Randomized Phase II Trial of S-1 plus Irinotecan Versus S-1 plus Paclitaxel as First-line Treatment for Advanced Gastric Cancer (OGSG0402)

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Abstract. Background: S-1-based regimens are commonly used for advanced gastric cancer (AGC) in Japan. We performed this trial to evaluate the efficacy and safety of S-1 plus irinotecan (SIri) and S-1 plus paclitaxel (SPac) as first-line treatments for AGC in order to select the optimal regimen for a subsequent phase III trial. Patients and Methods: Patients with previously untreated, locally advanced or metastatic measurable gastric adenocarcinoma were randomly assigned to receive SIri (irinotecan 80 mg/m² was administered intravenously (i.v.) on day 1 and 15, while 40 mg/m² S-1 was orally administered twice daily for three weeks from days 1-21 followed by a two-week pause) or SPac (paclitaxel 50 mg/m² was administered i.v. on day 1 and 8, while 40 mg/m² S-1 was orally administered twice daily for two weeks from day 1-14 followed by a one-week pause) regimen. The primary end-point was the overall response rate (ORR), and the secondary end-points were progression-free survival (PFS), overall survival (OS), and toxicity. Results: A total of 102 patients were enrolled. The ORR was 33.3% for SIri and 31.4% for SPac, which did not achieved the predicted ORR in either group. PFS and OS were 5.7 and 12.4 months for SIri, 4.6 and 11.9 months for SPac respectively. No treatment-related deaths occurred during the study. Although grade 3/4 neutropenia and anemia were more frequent in the SIri group, both regimens were well-tolerated. Conclusion: Both regimens were well-tolerated in patients with AGC, but we conclude that neither regimen was optimal for a phase III trial.

Gastric cancer is the second leading cause of cancer-related death in Japan, with about 50,000 deaths per year (1). Patients with advanced gastric cancer (AGC) have poor prognosis, with a median survival time, if untreated, of 3 to 5 months. In Western countries, 5-fluorouracil (5-FU) combined with cisplatin (FP therapy) (2) is often used as a reference arm in phase III trials (3), triplet regimen with added epirubicin (4) or docetaxel (5) to FP are the current standards, with modifications such as replacement of cisplatin with oxaliplatin and replacement of infusional 5-FU with oral agents such as capecitabine (6), but no regimen obtained a median survival time (MST) of beyond one year. Thus, more effective regimens are required. In Japan, JCOG9205 (7), a phase III study, failed to show superiority of the FP regimen over 5-FU alone. In the 1990s, S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral derivative of 5-FU, was developed for the treatment of gastric cancer (8-10). The response rate to S-1 as a single-agent was 46% and the toxicity was mild (10). Therefore, while S-1-based regimens are empirically used as a first-line therapy in Japan, there was...
no phase III data demonstrating its efficacy until 2006. In 2007, two phase III trials were reported from Japan. One was the JCOG9912 trial (11), which showed that S-1 was not inferior to S-FU. The other was the SPIRITS trial, which indicated that S-1 plus-cisplatin combination therapy was superior to S-1 monotherapy (12). S-1 plus cisplatin is therefore regarded as a component of first-line standard treatment for AGC in Japan.

There are other promising cytotoxic drugs for gastric cancer studies; irinotecan and paclitaxel. Irinotecan was also effective for gastric cancer, as a single agent in a phase II trial (13), and in combination with S-1 (Sri) achieved a median survival time of over 12 months, with a favorable safety profile (14). Paclitaxel has been reported to yield a good response for gastric cancer, not only as a single agent (15), but also in combination with S-1 (SPac) (16), achieving a median survival time of over 12 months. However, there are no data showing whether Sri or SPac are better in the first-line setting for metastatic gastric cancer. We therefore designed a randomized phase II study to evaluate the efficacy and safety of Sri versus SPac as first-line treatments for AGC to select the optimal candidate regimen for a subsequent phase III trial.

