original article

Phase II study with oxaliplatin and S-1 for patients with metastatic colorectal cancer


1Department of Internal Medicine; 2Department of Surgery and 3Department of Radiology, Hallym University Medical Center and Hallym University College of Medicine, Anyang, South Korea

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Background: To evaluate the efficacy and safety of the combination of oxaliplatin and S-1 (OS) in treating metastatic colorectal cancer.

Patients and methods: Eligible patients were those with measurable lesions, no previous history of chemotherapy (except adjuvant chemotherapy), an age of 18–70 years, and an Eastern Cooperative Oncology Group performance status of zero to two. Oxaliplatin 130 mg/m² was administered i.v. on day 1, and S-1 40 mg/m² b.i.d. was administered orally on days 1–14, every 3 weeks.

Results: Forty-eight patients (median age, 56 years) were enrolled: 23 had colon cancer, seven rectosigmoid colon cancer; and 18 rectal cancer. Of the 48 patients, 31 were diagnosed with metastatic cancer and 17 had relapsed cancer after surgery, with adjuvant chemotherapy or chemoradiotherapy. In total, 413 cycles were administered (median 6 per patient; range 2–24). Toxicity was evaluated in 48 patient and response in 46. Major toxic effects were grade 3/4 thrombocytopenia (13%) and neutropenia (10%). The overall response rate was 54% (95% confidence interval CI 40% to 68%). The median time to progression and median survival time were 8.5 (95% CI 6.2–10.9) months and 27.2 (95% CI 20.3–34.0) months, respectively.

Conclusions: These data indicate that the OS regimen is effective and well tolerated in patients with advanced colorectal cancer.

Key words: colorectal neoplasm, oxaliplatin, S1

introduction

The combination of oxaliplatin or irinotecan with bolus and infusional fluorouracil (FU) and folinic acid (FA) is considered the standard regimen for the first-line treatment of metastatic colorectal cancer [1–4]. However, this regimen is inconvenient owing to its requirement for continuous infusion of FU via vascular access.

To overcome this drawback, oral fluoropyrimidines such as capecitabine have been used as a substitute for infused FU/FA [5], and recent data have shown that capcitabine plus oxaliplatin (XELOX) was not inferior to infused FU/FA plus oxaliplatin (known as FOLFOX-4 or FUOX) [6, 7]. A novel dihydropyrimidine dehydrogenase-inhibitory oral fluoropyrimidine, S-1, has been used widely in patients with gastric cancer. In phase II studies, S-1 as a single agent showed an overall response rate (ORR) of 19%–40% with tolerable toxic effects in the first-line treatment of metastatic colorectal cancer [8–10].

To explore the possibility of using S-1 to replace the continuous FU infusion of the FOLFOX regimen, we carried out a phase II clinical trial with a regimen of oxaliplatin plus S-1 (OS) for the first-line treatment of metastatic colorectal cancer.

patients and methods

eligibility

Eligible patients met all the following criteria: presence of unresectable, metastatic, and histologically confirmed colorectal cancer; age from 18 to 70 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero to two; estimated life expectancy of >3 months; and adequate hematological, renal, and hepatic functions, as defined by a white blood cell count ≥4.0 × 10⁹/l or absolute granulocyte count ≥1.5 × 10⁹/l, platelet count ≥100 × 10⁹/l, hemoglobin level ≥9.0 g/dl, serum creatinine level ≤1.4 mg/dl, serum bilirubin level ≤1.8 mg/dl, and aspartate aminotransferase/alanine aminotransferase less than or equal to twice the upper limit of normal. The presence of a unidimensionally measurable lesion was also required for the study. Patients with a previous history of chemotherapy (except adjuvant or neo-adjuvant chemotherapy not including oxaliplatin or S-1), central nervous system metastasis, obvious bowel obstruction, serous gastrointestinal bleeding, or serious comorbid conditions were excluded from the study.
Each patient gave written informed consent before entering the study. The protocol was approved by the institutional review board of Hallym University Medical Center, Anyang, South Korea.

**pretreatment evaluations**
Baseline evaluations included medical history, physical examination, ECOG PS, complete blood count, serum chemistry and electrolytes, carcinoembryonic antigen determination, urine analysis, chest X-ray, and three-dimensional computed tomography.

**treatment scheme**
Oxaliplatin 130 mg/m² mixed with 250 ml of dextrose solution was administered i.v. over 2 h on day 1 and S-1 40 mg/m² [body surface area (BSA) < 1.25 m², 40 mg; 1.25 ≤ BSA < 1.5, 50 mg; BSA ≥ 1.5, 60 mg] was administered orally, twice daily from day 1 to 14, followed by a 7-day rest period. The treatment was repeated every 3 weeks until progression of the disease, the development of unacceptable toxicity, or consent withdrawal by the patient.

