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ORIGINAL ARTICLE

Phase II study of oxaliplatin, irinotecan and S-1 therapy in patients with advanced gastric cancer: the Korean Cancer Study Group ST14-11

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Abstract

Background Doublet chemotherapy of platinum and 5-fluorouracil is a standard first-line treatment for patients with unresectable gastric cancer. Although the addition of taxane or irinotecan to this regimen has yielded promising efficacy, its use has been limited due to severe toxicities. To overcome this limitation, we evaluated the efficacy and safety of the combination of irinotecan, oxaliplatin, and S-1 (OIS) for the treatment of advanced gastric cancer.

Methods Chemotherapy-naïve patients with pathologically proven advanced gastric adenocarcinoma were assessed for eligibility. Irinotecan (135 mg/m^2) and oxaliplatin (65 mg/m^2) were administered intravenously on day 1, and S-1 (80 mg/m^2/day) was administered orally on days 1–7 of every 2-week cycle.

Results Forty-four patients (median age 57 years) were enrolled and all but one patient had a good performance status (ECOG 0 or 1). A total of 529 cycles were administered, with a median of 9.5 (range 1–31) cycles per patient. The overall response rate was 61.4% (95% confidence interval [CI] 46.6–74.3). The median progression-free survival and overall survival were 10.8 months (95% CI 7.6–14.0) and 15.4 months (95% CI 12.6–18.2), respectively. Major toxicities included grade 3/4 neutropenia (38.6%), febrile neutropenia (13.6%), abdominal pain (9.1%), and diarrhea (9.1%).

Conclusion These data suggest that the OIS regimen is effective and relatively well tolerated in patients with advanced gastric cancer. Given that all the patients treated, but one, had a good performance status, these results must be confirmed in a patient population more representative of regular clinical practice.

Trial Registration ClinicalTrials.gov Identifier: NCT02527785.

Keywords Stomach neoplasm · Irinotecan · Oxaliplatin · S-1 · Phase II clinical trial

Introduction

The incidence and mortality rates of gastric cancer have decreased in recent years; however, advanced gastric cancer is still one of the leading causes of cancer-related death [1, 2]. Although cisplatin-based doublet (cisplatin/5-fluorouracil [5-FU]) or triplet regimens (cisplatin/epirubicin/5-FU) have been widely used as the treatment for the control arm in phase III trials, the clinical benefits of these treatments are moderate, and progression-free survival (PFS) and overall survival (OS) are still poor [3, 4].

The V325 study demonstrated that the addition of docetaxel to a doublet of cisplatin and 5-FU (DCF) improved the time to progression (TTP) and OS in patients with advanced gastric cancer; however, this triplet regimen has not been used commonly in clinical practice or as a reference treatment in clinical trials because of severe toxicity profiles [5].

Several clinical trials have been conducted to evaluate the efficacy and tolerability of various triplet regimens

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comprising newer cytotoxic drugs such as docetaxel, paclitaxel, oxaliplatin, irinotecan, epirubicin, and oral fluoropyrimidines (capecitabine and S-1) [6–12].

Oxaliplatin is non-inferior and is generally less toxic than cisplatin [13], and S-1 is also non-inferior and safer than 5-FU [14]. Irinotecan is active against gastric cancer, and the combination of irinotecan and 5-FU showed acceptable efficacy and safety profiles [15–17]. Considering these previous reports, the combination of oxaliplatin, irinotecan, and S-1 (OIS) might be as effective as, and less toxic than, DCF or DCF modifications (mDCF).

Therefore, this phase II trial was conducted to evaluate the efficacy and toxicity of OIS as a first-line treatment in patients with advanced gastric cancer.

Patients and methods

Study design and patients

This was a multicenter phase II clinical trial performed by the Korean Cancer Study Group (ST14-11). The protocol was approved by the institutional review board at each study site before protocol activation, and all patients provided written informed consent before enrollment (ClinicalTrials.gov Identifier: NCT02527785).