**Patients and Methods**

**Patient eligibility.** Patients were required to have histologically-proven unresectable advanced or recurrent gastric cancer with measurable lesions, no prior chemotherapy, except adjuvant chemotherapy completed four weeks or more before entry, a performance status (PS) of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale, age 20-75 years, ability to eat, life expectancy longer than three months, adequate hematological, renal, and hepatic function defined by the following criteria: leucocyte count ≥4,000 and <12,000/mm3, neutrophil count ≥2,000/mm3, hemoglobin ≥8.0 g/dl, platelet count ≥100,000/mm3, serum creatinine ≤2.5 times the upper limit of normal (ULN), serum bilirubin ≤2.5 mg/dl, and serum aspartate transaminase and alanine transaminase ≤2.5 times the upper limit of normal (ULN).

Patients were excluded if they had active double cancer, other severe diseases (ileus, interstitial pneumonia/pulmonary fibrosis, cardiac failure, renal dysfunction, liver dysfunction), infectious diseases, diarrhea, with marked pleural or abdominal effusion, history of drug allergy, were receiving fluoropyrimidine, anti-fungal fluconazole or azithromycin, had gastrointestinal bleeding requiring blood transfusion, liver cirrhosis or jaundice, with psychiatric or cardiac disease requiring medication, uncontrolled diabetes mellitus, metastasis to the central nervous system, pregnant or lactating, or exclusion by the physician for other reasons. All patients provided written informed consent. The study was registered at the University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN 000000638) and conducted in accordance with the World Medical Association Declaration of Helsinki (Edinburgh, Scotland, October 2000) and good clinical practice guidelines.

**Study design and treatment schedule.** This was an open-label, multi-center, randomized prospective phase II trial that evaluated the efficacy and safety of Sri and SPac as first-line treatments for AGC. Patients were randomly assigned 1:1 to receive either Sri or SPac. Before randomization, patients were stratified according to unresectable advanced cancer/recurrent cancer with adjuvant chemotherapy /recurrent cancer without adjuvant chemotherapy and ECOG PS 0/1/2 (Figure 1).

**Arm A: Sri:** Irinotecan (Campto; Yakult Honsha, Tokyo, Japan) was administered intravenously (i.v.) over 1.5 h at 80 mg/m2 on day 1 and 15, while 40 mg/m2 S-1 (Taiho Pharmaceutical, Tokyo, Japan) was orally administered twice daily for three weeks from days 1-21 followed by a two-week pause.

**Arm B: SPac:** Paclitaxel (Taxol; Bristol Meyers Squibb, New York City, NY state, USA) was administered i.v. over 1 h at a dose of 50 mg/m2 on day 1 and 8, while 40 mg/m2 S-1 was orally administered at twice-daily for two weeks from day1-14 followed by a one-week pause.

**Assessment of response and toxicity.** All measurable lesions were evaluated for tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) (17). All radiological assessments were confirmed by extratumoral review. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (18).

**Statistical analysis.** This study was designed to reject an overall response rate (ORR) of 30% under the expectation of 50% with a power of 80% and a two-sided α-value of 5%. A total of 50 patients per group were required according to calculations made with nQuery Advisor version 4.0 (Cork, Ireland) and the sample size was therefore as 100 (50 patients per group).

The primary end-point was overall response rate (ORR). Secondary end-points were progression-free survival (PFS), overall survival (OS), and safety. Tumors were measured every six weeks by principal investigators at each participating Center until onset of progressive disease.

PFS was defined as the time from the date of registration to the date of progressive disease or death. OS was defined as the interval from the date of registration to the date of the death. Survival curves were estimated by the Kaplan-Meier method, and differences were analyzed with the stratified log-rank test. Hazard ratios (HRs) were calculated using the stratified Cox proportional hazard model. We planned accrual and follow-up for two years and three years, respectively.

**Results**

**Patients’ characteristics.** Between December 2004 and November 2007, a total of 102 patients (Sri, n=51; SPac, n=51) were enrolled from 13 Institutions and randomized (Figure 1). Two patients died before the initiation of treatment and one patient was lost to follow-up (Sri). Baseline patients’ characteristics are shown in Table I.

