Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer


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Background: We evaluated the efficacy and safety of S-1 plus oxaliplatin (SOX) as an alternative to cisplatin plus S-1 (CS) in first-line chemotherapy for advanced gastric cancer (AGC).

Patients and methods: In this randomized, open-label, multicenter phase III study, patients were randomly assigned to receive SOX (80–120 mg/day S-1 for 2 weeks with 100 mg/m² oxaliplatin on day 1, every 3 weeks) or CS (S-1 for 3 weeks with 60 mg/m² cisplatin on day 8, every 5 weeks). The primary end points were noninferiority in progression-free survival (PFS) and relative efficacy in overall survival (OS) for SOX using adjusted hazard ratios (HRs) with stratification factors; performance status and unresetable or recurrent (+adjuvant chemotherapy) disease.

Results: Overall, 685 patients were randomized from January 2010 to October 2011. In per-protocol population, SOX (n = 318) was noninferior to CS (n = 324) in PFS [median, 5.5 versus 5.4 months; HR 1.024, 95% confidence interval (CI) 0.840–1.219; predefined noninferiority margin 1.30]. The median OS for SOX and CS were 14.1 and 13.1 months, respectively (HR 0.958 with 95% CI 0.803–1.142). In the intention-to-treat population (SOX, n = 339; CS, n = 337), the HRs in PFS and OS were 0.979 (95% CI 0.821–1.167) and 0.934 (95% CI 0.786–1.108), respectively. The most common grade 3 adverse events (SOX versus CS) were neutropenia (19.5% versus 41.8%), anemia (15.1% versus 32.5%), hypomagnesemia (2.5% versus 0.9%), and sensory neuropathy (4.7% versus 0%).

Conclusion: SOX is as effective as CS for AGC with favorable safety profile, therefore SOX can replace CS.

Clinical trial number: JapicCTI-101021.

Key words: advanced gastric cancer, oxaliplatin, cisplatin, S-1, phase III study

introduction

Combination therapies using cisplatin and fluoropyrimidines with or without epirubicin or docetaxel have been widely used as first-line treatments for advanced gastric cancer (AGC) [1–4].

The German Arbeitsgemeinschaft Internistische Onkologie (AIO) trial showed that 5-fluorouracil (5-FU)/leucovorin plus oxaliplatin treatment was equivalent to 5-FU/leucovorin plus cisplatin treatment [5]. The randomized two-by-two phase III study (REAL-2) of triplet therapy of epirubicin, 5-FU or capecitabine, and cisplatin or oxaliplatin for advanced esophagogastric cancer showed that oxaliplatin was as effective as cisplatin with respect to overall survival (OS) and progression-free survival (PFS) [6].
S-1 is an oral anticancer preparation that combines tegafur, a pro-drug of 5-FU, with two modulators, i.e. gimeracil and oteracil [7]. Phase III clinical trials showed that S-1 was noninferior to 5-FU, and that cisplatin plus S-1 (CS) was superior to S-1 (SPIRITS trial) [8, 9]. CS is regarded as a standard first-line treatment of AGC in Japan. A phase III study (FLAGS) suggested that CS could be a substitute for 5-FU plus cisplatin as first-line chemotherapy for AGC [10, 11]. A phase II trial of first-line chemotherapy with S-1 plus oxaliplatin (SOX) yielded promising outcomes, a median PFS and OS of 6.5 and 16.5 months, respectively, with good tolerability [12]. To confirm and extend these results, we carried out a phase III study comparing SOX with CS as first-line chemotherapy for AGC.

methods

patients

The main eligibility criteria included histologically proven, curatively unresectable, advanced or recurrent gastric cancer, age ≥ 20 years, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, the presence of measurable lesions as confirmed by computed tomography (CT), no previous chemotherapy or radiotherapy, oral intake capability, adequate function of the major organs, and written informed consent of the patient. The main exclusion criteria were active infection, serious concurrent disease, markedly impaired cardiac function, gastrointestinal bleeding, sensory neuropathy, serious diarrhea, ascites beyond the pelvic cavity or pleural effusion, a history of blood transfusion within 3 weeks before enrollment, interstitial pneumonia, or previous treatment with platinum as adjuvant chemotherapy.