Eligible patients were ≥ 19 years old with pathologically confirmed metastatic or recurrent gastric adenocarcinoma. Radiographically measureable disease according to the response evaluation criteria in solid tumors (RECIST) version 1.1 was required. Prior palliative chemotherapy was an exclusion criterion. Prior adjuvant (and/or neoadjuvant) chemotherapy was permitted if relapse occurred more than 6 months after the completion of chemotherapy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and adequate organ functions.

The major exclusion criteria were histologically proven human epidermal growth factor receptor 2-positive disease, brain or CNS metastasis, gastrointestinal bleeding or obstruction, severe hypersensitivity to the study drugs, significant cardiovascular disease (unstable angina, myocardial infarction, stroke, or cerebrovascular accident within 6 months of study entry) and sensory neuropathy.

Treatment plan

We conducted a dose-finding study for the OIS regimen and identified the recommended dose (RD) for the phase II study [18]. Irinotecan (180 mg/m^2) was infused intravenously for 90 min, followed by intravenous administration of oxaliplatin (85 mg/m^2) for 2 h on day 1. S-1 (50 mg/m^2) was given orally twice daily on days 1–7 of each cycle. The dose of S-1 was 100 mg/day for patients with a body surface area (BSA) < 1.25 m^2, 125 mg/day for those with a BSA ≥ 1.25 m^2 but < 1.5 m^2, and 150 mg/day for those with a BSA ≥ 1.5 m^2. The treatment was administered every 2 weeks up to 12 cycles and patients could be treated more than 12 cycles under the investigator's decision. The patients were dropped from study when disease progression, unacceptable toxicity, or withdrawal of consent occurred.

However, when 13 cycles of OIS were given to the initial four patients in this phase II study, four grade 3 toxicities occurred (two febrile neutropenia, one diarrhea, and one skin rash case). Subsequent treatments were delayed and the doses reduced. The relative dose intensity of OIS in 13 cycles was ~ 70%, so we decided to adjust the RD of OIS to prevent severe toxicities. After 8 patients were treated with the initial RD, the remaining 36 patients were treated with reduced RD of oxaliplatin (65 mg/m^2), irinotecan (135 mg/m^2), and S-1 (80 mg/m^2/day).

Dose modifications were applied for the subsequent cycle according to the grade of the toxicities observed during the previous cycle. The degree of the modification depended on the frequency of grade 3 or 4 toxicities, with reductions of 25 or 50% or with permanent interruption. Treatment was delayed until the toxicities resolved to grade 1 or lower. The requirements for the neutrophil and platelet counts were ≥ 1500 and ≥ 100,000/μL, respectively, at initiation of the subsequent cycle. Prophylactic granulocyte colony stimulating factor (G-CSF) and prophylactic antibiotics were not allowed in patients who had experienced neutropenic events in the previous cycle; however, G-CSF was administered to treat patents in neutropenic events.

Assessments

Response to treatment was assessed every three cycles by the local onsite radiologist independently according to RECIST version 1.1. Confirmation of all complete and partial responses was required 4 weeks later. After discontinuation of the study regimen, patients were followed up every 6 weeks until disease progression or death.

All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Toxicity was assessed every week during the first treatment cycle and then every 2 weeks during the subsequent cycles.

Outcomes and statistical analysis

The intention-to-treat (ITT) population included all of the enrolled patients, while the per-protocol (PP) population included only accessible patients who received the study

treatment and had at least one post-treatment tumor evaluation without any major protocol violation. The primary end point was the overall response rate (ORR), and the secondary end points were OS, PFS, and toxicities in the ITT population. The response and toxicity data were described using simple descriptive statistics. PFS and OS were estimated using the Kaplan–Meier method and were compared with other prognostic factors using the log-rank test. A forward, stepwise Cox regression analysis was used to identify the prognostic factors for OS.