**Treatments.** The median number of treatment courses was four (range 1-16) for Sri the duration of which was five weeks, and five (range 1-40) for SPac, the duration of which was three weeks. The main reasons for treatment discontinuation were disease progression [Sri vs. SPac, 33/51 (64.7%) vs. 37/51 (72.5%), adverse events [4/51 (7.8%) vs. 7/51 (13.7%)], attending physician’s decision [1/51 (1.9%) vs.
0/51 (0%)], consent withdrawal [4/51 (7.8%) vs. 3/51 (5.9%)], and other reasons [5/51 (9.8%) vs. 3/51 (5.9%)].

**Response and survival.** The ORR was determined by the RECIST criteria as, 33.3% (95% Confidence Interval, CI=20.3-47.9) for SIri (n=51) compared to 31.4% (95% CI=19.1-45.9) for SPac (n=51), with no statistically significant difference (p=0.841) (Table II). The MST was 379 days for SIri and 364 days for SPac (HR=0.988, p=0.956) (Figure 2). The 1-year survival rates were 53.1% (95% CI=40.9-69.1%) for SIri and 49.4% (95% CI=37.2-65.6%) for SPac, respectively (Figure 3).

PFS was 173 days for SIri compared with 141 days for SPac (HR=1.18, p=0.421). The 1-year PFS rates were 22.6% (95% CI=13.5-38.0%) for SIri and 13.7% (95% CI=6.9-27.3%) for SPac, respectively (Figure 3).

Figure 4 shows the results of subgroup analysis of ORR. No interaction was identified between PS, primary site, or disease status. A tendency for interaction was noted between therapy efficacy and histological type (differentiated vs. undifferentiated), PS (0 vs. 1 and 2) and age (over 65 years or not).

**Safety.** Adverse events that occurred in each group are shown in Table III. 48 (SIri) and 51 (SPac) patients were included. The incidence of major hematological toxicities was higher with SIri than with SPac. Grade 3 or 4 neutropenia was observed in only 2% of patients treated with SPac versus 19% of patients treated with SIri, while the corresponding incidences of febrile neutropenia were 2% vs. 0%, respectively. The most common grade 3 or 4 non-hematological toxicities were diarrhea (SIri vs. SPac, 6% vs. 2%), anorexia (13% vs. 10%), nausea and vomiting (4% vs. 6%). There were no treatment-related deaths in either arms.

**Discussion**

In Japan, many clinical trials with S-1-containing regimens for gastric cancer have been performed since the 1990s (19). The aim of this study was to evaluate the efficacy of SIri and

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**Table I. Patients’ characteristics.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SIri (n=51)</th>
<th>SPac (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>38/13</td>
<td>38/13</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>64 (25-75)</td>
<td>62 (30-75)</td>
</tr>
<tr>
<td>PS (0/1/2)</td>
<td>41/8/2</td>
<td>39/12/0</td>
</tr>
<tr>
<td>Histology (intestinal/diffuse/others)</td>
<td>28/22/1</td>
<td>33/16/2</td>
</tr>
<tr>
<td>Primary lesions (yes/no)</td>
<td>37/14</td>
<td>37/14</td>
</tr>
<tr>
<td>Advanced/recurrent</td>
<td>40/11</td>
<td>40/11</td>
</tr>
<tr>
<td>Recurrence after adjuvant chemotherapy (yes/no)</td>
<td>3/8</td>
<td>1/10</td>
</tr>
</tbody>
</table>

SIri: S-1+CPT; SPac: S-1+paclitaxel; PS: performance status.
SPac for an ORR of 30% under the expectation of 50% in the same patient background. Since there was no such study except for a single-arm phase II study (14, 16). The SIri regimen has yielded tolerable toxicity and efficacy (14). On the other hand, the SPac regimen has also achieved promising efficacy with tolerable toxicity (16).