This study was carried out according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Each hospital’s institutional review board approved this study protocol.

study design

This study was a prospective, multicenter, randomized, open-label, parallel-group phase III clinical trial conducted at 51 centers in Japan. Eligible patients were centrally randomized to CS or SOX in a 1:1 ratio, considering the institution, PS, and unresectable or recurrent disease with or without postoperative adjuvant chemotherapy as adjustment factors using the minimization method [13]. The randomization sequence was generated by an independent team from the trial sponsor and investigators. Enrollment was done by a local principal or subinvestigator via a web-based system, which automatically assigned either treatment to a patient. The allocated study treatments were not masked from the patients and investigators.

treatment

In CS, S-1 was given orally twice daily for the first 3 weeks of a 5-week cycle. The dose was 80 mg/day for body surface area (BSA) < 1.25 m², 100 mg/day for BSA ≥ 1.25 to < 1.5 m², and 120 mg/day for BSA ≥ 1.5 m². Cisplatin was administered at 60 mg/m² as an i.v. infusion with adequate hydration on day 8 of each cycle [9]. In SOX, S-1 was given as the same way for the first 2 weeks of a 3-week cycle. Oxaliplatin at 100 mg/m² was infused for 2 h i.v. on day 1 of each cycle [12]. The treatments were continued until one of the criteria for withdrawal of the study treatment was encountered.

In both treatment groups, the dose of each drug was reduced to 1.25 to < 1.5 m², and 120 mg/day for BSA ≥ 1.5 m². Cisplatin was administered at 60 mg/m² as an i.v. infusion with adequate hydration on day 8 of each cycle [9]. In SOX, S-1 was given as the same way for the first 2 weeks of a 3-week cycle. Oxaliplatin at 100 mg/m² was infused for 2 h i.v. on day 1 of each cycle [12]. The treatments were continued until one of the criteria for withdrawal of the study treatment was encountered.

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assessments

PFS was defined as the time from the randomization to documented progressive disease (PD) or death without prior PD, whichever came first. Patients who were alive and free of progression (i.e. second-line treatment was started due to any cause) were regarded as censored cases at the date of the last assessment. Lesions were evaluated by CT at the baseline and every 6 weeks from the randomization to the initiation of second-line treatment. The assessments were done under the same imaging way as the baseline in all patients. All images for PFS and tumor responses were reviewed by an independent review committee, according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 [14]. OS was defined as the interval from the date of randomization to the date of death from any cause or the last follow-up date. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE version 3.0).

statistical considerations

We aimed to assess two primary end points. One primary end point was to demonstrate noninferiority in PFS for SOX compared with CS which was used for sample size determination. The other primary end point was to evaluate the relative efficacy in OS between SOX and CS. The noninferiority analysis was carried out in the per-protocol population. The noninferiority margin in PFS was defined at 1.30 in reference to the results of SPIRITS trial and phase II study of SOX (supplementary Appendix A1, available at Annals of Oncology online). Since the required number of events was estimated as 456 with a one-sided α value of 0.025 and a power of 80%, we estimated that 600 patients would be needed to achieve the required number of events within the patient accrual (1.5 years) and follow-up periods (1 year after the last patient randomization). In February 2011, it appeared to be difficult to achieve the required number of events within the preplanned timetable, and the target number of patients was revised to 680 according to the predefined procedure in the protocol. For OS, the noninferiority margin was defined to be 1.15 as a guide of evaluation. The number of events required for OS analysis was set as 508 with a one-sided α value of 0.025 and a power of 80% when median OS for SOX and CS were expected as 14.5 and 13.0 months, respectively.

Time-to-events were analyzed using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the stratified Cox proportional hazards model. The stratification factors were unresectable or recurrent disease, with or without postoperative adjuvant chemotherapy, and PS of 0, 1, or 2, excluding institution from adjustment factors in randomization. We also did the analyses in the intention-to-treat (ITT) population: all randomized patients excluding patients who took no trial medication. In exploratory analyses, subgroup efficacy and multivariable analyses were carried out on stratification factors and demographic factors in the Cox proportional hazards model. Statistical analyses were carried out using SAS v9.1.3.

results

patients disposition and characteristics

From 14 January 2010 through 17 October 2011, 685 patients were enrolled; 343 and 342 patients were randomly assigned to SOX or CS (Figure 1). The demographic characteristics in the per-protocol population were well balanced between SOX and CS (Table 1).
The median treatment cycles in SOX and CS were 7.0 (range 1–43) and 5.0 (range 1–19), respectively. The relative dose intensity was 79.0% [interquartile range (IQR), 62.3–95.1] for oxaliplatin and 78.9% (IQR 65.9–91.3) for S-1 in SOX; it was 80.7% (IQR 64.2–94.6) for cisplatin and 79.8% (IQR 68.1–90.9) for S-1 in CS.