We referred to the results of two trials to calculate a sample size [5, 12]. Response rates of doublet are around 25% and those of triplet are 25.6–46.6%. Based on these results, study sample size was calculated to test whether the ORR is 25% (the null hypothesis) versus 45% (alternative hypothesis) at a significance level of 0.05 with a power of 80%. Assuming a drop-out rate of 10%, the target recruitment was 40 patients.

Results

Patient characteristics

Forty-four patients were screened at eight hospitals in South Korea from February 2015 to April 2016 and enrolled in this study. The majority of patients were male, and the median age was 57 years (range 29–79 years). Most patients had a good performance status. Forty-two patients had distant metastatic disease, and 33 patients (75.0%) were diagnosed with metastatic disease initially. Nine patients (20.5%) had recurrent gastric cancer after curative surgery. Twenty-nine patients (65.9%) had poorly differentiated cancers, and the most common metastatic sites were distant lymph nodes (59.1%) and the peritoneum (29.6%). The baseline characteristics of the patients are described in Table 1.

Table 1 Patient characteristics ($n = 44$)

Characteristics	No. of patients (%)
Median age, years (range)	57 (29–79)
Gender	
Male	31 (70.5)
Female	13 (29.5)
Performance status (ECOG)	
0	9 (20.5)
1	34 (77.3)
2	1 (2.3)
Location of primary tumor site	
Cardia	6 (13.6)
Fundus	1 (2.3)
Body	22 (50.0)
Antrum or pylorus	18 (40.9)
Diffuse	2 (4.5)
Histology	
Well differentiated	1 (2.3)
Moderately differentiated	12 (27.3)
Poorly differentiated	29 (65.9)
Unknown	2 (4.5)
Prior surgery	
Curative	9 (20.5)
Palliative	2 (4.5)
Metastatic site	
Liver	11 (25.0)
Lung	3 (6.8)
Lymph node	26 (59.1)
Peritoneum	13 (29.6)
Ovary	5 (11.4)
Bone	4 (9.1)
Others	9 (20.5)
No. of metastatic sites	
1	26 (59.1)
2	12 (27.3)
3	3 (6.8)
≥ 4	3 (6.8)

ECOG Eastern Cooperative Oncology Group

Treatment delivery

A total of 529 cycles of the study treatment were administered to the 44 patients, with a median of 9.5 (range 1–31) cycles per patient. All patients had discontinued the study treatment at the time of analysis. The most common reasons for discontinuation were disease progression (28 patients, 63.6%) and withdrawal from the study (6 patients, 13.6%). Other reasons were operation (5 patients with CR or PR state, 11.4%), loss of follow up (3 patients, 6.8%) and physician's decision after completing 12 cycles (1 patient, 2.3%). Only one patient was dropped due to an adverse event (grade 3 fatigue).

Of the 21 patients who completed the planned 12 cycles of treatment, 17 received 13 or more cycles of treatment. Thirty-three patients experienced dose delays, and 28 patients received reduced doses of the study drugs. The mean relative dose intensities (the ratio of dose received to dose planned; RDI) of irinotecan, oxaliplatin, and S-1 for all of the administered cycles were 0.82 (95% confidence interval [CI] 0.79–0.85), 0.86 (95% CI 0.84–0.88), and 0.91 (95% CI 0.90–0.92), respectively. The RDIs of the study drugs exhibited gradually decreasing trends, with a greater number of cycles during the first 12 cycles (Fig. 1).