Although both combination therapies were well-tolerated in patients with AGC, the predicted ORR was not achieved by either regimen. Therefore, neither regimen is deemed optimal for a phase III trial. In sub-group analyses, SIri was better concerning RR than SPac for these with differentiated-type histology, and PS=0 without statistical difference. In contrast, SPac tended to lead to better RR than SIri for these with undifferentiated-type histology, and a poor PS (i.e. 1 or 2). In the GC0301/TOP-002 study, SIri yielded significantly better efficacy than S-1 monotherapy in AGC with diffuse-type histology and poor PS (19). In contrast, OGSG 0002 showed SIri was more effective in patients with differentiated histology type, and OGSG 0105 showed SPac was more effective in undifferentiated type. For patients with undifferentiated tumor or poor PS, patients who were symptomatic, both regimen were allocated; for those with differentiated tumor and/or good PS, we did not conduct SPac. Moreover, in the 2011 ASCO-GI meeting reports, S-1-plus-docetaxel did not show superiority to S-1 monotherapy in the START trial (20). Except for S-1-plu-
cisplatin, S-1 combination therapy has not achieved survival benefit compared any to S-1 monotherapy. Thus S-1 plus cisplatin remains the first-line chemotherapy recommended for Japanese patients, while patients who are frail or those who wish to refrain from short stay in the hospital required for hydration could turn to S-1 monotherapy. However, two combination therapies are promising. One is capecitabine-plus-cisplatin (XP), and the other is S-1-plus-oxaliplatin (SOX). XP has been already one of the standard regimen as 5-FU plus cisplatin in many countries, hence XP has been used as a platform for molecular targeting agents in the ToGA (21) and AVAGAST (22) studies. In Japanese patients enrolled in the ToGA and AVAGAST studies, the response rate, PFS and OS were 58.5% and 49.2%, 5.6 months and 5.7 months, 17.7 months and 14.2 months, respectively. SOX was reported as promising in 2009 (23), and showed non-inferiority to S-1-plus-cisplatin in PFS (24), hence SOX will be one of the standard regimen in Japan in the near future.

We were unable to demonstrate efficacy of S1ri or SPac regimens as first-line chemotherapy for patients with AGC, and their efficacy as second-line is also unknown. Sugimoto et al. reported S-1 combination chemotherapy is effective as

Table III. Adverse Events due to therapy by National Cancer Institute Common Toxicity Criteria, version 3.0. One grade 4 cerebral infarction occurred 7 days after completion of the third course of treatment in the S1ri arm.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>S1ri (n=48)</th>
<th>SPac (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>7/0 (15%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>8/1 (19%)</td>
<td>1/0 (2%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>6/0 (13%)</td>
<td>2/1 (6%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>0/0 (0%)</td>
<td>0/1 (2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3/0 (6%)</td>
<td>1/0 (2%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2/0 (4%)</td>
<td>3/0 (6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2/0 (4%)</td>
<td>1/0 (2%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1/0 (2%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6/0 (13%)</td>
<td>5/0 (10%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1/0 (2%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1/0 (2%)</td>
<td>1/0 (2%)</td>
</tr>
<tr>
<td>AST</td>
<td>0/0 (0%)</td>
<td>1/0 (2%)</td>
</tr>
<tr>
<td>ALT</td>
<td>0/0 (0%)</td>
<td>2/0 (4%)</td>
</tr>
</tbody>
</table>

S1ri: S-1+CPT, SPac: S-1+paclitaxel, AST: aspartate aminotransferase, ALT: alanine aminotransferase.
second-line treatment for patients with advanced/recurrent gastric cancer who have failed to response to S-1-based chemotherapy as first-line treatment in a retrospective study (24). The OGS0701 prospective study (irinotecan with/without S-1 vs. Paclitaxel with/without S-1 for S-1-refractory AGC) is ongoing in Japan.

In conclusion, neither S1ri nor SPlac regimens were found to be optimal for a phase III trial. 5-FU-based combination chemotherapy with cisplatin remains in the first-line setting for AGC.

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Disclosure

None of the Authors declare conflicts of interest.


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