Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study)

W. Koizumi¹*, H. Takiuchi², Y. Yamada³, N. Boku⁴, N. Fuse⁵, K. Muro⁶, Y. Komatsu⁷ & A. Tsuburaya⁸

¹Department of Gastroenterology/Gastrointestinal Oncology, Kitasato University School of Medicine, Sagamihara; ²Department of Gastroenterology, Osaka Medical College, Takatsuki; ³Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo; ⁴Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun; ⁵Division of Gastrointestinal Oncology and Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa; ⁶Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya; ⁷Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo and ⁸Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan

Background: The efficacy and safety of oxaliplatin combined with S-1 (SOX regimen) for unresectable advanced or recurrent gastric cancer were investigated.

Patients and methods: Oxaliplatin was administered i.v. (100 mg/m²) on day 1, while S-1 was administered orally (80 mg/m²/day, b.i.d.) for 14 days followed by a 7-day rest. This schedule was repeated every 3 weeks.

Results: Among 55 patients enrolled, one patient received oxaliplatin for the other study, and three patients were considered unsuitable against the inclusion criteria. Accordingly, 51 patients were assessable for efficacy. The response rate was 59%, and the disease control rate was 84%. The median progression-free survival time was 6.5 months, the 1-year survival rate was 71%, and the median survival time was 16.5 months. In 54 patients assessed for safety, the major grade 3/4 toxic effects were neutropenia (22%), thrombocytopenia (13%), anemia (9%), anorexia (6%), fatigue (6%), and sensory neuropathy (4%).

Conclusion: These findings indicate that SOX regimen with oxaliplatin at a dose of 100 mg/m² is feasible and shows promising efficacy against advanced gastric cancer.

Key words: advanced gastric cancer, oxaliplatin, phase II, S-1, SOX

Introduction

Chemotherapy for advanced gastric cancer was proven to be superior to best supportive care in terms of survival and quality of life [1–3]. Phase III studies have been carried out to compare epirubicin/cisplatin/5-fluorouracil (5-FU) with 5-FU/doxorubicin/methotrexate, cisplatin/5-FU with docetaxel/cisplatin/5-FU, and 5-FU/cisplatin with capecitabine/cisplatin [4–6]. On the basis of the results of these studies, advanced gastric cancer is mainly treated with combination chemotherapy that includes fluoropyrimidine derivatives and platinum compounds.

Oxaliplatin is a third-generation platinum compound that was developed to improve tolerability and ease of administration compared with cisplatin [7]. The non-inferiority of oxaliplatin-based regimens to cisplatin-based regimens was demonstrated in the Revised European-American Lymphoma (REAL)-2 phase III study [8]. In addition, the result of phase III study comparing 5-FU/leucovorin/cisplatin with 5-FU/leucovorin/oxaliplatin showed that oxaliplatin was at least as effective as cisplatin [9].

S-1 is an orally active prodrug of 5-FU that contains tegafur (which is continuously metabolized to 5-FU) blended with two modulators, gimeracil and potassium oxonate [10]. In Japan, advanced gastric cancer is mainly treated with S-1 alone or S-1 combined with other drugs. The SPIRITS phase III study demonstrated the superiority of S-1 plus cisplatin to S-1 alone [11]. The S-1 plus cisplatin regimen was also investigated by the FLAGS phase III study carried out in Western countries, which demonstrated that S-1 plus cisplatin was at least as effective as 5-FU plus cisplatin and less toxic [12].

We conducted a multicenter phase II study to evaluate the efficacy and safety of the combination regimen of S-1 and oxaliplatin (SOX regimen) in advanced gastric cancer as first-line therapy.

Patients and methods

Patients’ eligibility

The following criteria were used to enroll patients for the present study. All patients had unresectable advanced or recurrent gastric cancer excluding the esophagus and gastroesophageal junction, confirmed by histological or...

*Correspondence to: Dr W. Koizumi, Department of Gastroenterology/Gastrointestinal Oncology, Kitasato University School of Medicine, 2-1-1 Asamizodai, Sagamihara, Kanagawa 228-8520, Japan. Tel: +81-42-748-9111; Fax: +81-42-748-5120; E-mail: koizumi@med.kitasato-u.ac.jp

© The Author 2009. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oxfordjournals.org
review boards of all participating medical institutions.

and Good Clinical Practice guidelines and was approved by the institutional

provided written informed consent.