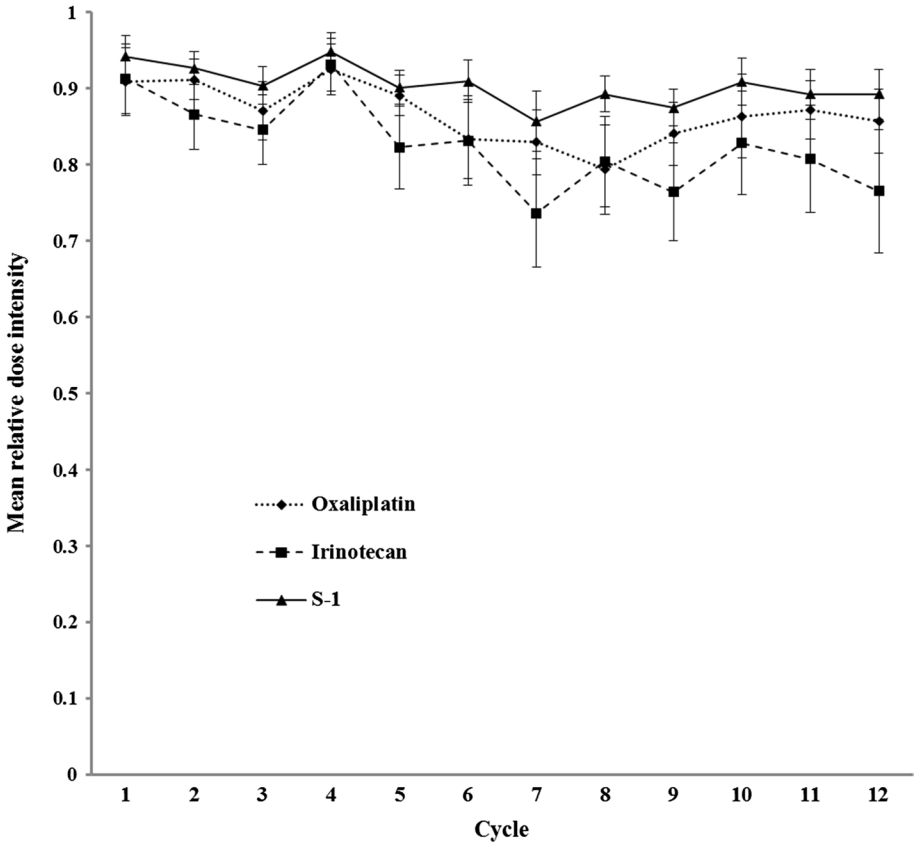

Fig. 1 Mean relative dose intensities of oxaliplatin, irinotecan, and S-1 in planned 12 cycles of treatment

Twenty-one patients (47.7%) who discontinued the study treatment received subsequent treatment. Six patients (13.6%) underwent surgery, of whom two, who were in the complete response (CR) state underwent curative surgery and four [three in the partial response (PR) state and one in the progressive disease (PD) state] underwent palliative surgery. Fifteen patients (34.1%) received second-line chemotherapies including ramucirumab and paclitaxel in three patients, docetaxel and cisplatin in two patients, taxane monotherapy in eight patients, FOLFOX in one patient and ramucirumab and durvalumab in one patient. Third-line chemotherapy was administered to six patients.

Safety

All patients who received at least one cycle of the study treatment were subjected to a safety analysis. The most common hematological and non-hematological adverse events are summarized in Tables 2 and 3. Grade 3/4 neutropenia was observed most frequently (38.6%), and febrile neutropenia was reported in six patients (13.6%); all of these

Table 2 Hematological adverse events

	All patients ($n = 44$)					Patients treated with reduced recommended dose ($n = 36$)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Leukopenia	20	6	0	0	0.0	18	5	0	0	0.0
Neutropenia	5	13	15	2	38.6	4	13	9	0	25.0
Anemia	16	5	2	0	4.5	13	4	2	0	5.6
Thrombocytopenia	18	1	0	0	0.0	17	1	0	0	0.0
Febrile neutropenia	–	–	5	1	13.6	–	–	1	1	5.6