In SOX, 261 of 308 (84.7%) patients who discontinued treatment received second-line chemotherapies: taxanes-containing regimens in 131 of 261 (50.2%) patients, irinotecan-containing...
The median follow-up for PFS was 6.9 months (IQR 2.9–17.1%) patients. Other details are shown in supplementary Appendix A2, available at https://academic.oup.com/annonc/article-abstract/26/1/141/2802628.

Treatment regimens in 87 of 261 (33.3%) patients, and S-1-containing regimens in 20 of 261 (7.7%) patients. In CS, 269 of 319 (84.3%) patients who discontinued treatment received second-line chemotherapy: taxanes-containing regimens in 102 of 269 (37.9%) patients, irinotecan-containing regimens in 84 of 269 (31.2%) patients, and S-1-containing regimens in 46 of 269 (17.1%) patients. Other details are shown in supplementary Appendix A2, available at https://academic.oup.com/annonc/article-abstract/26/1/141/2802628.

### efficacy

The median follow-up for PFS was 6.9 months (IQR 2.9–9.6). The median PFS in SOX and CS were 5.5 months (95% CI 4.4–5.7, 260 events) and 5.4 months (95% CI 4.2–5.7, 249 events), respectively (Figure 2A). The HR was 1.004 (95% CI 0.840–1.199, \(P_{\text{noninferiority}} = 0.0044\)), and the upper limit of 95% CI was less than the noninferiority margin of 1.30.

The median follow-up for OS was 25.9 months (IQR 21.0–29.2). The median OS in SOX and CS were 14.1 months (95% CI 13.0–15.8, 249 events) and 13.1 months (95% CI 12.1–15.1, 259 events), respectively (Figure 2B). The HR was 0.969 (95% CI 0.812–1.157). However, one eligible patient was not included in the stratified analysis. The analysis including all eligible patients resulted in giving that the HR was 0.958 (95% CI 0.803–1.142) (supplementary Appendix A3, available at https://academic.oup.com/annonc/article-abstract/26/1/141/2802628).

The response rate and disease control rate were 55.7% and 85.2% (2 complete response, 175 partial response, and 94 stable disease) in SOX, and 52.2% and 81.8% (4 complete response, 165 partial response, and 96 stable disease) in CS, respectively. The median time from the randomization to the first date that documented to reach 30% tumor reduction were 1.5 months (95% CI 1.4–2.5) in SOX and 1.5 months (95% CI 1.4–1.6) in CS.

Figure 3 summarizes the subgroup analysis of OS. SOX showed significantly longer OS in patients with peritoneal metastasis. Multivariate analyses showed that ECOG PS (1, 2), unresectable disease, diffuse-type, and sum of tumor diameter (≥median) correlated with poor prognosis in OS. The adjusted HR in treatment efficacy for OS was 0.955 (95% CI 0.802–1.138) (Table 2).

### safety

Table 3 summarizes the main adverse events in the safety analysis population. Grade 3 or worse leukopenia, neutropenia, anemia, febrile neutropenia, and hyponatremia were more frequently seen in CS than in SOX. Grade 3 or worse sensory neuropathy was more frequently observed in SOX than in CS. There were no remarkable differences in the incidence of thrombocytopenia between the treatment groups. Grade 3 or worse febrile neutropenia in CS was seen in 12/111 (10.8%) of patients with a creatinine clearance (Ccr) <70 ml/min and 11/224 (4.9%) of patients with Ccr ≥70 ml/min; and in SOX, in 3/113 (2.7%) of patients with Ccr <70 ml/min and 0/225 (0%) of patients with Ccr ≥70 ml/min. Further, grade 3 or worse febrile neutropenia in CS was seen in 12/234 (5.1%) of patients aged <70 years and 11/101 (10.9%) of patients aged ≥70 years; and in SOX, in 1/224 (0.4%) of patients aged <70 years and 2/114 (1.8%) of patients aged ≥70 years. Serious adverse events were more frequently observed in CS than in SOX [127 (37.9%) versus 99 (29.3%), \(P = 0.017\)]. There were 12 treatment-related deaths (8 in CS and 4 in SOX).

