schedule was investigated in a phase II study in patients with metastatic gastric cancer; however, grade 3 diarrhea (10.9%) and stomatitis (25.5%) were observed despite the attenuated dose of capcitabine (6).

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References


S-1 and Docetaxel Combination in Gastric Cancer

Acknowledgments

We thank the data coordinator, Kana Yamashita, the study nurse, Yukari Moroika, all of the clinical study teams at the participating institutions, and the Hiroshima Cancer Treatment Development Organization.

www.aacrjournals.org Clin Cancer Res 2006;12(11) June 1, 2006 3407

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Phase II Study of Docetaxel and S-1 Combination Therapy for Advanced or Recurrent Gastric Cancer

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