Table 3 Non-hematological adverse events

	All patients ($n = 44$)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Abdominal pain	2	17	4	0	9.1
Diarrhea	11	7	4	0	9.1
Vomiting	8	6	3	0	6.8
Ileus	0	0	3	0	6.8
Nausea	19	6	2	0	4.5
Anorexia	15	4	2	0	4.5
Peripheral neuropathy	8	6	2	0	4.5
Oral mucositis	5	1	2	0	4.5
Fatigue	9	8	1	0	2.3
Pain	7	4	1	0	2.3
Pruritus	2	1	1	0	2.3
UGI bleeding	2	0	1	0	2.3
Infection	0	1	1	0	2.3
Stomatitis	0	0	1	0	2.3
Urine output decreased	0	0	1	0	2.3
Dyspepsia	11	3	0	0	0.0
Flu like symptoms	11	1	0	0	0.0
Alopecia	8	1	0	0	0.0
Constipation	7	2	0	0	0.0
Edema	7	1	0	0	0.0
Headache	5	0	0	0	0.0
Fever	5	0	0	0	0.0
Hand-foot syndrome	1	0	0	0	0.0

UGI upper gastrointestinal

patients recovered without complications. Eight patents in febrile neutropenia or grade 4 neutropenia were treated with G-CSF.

As mentioned above, the doses of the study drugs were adjusted to prevent severe adverse events. A total of 15 cycles of the initial RD were given to eight patients, four (50%) of whom experienced grade 3 febrile neutropenia. On the other hand, 36 patients were treated with reduced RD of the study drugs, and grade 3/4 febrile neutropenia occurred in only two patients (5.6%). Non-hematologic toxicities were usually mild and manageable. The most commonly reported grade 3/4 non-hematological toxicities were abdominal pain, diarrhea, vomiting, and ileus. Grade 3 peripheral neuropathy was observed in two patients (4.5%), who continued with the study treatment omitting oxaliplatin.

Table 4 Treatment efficacy

Response	No. of patients	%	95% CI
Complete response	3		
Partial response	24		
Stable disease	8		
Progressive disease	4		
Not evaluable	5		
ITT			
Overall response		61.4	46.6–74.3
Disease control		79.5	65.5–88.9
PP			
Overall response		69.2	53.6–81.4
Disease control		89.7	76.4–96.0

CI confidence interval, *ITT* intention-to-treat, *PP* per protocol

Efficacy

Of the 44 patients, follow-up response evaluation was conducted in 39 patients; 3 were lost to follow-up, and 2 withdrew their consent prior to the response evaluation. The tumor responses are presented in Table 4. There were 3 and 24 complete and partial responses observed, respectively. The confirmed ORR was 61.4% (95% CI 46.6–74.3) in the ITT population and 69.2% (95% CI 53.6–81.4) in the PP population. The disease control rate was 79.5% (95% CI 65.5–88.9) in the ITT population and 89.7% (95% CI 76.4–96.0) in the PP population. The median time to response was 1.5 months, and the median duration of the response was 5.6 months.