### discussion

This randomized phase III study for AGC showed that SOX was noninferior to CS in terms of PFS and OS. As far as we know, this is the first large comparative study of the oxaliplatin plus S-1 doublet with CS. The results of CS in the present study are similar to those observed in the SPIRITS trial that demonstrated the superiority of CS (median PFS 6.0 months and median OS 13.0 months) to S-1, and this suggests the robustness of our results for noninferiority [9].

The adverse events observed for CS and SOX were consistent with previously reported results. Notably, in the present study,
SOX provided considerable advantages in safety over CS: ≥grade 3 neutropenia and febrile neutropenia were more frequently observed in CS. All grades of diarrhea, stomatitis, nausea, anorexia, and renal impairment developed more commonly in CS. SOX was safer particularly in patients ≥70 years with Cr < 70 ml/min with respect to febrile neutropenia. In patients with compromised renal function, the decreased renal clearance of gimeracil (a dehydropyrimidine dehydrogenase inhibitor and a component of S-1) increases blood 5-FU concentrations and causes severe adverse effects. Renal

**Figure 2.** Kaplan–Meier curves for (A) progression-free survival assessed with RECIST and (B) overall survival. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; HR, hazard ratio; CI, confidence interval. Data cut off for PFS was on 1 June 2012 and that for OS was on 16 April 2013.
function is likely impaired during treatment with a cisplatin-containing regimen, even when adequate hydration to prevent renal toxicity is provided, while oxaliplatin does not affect renal function. These were the probable reasons underlying the favorable results of SOX in elderly patients or patients with renal dysfunction. As expected, the incidence of peripheral sensory neuropathy was higher in SOX. Nonetheless, 50% of patients in SOX received a second-line chemotherapy regimen containing taxanes, suggesting that the peripheral sensory neuropathy induced by oxaliplatin did not clinically hinder the administration of subsequent taxanes-containing chemotherapy.

S-1 has been available for AGC in European and Asian countries. The pharmacokinetics and toxicities of S-1 are different among Caucasian and Asian patients [15, 16]. A couple of the causes are considered as follows; first, the activity of CYP2A6 which is converted to 5-FU from tegafur not only in the liver but also in intestinal mucosa; second, the effect of food intake on the metabolism of oxonic acid which should be localized in the intestinal mucosa and protects mucosal injury by 5-FU, and is converted to cyanuric acid (CA) by gastric juice; third, the difference of folic acid levels in diet among Caucasians and Asians. The larger AUCs of 5-FU and CA in Caucasians than Asians were correlated to the higher incidence of diarrhea by S-1. The oral dosing of S-1 before meal might be one of solutions for avoiding severe diarrhea especially for Caucasians. If dose of S-1 is adequately adjusted by toxicities with enough patient education and self-management, SOX provides considerable improved safety without compromising efficacy for AGC in Caucasians as well.

During the study period, we did not test HER2 expression in tumors and could not know its exact influence on our results. The proportion of patients who received trastuzumab after the study treatment was small (<10%) and similar in both groups.

**Figure 3.** Subgroup analyses of overall survival. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group. aMedian of sum of tumor diameter: 76.5 mm. bMedian of ALP: 258 IU/l.
Therefore, trastuzumab treatment would not seem to impact on comparing OS between both groups.

In conclusion, SOX was as effective as CS for AGC. Generally, SOX was less toxic and more convenient clinically, in which forced hydration is not needed unlike cisplatin, than CS. SOX can thus replace CS in the first-line treatment of AGC.