institutional upper limit of normal), and renal function (serum creatinine

aspartate aminotransferase/alanine aminotransferase £

treatment was discontinued if subsequent reduction was indicated. The

if grade 2 thrombocytopenia continued

neuropathy failed to recover by the time when the next cycle was scheduled,

diarrhea, stomatitis, or sensory neuropathy occurred, if grade 3 sensory

day, respectively, for each level. Treatment was discontinued if grade 4

function (total bilirubin £

eligible. They had at least one measurable lesion according to RECIST

not received prior chemotherapy, but those who had completed

cykological examination. They had survived at least 4 weeks if extended or

standard surgery had been carried out (or at least 2 weeks after minor

were able to take oral drugs. They were aged ≥20 years, had an

Eastern Cooperative Oncology Group performance status (PS) of zero to

two, and were expected to survive for at least 2 months. In general, they had

not received prior chemotherapy, but those who had completed

postoperative adjuvant therapy at least 180 days before enrollment were

eligible. They had at least one measurable lesion according to RECIST
guidelines [13]. They also had adequate bone marrow function
(hemoglobin level ≥ 80 g/L, white blood cell count of 3–12 × 10⁹/L,
neutrophil count ≥ 1.5 × 10⁹/L, and platelet count ≥ 100 × 10⁹/L), liver
function (total bilirubin ≤ 1.5 × the institutional upper limit of normal, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × the
institutional upper limit of normal, and alkaline phosphatase ≤ 2.5 × the
institutional upper limit of normal), and renal function (serum creatinine
level ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min). All patients
provided written informed consent.

This study was carried out in accordance with the Helsinki declaration and Good Clinical Practice guidelines and was approved by the institutional review boards of all participating medical institutions.

treatment plan

Oxaliplatin was administered i.v. at a dose of 100 mg/m² on day 1. S-1 was
administered orally at a dose of 80 mg/m²/day b.i.d. for 14 days (from
the evening on day 1 until the morning on day 15), followed by a 7-day rest
period in the 3-weekly schedule. Treatment was repeated until there was
disease progression, unacceptable toxicity, or withdrawal of consent.

In the event of grade 4 neutropenia or febrile neutropenia or grade 3
diarrhea or stomatitis, the doses of oxaliplatin and S-1 were reduced by one
dose level from the next cycle after

oxaliplatin was reduced by one dose level from the next cycle after
recovering to grade 2 or less. If grade 2 thrombocytopenia continued 28
days after the scheduled day for starting the next cycle or if platelet
transfusion was required, oxaliplatin was reduced by one dose level from
the next cycle. Oxaliplatin and S-1 could be reduced by two dose levels, but
treatment was discontinued if subsequent reduction was indicated. The
doses of oxaliplatin and S-1 could be reduced by 25 mg/m² and 10–30 mg/
day, respectively, for each level. Treatment was discontinued if grade 4
diarrhea, stomatitis, or sensory neuropathy occurred, if grade 3 sensory
neuropathy failed to recover by the time when the next cycle was scheduled,
if grade 2 thrombocytopenia continued ≥15 days after the scheduled day for
starting the next cycle, or if the rest period of S-1 was over 21 days.

evaluation

The data on the patients’ characteristics, a 12-lead electrocardiogram,
computed tomography (CT) scans, and tumor marker levels (CA19-9 and
carcinoembryonic antigen) were obtained within 14 days of enrollment,
while hematology tests, biochemistry tests, and assessment of symptoms
and signs were carried out within 7 days before enrollment. During the study,
hematology tests, biochemistry tests, and assessment of symptoms
and signs were carried out every week until the end of the fourth cycle
and subsequently every 3 weeks. CT scans were carried out and tumor
markers were measured every 6 weeks (every 2 months after the best overall
response was achieved).

Responses were evaluated according to the RECIST guidelines. To
confirm partial response (PR) (30% or greater decrease in the sum of the
longest diameter of target lesions, referenced against the baseline sum of the
longest diameter of target lesions together with stabilization or decrease in
size of nontarget lesions) or complete response (CR) (disappearance of all
target and nontarget lesions together with normalization of tumor marker
levels), tumor measurements were repeated no ≤4 weeks after objective
response was firstly obtained. Responses were assessed by the independent
review committee. Overall survival (OS) was defined as the time from
treatment initiation to death from any cause. Progression-free survival
(PFS) was the time from treatment initiation to first documentation of
disease progression detected by the review committee or death from any
cause (censored at second-line chemotherapy). Time-to-treatment failure
(TTF) was the time from treatment initiation to discontinuation of
treatment, first documentation of disease progression by the review
committee, or death from any cause. Toxic effects were evaluated according
to the Common Terminology Criteria for Adverse Events V3.0.

statistical analysis

The primary end point was the response rate (RR), while the secondary end
points were OS, PFS, TTF, and safety. The required sample size was
calculated to be at least 49 patients on the null hypothesis of the RR of
≤40% versus the alternative hypothesis of the RR of >60%, power 80%, and
α 2.5% (one sided). The 95% confidence interval (CI) was calculated for
the RR, PFS, and TTF. OS, PFS, and TTF were calculated by the Kaplan–
Meier method. Safety was analyzed in all patients who received at least
one dose of study medication.