**dose modifications**
The dose of a specific agent was adjusted when the cause of toxicity could be distinguished. When both agents were believed to have caused the toxicity, the doses of both were reduced. Treatment was interrupted in the case of grade 2 or higher toxicity and was not resumed until the toxicity resolved or had improved to grade 0 or 1. The dose of oxaliplatin was reduced by 25% of the initial dose for related grade 3 toxic effects or for the second occurrence of same grade 2 toxicity. The dose of S-1 was reduced by 20 mg/day for related grade 3 toxic effects or for second occurrence of the same grade 2 toxicity. The dose of oxaliplatin was reduced by 50% of the initial dose for related grade 4 toxic effects or for second occurrence of the same grade 3 toxicity. The initial dose of S-1 was reduced by 40 mg/day for related grade 4 toxic effects or for second occurrence of the same grade 3 toxicity. No dose increase was allowed. Treatment was discontinued if, despite the dose reduction, the same toxicity occurred for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4. In addition, if the toxicity had not improved to grade 0 or 1 after 3 weeks to allow the continuation of treatment, the patient was removed from the study.

**response and toxicity evaluation**
The Response Evaluation Criteria in Solid Tumors guidelines [11] were used to evaluate tumor responses, and the National Cancer Institute—Common Toxicity Criteria (version 3.0) were used to assess toxicity. (Complete response was defined as the disappearance of all target and nontarget lesions. Partial response was a 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. Progressive disease required a 20% or greater increase in the sum of the longest diameter of target lesions, an unequivocal increase in the nontarget lesions, or appearance of any new lesions. Stable disease was defined as insufficient shrinkage to qualify for partial response and insufficient increase to qualify for progressive disease.) Tumor responses were evaluated every two cycles by three-dimensional computed tomography and were determined by an independent response review committee. All partial and complete responses were confirmed not <4 weeks after the criteria for response were first met. After completion of the study treatment, patients were followed up every 3 months until disease progression or death.

**statistical analysis**
The primary aim of this phase II study was to assess the ORR, and the secondary end points were safety profile, time to progression (TTP), overall survival time, and duration of response. Simon’s MinMax two-stage design [12] was used to calculate the sample size. The first stage required at least 7 of 19 patients to have a confirmed response, assuming \( P_1 = 0.40, P_0 = 0.20, \alpha = 0.05, \) and \( \beta = 0.20, \) before proceeding to the second stage. In the second stage, 20 additional patients were to be entered to achieve a target sample size of 43 assessable patients. Assuming a dropout rate of 10%, 48 patients were initially enrolled for the study. The duration of response, TTP, and survival time was estimated using the Kaplan–Meier method. TTP was defined as the time from the initiation of treatment to the first documentation of disease progression by the investigators or death from any cause.

**results**

**patient characteristics**
From October 2005 to February 2008, 48 patients were enrolled in this study. All patients were assessed for safety and survival. Response was evaluated in all patients, except one patient who died due to the rupture of an underlying aortic aneurysm after the second cycle but before the evaluation and one patient who...
had only nonmeasurable lesions and peritoneal seeding with malignant ascites. Patient characteristics are listed in Table 1. There were 25 men, and the median age was 56 years (range 24–70). Twenty-three (48%) had colon cancer, seven (15%) had rectosigmoid colon cancer, and 18 (38%) had rectal cancer. Thirty-one patients (65%) were diagnosed with metastatic disease. Seventeen patients (35%) had recurrent colorectal cancer that relapsed after surgery, with adjuvant chemotherapy or chemoradiotherapy. Moderately differentiated cancers (58%) were most commonly observed, and the most common metastatic sites were distant lymph nodes (56%), liver (56%), and lung (31%). The median number of metastatic organs was two (range 1–6).

efficacy
In total, 413 treatment cycles were administered to 48 patients, with a median of six cycles (range 2–24) per patient.

Tumor response data are listed in Table 2. There were three complete responses, 23 partial responses, 17 cases of stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions), and three cases of progression. The confirmed ORR in the intention-to-treat (ITT) population was 54% [95% confidence interval (CI) 40% to 68%], and the disease control rate was 90% (95% CI 82% to 98%). The median time to response was 1.5 months (95% CI 1.3–1.7), and the median duration of response was 9.3 months (95% CI 6.5–12.1).