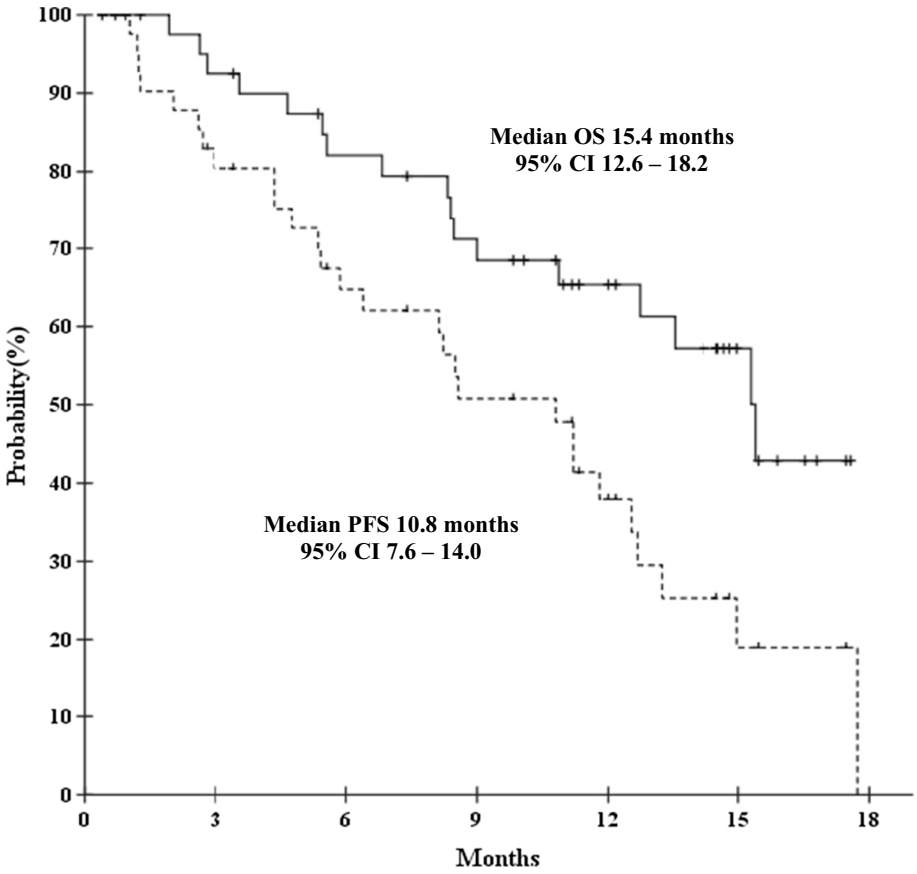

Fig. 2 Kaplan-Meier estimates of progression-free survival and overall survival

As of the study cut-off date (April 14, 2017), 27 patients (61.4%) were still alive, and 28 experienced disease progression, with a median follow-up duration of 10.8 months (range 0.4–17.6). The median PFS was 10.8 months (95% CI 7.6–14.0), and the median OS was 15.4 months (95% CI 12.6–18.2) in the ITT population as shown in Fig. 2. Univariate and multivariate analyses showed that the response to treatment was a favorable prognostic factor among the various clinical parameters (Supplementary Tables 1 and 2).

Discussion

This study showed that the triplet regimen consisting of oxaliplatin, irinotecan, and S-1 repeated every 2 weeks was active and feasible as a first-line palliative treatment in patients with advanced gastric cancer. In the ITT population, the ORR, which was the primary outcome, was 61.4%. The median PFS and OS were 10.8 and 15.4 months, respectively.

The combination of S-1 plus irinotecan and oxaliplatin (TIROX) was previously evaluated in a phase II trial [19]. The TIROX regimen consisted of 150 mg/m^2 irinotecan and 85 mg/m^2 oxaliplatin on day 1 plus 40 mg/m^2 oral S-1 twice daily on days 1–14, repeated every 3 weeks. TIROX yielded encouraging results such as an ORR of 75%, a median TTP of 10.2 months, and a median OS of 17.6 months. However, grade 3/4 neutropenia and febrile neutropenia were observed in 66 and 16% of patients, respectively. Compared with TIROX, OIS seems to have comparable efficacy but much lower rates of grade 3/4 neutropenia and febrile neutropenia, especially when including only the patients who received a reduced RD of the regimen (febrile neutropenia 5.6%). Non-hematological toxicities such as abdominal pain, diarrhea, and anorexia were also observed less frequently in patients on the OIS regimen. A shorter exposure time of S-1 in OIS seems to reduce these toxicities.

Recently, a phase III trial evaluated the efficacy and safety of S-1 plus oxaliplatin (SOX) as an alternative to cisplatin plus S-1 as first-line chemotherapy for advanced gastric cancer [20]. Patients assigned to the SOX group received 100 mg/m^2 oxaliplatin on day 1 and 40 mg/m^2 S-1 twice daily for 2 weeks every 3 weeks. The SOX treatment yielded an ORR of 55.7%, a median PFS of 5.5 months, and a median OS of 14.1 months. Grade 3/4 neutropenia and febrile neutropenia were seen in 19.5 and 0.9% of patients in the SOX group, respectively. The ORR was slightly higher for OIS than for SOX numerically; however, the addition

of irinotecan seemed to cause more cases of neutropenia. Therefore, comparative clinical trials of OIS and SOX seems to be warranted to identify the role of irinotecan in combination with oxaliplatin and S-1.