The cut-off date for RR, PFS, TTF, and safety was 27 May 2008, while
that for OS was 13 July 2009.

results

patients’ characteristics

Fifty-five patients were enrolled from April to December in
2007. Among them, one patient who received oxaliplatin for the other study by mistake was excluded from all analyses. Three other patients were excluded from efficacy analysis because of prior chemotherapy (methotrexate), severe interstitial pneumonia, or absence of measurable lesions (one patient each). Accordingly, 51 patients formed the efficacy analysis set (Table 1), while 54 patients were analyzed for safety. The median age of the 51 patients was 63 years (range 30–77
years) and the PS was zero or one in 50 patients. Prior adjuvant chemotherapy with S-1 had been carried out in one patient, while 50 patients had received no prior chemotherapy.

treatment

At the data cut-off date, treatment was ongoing in eight patients. The major reasons for discontinuation of treatment in
46 patients were disease progression (63%), adverse events
(28%), and withdrawal of consent (2%).

The median number of treatment cycles was 6.0 (range
1–16+). The median dose intensity was 88 mg/m²/3 weeks for
oxaliplatin and 867 mg/m²/3 weeks for S-1, and the median
relative dose intensity was 87.5% and 85.7%, respectively.

The median total dose was 600 mg/m² for oxaliplatin and
5966 mg/m² for S-1.

efficacy

The response was assessed as PR, stable disease (SD) (less than
a 30% reduction and less than a 20% increase in the sum of the
longest diameter of target lesions, referenced against the
baseline sum of the longest diameter of target lesions together
with stabilization or decrease in size of nontarget lesions), and
progressive disease (PD) in 30, 13, and 5, respectively, of the 51
patients in the efficacy analysis set (three were not assessable). The RR was 59% (95% CI 44.2% to 72.4%) and the disease control rate (CR + PR + SD) was 84% (95% CI 71.4% to 93.0%) (Table 2).

The median follow-up period was 16.5 months as of 13 July 2009. The median survival time (MST) was 16.5 months (95% CI 13.2–22.3 months) (Figure 1), median PFS was 6.5 months (95% CI 4.8–11.2 months) (Figure 2), and median TTF was 4.8 months (95% CI 4.0–5.6 months). The patients who received the second-line chemotherapy without PD were censored at the date of image examination immediately before the second-line chemotherapy in PFS analysis. The 1-year survival rate was 70.6% (95% CI 58.1% to 83.1%). Forty-one of the 46 patients (89%) who discontinued treatment received second-line chemotherapy. One patient (2%) with PR underwent surgery and pathological CR was observed.

safety assessment

Grade 3/4 toxicity occurred in 33 of the 54 patients (61%) in the safety analysis set. Grade 3/4 leukopenia, neutropenia, thrombocytopenia, anemia, anorexia, and fatigue were noted in 2 (4%), 12 (22%), 7 (13%), 5 (9%), 3 (6%), and 3 patients (6%), respectively (Table 3). The median onset of thrombocytopenia in all grades was after 42 days and the nadir platelet count was seen at 113 days. The median time from the nadir to grade 0 or platelet count of treatment initiation was 15 days and the duration of thrombocytopenia in all grades was 21 days. Sensory neuropathy was observed in 48 patients (89%), but grade 3/4 neuropathy occurred only in two patients (4%). The median cumulative dose of oxaliplatin associated with sensory neuropathy of any grade was 150 mg/m² (grade 1: 150 mg/m², grade 2: 900 mg/m²). There were no treatment-related deaths.
Discussion

Advanced gastric cancer is usually treated by combination chemotherapy with fluoropyrimidine derivatives and platinum compounds. Several recent large-scale phase III studies have shown that the RR ranges from 25% to 54%, median PFS from 2.9 to 7 months, and MST from 8.6 to 13 months [5, 6, 8, 9, 11, 14]. Unfortunately, these results are not satisfactory. In Japan, S-1 plus cisplatin is considered to be the standard treatment for advanced gastric cancer on the basis of the results of two phase III studies: the JCOG9912 study demonstrated non-inferiority of S-1 to i.v. infusion of 5-FU [14] and the SPIRITS study showed that S-1 plus cisplatin was superior to S-1 alone [11]. In the SPIRITS study, the RR, median PFS, and MST achieved with S-1 plus cisplatin were 54%, 6.0 months, and 13 months, respectively. However, more frequent incidences of grade 3/4 adverse events were reported as compared with S-1-alone group, and the combination regimens with improved safety are expected.