**Table 2. Multivariate analysis for overall survival**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>HR</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>SOX (versus CS)</td>
<td>0.955</td>
<td>0.802–1.138</td>
<td>0.61</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (versus female)</td>
<td>1.108</td>
<td>0.904–1.357</td>
<td>0.32</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≥70 (versus &lt;70)</td>
<td>0.924</td>
<td>0.762–1.119</td>
<td>0.42</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>1, 2 (versus 0)</td>
<td>1.603</td>
<td>1.328–1.935</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease status</td>
<td>Recurrent (versus unresectable)</td>
<td>0.588</td>
<td>0.451–0.767</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tumor histology</td>
<td>Diffuse (versus intestinal)</td>
<td>1.378</td>
<td>1.151–1.649</td>
<td>0.0005</td>
</tr>
<tr>
<td>Peritoneal metastasis</td>
<td>Yes (versus no)</td>
<td>1.099</td>
<td>0.878–1.377</td>
<td>0.41</td>
</tr>
<tr>
<td>Sum of tumor diameter&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥Median&lt;sup&gt;a&lt;/sup&gt; (versus &lt;median)</td>
<td>1.437</td>
<td>1.195–1.728</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALP</td>
<td>≥Median&lt;sup&gt;a&lt;/sup&gt; (versus &lt;median)</td>
<td>1.097</td>
<td>0.916–1.315</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Multivariate analyses showed that ECOG performance status (1, 2), unresectable, diffuse-type, and sum of tumor diameter (≥median) correlated with poor prognosis in overall survival.

*Wald test.

<sup>b</sup>Sum of tumor diameter, according to the Response Evaluation Criteria In Solid Tumors version 1.0.

<sup>a</sup>Median of sum of tumor diameter: 76.5 mm.

<sup> median of ALP: 258 IU/l.

HR, hazard ratio; CI, confidence interval; SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ECOG, Eastern Cooperative Oncology Group; ALP, alkaline phosphatase.

**Table 3. Treatment-related adverse events**

<table>
<thead>
<tr>
<th></th>
<th>SOX (N = 338)</th>
<th>CS (N = 335)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>≥Grade 3</td>
<td>Any</td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>205 (60.7)</td>
<td>4 (1.2)</td>
<td>248</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>233 (68.9)</td>
<td>66 (19.5)</td>
<td>266</td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (55.3)</td>
<td>51 (15.1)</td>
<td>247</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>265 (78.4)</td>
<td>34 (10.1)</td>
<td>232</td>
</tr>
<tr>
<td>Nonhematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (0.9)</td>
<td>3 (0.9)</td>
<td>23</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>131 (38.8)</td>
<td>9 (2.7)</td>
<td>80</td>
</tr>
<tr>
<td>AST</td>
<td>205 (60.7)</td>
<td>10 (3.0)</td>
<td>77</td>
</tr>
<tr>
<td>ALT</td>
<td>136 (40.2)</td>
<td>10 (3.0)</td>
<td>80</td>
</tr>
<tr>
<td>Creatinine</td>
<td>30 (8.9)</td>
<td>1 (0.3)</td>
<td>132</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>74 (21.9)</td>
<td>15 (4.4)</td>
<td>154</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>163 (48.2)</td>
<td>19 (5.6)</td>
<td>196</td>
</tr>
<tr>
<td>Nausea</td>
<td>208 (61.5)</td>
<td>13 (3.8)</td>
<td>231</td>
</tr>
<tr>
<td>Vomiting</td>
<td>118 (34.9)</td>
<td>2 (0.6)</td>
<td>119</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>109 (32.2)</td>
<td>5 (1.5)</td>
<td>138</td>
</tr>
<tr>
<td>Anorexia</td>
<td>252 (74.6)</td>
<td>52 (15.4)</td>
<td>271</td>
</tr>
<tr>
<td>Fatigue</td>
<td>195 (57.7)</td>
<td>22 (6.5)</td>
<td>203</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>289 (85.5)</td>
<td>16 (4.7)</td>
<td>79</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

<sup>p2</sup> test; comparing frequency of adverse events of any grades, and grade 3 or higher.

SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Therefore, trastuzumab treatment would not seem to impact on comparing OS between both groups.

In conclusion, SOX was as effective as CS for AGC. Generally, SOX was less toxic and more convenient clinically, in which forced hydration is not needed unlike cisplatin, than CS. SOX can thus replace CS in the first-line treatment of AGC.

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disclosure

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references