Since the phase II/III V325 study showed that the addition of docetaxel to a cisplatin and 5-FU regimen significantly improved the TTP and OS in untreated patients with advanced gastric cancer, a number of studies have investigated various mDCF regimens to achieve the same efficacy with fewer adverse events [21, 22]. In a phase II trial by Shah et al., mDCF consisting of 2000 mg/m^2 5-FU over 48 h, 40 mg/m^2 docetaxel IV on day 1, and 40 mg/m^2 cisplatin IV on day 3 every 2 weeks was administered. The mDCF regimen was less toxic and more efficacious than DCF, with an ORR of 48%, median PFS of 9.7 months, and median OS of 18.8 months. A phase III trial by Wang et al. reported that mDCF consisting of 60 mg/m^2 docetaxel, 60 mg/m^2 cisplatin, and 600 mg/m^2 5-FU over 5 days every 3 weeks achieved an efficacy comparable to that of DCF, but with fewer toxicities. Although mDCF was less toxic than the original DCF regimen, grade 3/4 neutropenia and febrile neutropenia occurred in 56.0–60.5 and 9.0–12.6% of patients, respectively, and these rates are higher than those associated with the OIS regimen.

Our group conducted a phase II study that evaluated a combination of docetaxel, oxaliplatin, and S-1 (DOS) in patients with metastatic gastric cancer [23]. The DOS regimen consisted of 52.5 mg/m^2 docetaxel and 105 mg/m^2 oxaliplatin on day 1 and 80 mg/m^2 S-1 on days 1–14 every 3 weeks. The treatment outcomes of DOS (ORR 54.5%, median PFS 7.6 months, and median OS 12.0 months) were comparable with those of mDCF, but less toxic (rate of grade 3/4 neutropenia, 37.2%; rate of febrile neutropenia, 14.0%). The efficacy of OIS seems to be comparable with that DOS, but grade 3 peripheral neuropathy was observed less frequently in patients receiving OIS (4.5 vs. 14.0%).

The OIS treatment was generally well tolerated by most patients. There was no death related to the study treatment. The most common grade 3/4 adverse events were neutropenia (38.6%) and febrile neutropenia (13.6%). However, the rate of febrile neutropenia was reduced to 5.6% in patients receiving a reduced RD of OIS. Grade 3 peripheral neuropathy was observed in two patients who received 19 and 29 cycles, respectively, of the study treatment. A few grade 3/4 non-hematologic toxicities such as abdominal pain, diarrhea, vomiting, and ileus were observed.

The limitations of this study should be mentioned. The study population was relatively young (median age 57 years), and all but one patient had a good ECOG performance status (0 or 1). Furthermore, tumor burdens of patients in this study were lower than other trials evaluating triple regimens [5, 12, 22]. These could be possible explanations for the favorable toxicity profiles and efficacy results. In addition, treatment was interrupted in cases with grade 2 or higher toxicities, and dose modification was conducted strictly according to the study protocol. This policy might have prevented the development of more severe (grade 3/4) toxicities in subsequent cycles.

OIS seems to have a comparable efficacy with mostly favorable toxicity profiles among triple combination regimens and could be a reasonable three-drug chemotherapy option for patients with advanced gastric cancer.

These data suggest that the OIS regimen is effective and relatively well tolerated in selected patients with advanced gastric cancer. Therefore, the phase III trial that enrolls only patients with PS of ECOG 0-1 is going to be conducted to confirm the feasibility and safety of an OIS regimen after approval of IRB and Korea Ministry of Food and Drug Safety.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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