With the present SOX regimen, the RR was 59%, median PFS was 6.5 months, 1-year survival was 70.6%, and MST was 16.5 months, indicating similar efficacy to that of S-1 plus cisplatin. The excellent result of our SOX regimen in MST may be explicable by good PFS and feasible safety profile, which enabled patients to receive the second-line chemotherapy in the high proportion (89%). The efficacy of SOX regimen was also comparable with epirubicin and oxaliplatin plus capecitabine in the REAL-2 study [8], which demonstrated that oxaliplatin was as effective as cisplatin combined with epirubicin and 5-FU or capecitabine.

Comparison of safety between the present SOX regimen and S-1 plus cisplatin that were reported previously [11] indicates a lower incidence of grade 3/4 toxicity with SOX regimen than S-1 plus cisplatin for leucopenia (4% versus 11%), neutropenia (22% versus 40%), anemia (9% versus 26%), anorexia (6% versus 30%), and nausea (2% versus 11%). The incidence of grade 3/4 thrombocytopenia was higher with SOX regimen (89%) than with S-1 plus cisplatin (44%). Sensory neuropathy is a characteristic toxicity of oxaliplatin, and 89% of the patients receiving SOX regimen had neuropathy, but only 4% had severe (grade 3/4) neuropathy. These results indicate that SOX regimen is more tolerable and tends to be superior to S-1 plus cisplatin in terms of safety.

Yamada et al. [15] reported that the treatment was discontinued at high frequency (28%) due to prolonged thrombocytopenia when metastatic colorectal cancer patients were treated with S-1 plus 130 mg/m² of oxaliplatin. This discontinuation was supposed to be caused by the geniality of dose reduction criteria which allowed the reduction of oxaliplatin only in case of occurrence of grade 3 or more toxicity in terms of thrombocytopenia. The incidence of thrombocytopenia was 93% in all grades and 28% in grade 3/4, resulting in low median relative dose intensity of S-1 74.6% and that of oxaliplatin 82.8%. Zang et al. [16] also reported the study of SOX regimen with 130 mg/m² of oxaliplatin in patients with metastatic colorectal cancer. In their study, the treatment was interrupted in cases of grade 2 or higher toxicity until the recovery to grade 0 or 1, and the doses of oxaliplatin and S-1 were reduced after a second occurrence of grade 2 toxicity. As a result, the incidence of thrombocytopenia was 13% in grade 3/4, and the median relative dose intensity of oxaliplatin and S-1 was 82% and 82%, respectively. In this study, we used 100 mg/m² dose of oxaliplatin as SOX regimen for advanced gastric cancer to decrease the incidence of thrombocytopenia considering the possible bleeding from the primary tumor and to maintain the dose intensity of S-1, which have been demonstrated to a key drug against advanced gastric cancer as a single agent. In this new regimen, the incidence of

<table>
<thead>
<tr>
<th>Table 3. Toxicity of therapy (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity (CTCAE)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Hematological</td>
</tr>
<tr>
<td>Leukopenia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Non-hematological</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Pigmentation</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
</tr>
<tr>
<td>Stomatitis</td>
</tr>
<tr>
<td>Increased creatinine</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
</tr>
</tbody>
</table>

CTCAE, Common Terminology Criteria for Adverse Events V3.0.
thrombocytopenia was 13% in grade 3/4 without reducing the antitumor activity. The median relative dose intensity of oxaliplatin and S-1 was 87.5% and 85.7%, respectively, indicating that the treatment was carried out as scheduled in most of patients in this study.

In conclusion, SOX regimen with oxaliplatin at a dose of 100 mg/m² was effective and well tolerated in patients with advanced gastric cancer. SOX regimen has the potential to replace current regimens such as S-1 plus cisplatin or 5-FU plus cisplatin because of similar efficacy with less toxicity and more convenient treatment. Further investigation of this SOX regimen is expected.

funding
Yakult Honsha Co., Ltd.

acknowledgements
We are grateful to I. Hyodo, Y. Sakata, N. Masuda, and F. Nagamura for their kind advice and to A. Sato, K. Yoshikawa, and K. Miyagawa who carried out the independent review committee. We also thank S. Sugiyama and S. Takahashi for their helpful advice. This study has been presented at the Annual Conference of the American Society of Clinical Oncology, Orlando, FL, 2009. This study was registered with Japan Pharmaceutical Information Center Clinical Trials Information (no. 070374).

disclosure
All authors declared no conflicts of interest.

references