The median duration of follow-up was 21.2 months (95% CI 17.9–23.6). The median TTP in the ITT population was 8.5 months (95% CI 6.2–10.9; Figure 1). The median survival time was 27.2 months (95% CI 20.3–34.0), and the 2-year survival rate in the ITT group was 53% (Figure 2).

safety
Safety was assessed in 48 patients based on a total of 413 cycles. The adverse events are listed in Table 3. Thrombocytopenia, which developed in 13% of the patients, was the most common grade 3/4 adverse event. There was no case of symptomatic thrombocytopenia. Neutropenia, observed in 10% of the patients, was the second most common grade 3/4 toxicity, and febrile neutropenia developed in one patient. Anemia, observed in 6% of the patients, was the third most common grade 3/4 toxicity. Non-hematologic toxic effects were usually mild (mostly grade 1/2) and manageable. The most common non-hematologic toxic effects were anorexia, neuropathy, nausea, asthenia, and hyperbilirubinemia.

The median relative dose intensities (ratio of dose received to dose planned) of oxaliplatin and S-1 for all cycles administered were 0.82 (range 0.46–1.00) and 0.82 (range 0.52–1.00), respectively. The mean relative dose intensities of oxaliplatin and S-1 for all cycles administered were 0.79 and 0.83, respectively. The mean relative dose intensities of both drugs in each cycle during one to nine treatment cycles are shown in Figure 3. The dose reductions and delays during one to nine treatment cycles (total, 311 cycles in 48 patients) were as follows. Oxaliplatin was reduced in 37 cycles (12%), primarily

<table>
<thead>
<tr>
<th>Table 2. Analysis of response in the intention-to-treat population (independent response review committee assessed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td>Overall response</td>
</tr>
<tr>
<td>Complete</td>
</tr>
<tr>
<td>Partial</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Disease control</td>
</tr>
<tr>
<td>Progression</td>
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<tr>
<td>Not evaluable</td>
</tr>
<tr>
<td>Median time to response (months)</td>
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<tr>
<td>Median duration of response (months)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Figure 1. Kaplan–Meier estimates of time to progression.

Figure 2. Kaplan–Meier estimates of overall survival time.
because of thrombocytopenia (18 cycles), neutropenia (10 cycles), and thrombocytopenia with neutropenia (nine cycles). S-1 was reduced in 28 cycles (9%), primarily because of thrombocytopenia (14 cycles), neutropenia (eight cycles), and thrombocytopenia with neutropenia (six cycles). Eighty-six cycles (28%) were delayed owing to thrombocytopenia (39 cycles), neutropenia (34 cycles), thrombocytopenia with neutropenia (10 cycles), and other reasons (three cycles).

### discussion

The primary outcome of the study was the ORR, and the secondary outcomes were safety, TTP, overall survival time, and duration of response. This study demonstrated an ORR of 54%, a median TTP of 8.5 months, and a median survival time of 16.2–20.8 months obtained with infused FU/FA and oxaliplatin (FOLFOX or FUFOX) as first-line chemotherapy for metastatic colorectal cancer in phase III studies [1, 2, 6, 7, 13–15]. Capecitabine plus oxaliplatin (XELOX or CAPOX) is another regimen commonly used in treating colorectal cancer. When oxaliplatin 130 mg/m² (day 1) or 70 mg/m² (days 1, 8) was administered i.v. and capecitabine 1000 mg/m² was administered orally, twice daily on days 1–14, every 3 weeks, the ORR, median TTP, and median overall survival with the XELOX or CAPOX regimen were 37%–55%, 6.0–8.9, and 16.8–19.8 months, respectively [5–7, 14, 16–18]. Those efficacy data for oxaliplatin combined with infused 5-FU/FA or capecitabine are similar to the data for oxaliplatin combined with S-1 in the present study.

The median age of the subjects was 56 years, which was relatively younger than in other studies, which typically had median ages between 58 and 67 years [1–3, 5–10, 13–18]. The inclusion criterion for the age of the patients was 18–70 years old, while the criterion used in many other studies was age 18–75 years old or <18 years old. This might explain the relatively young median age of 56 (range 24–70) years in our study.

The treatment was generally well tolerated by most patients. The most common and second most common grade 3/4 adverse events were thrombocytopenia (13% of all patients) and neutropenia (10%), respectively. There was no symptomatic thrombocytopenia, and only one patient experienced febrile neutropenia. Although peripheral neuropathy was commonly observed (75%), most cases were grade 1. Hand–foot syndrome was rarely observed in this study. The toxicity profile observed in the present study is different from those of the FOLFOX/FUFOX and XELOX/CAPOX regimens. Diarrhea, neutropenia, and neuropathy are major toxic effects of FOLFOX/FUFOX regimens, and diarrhea, hand–foot syndrome, and neuropathy occur most commonly with XELOX/CAPOX regimens [6, 7, 14]. There were few observed grade 3/4 non-hematologic toxic effects, with just one

### Table 3. Observed adverse events according to number of patients and number of cycles

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of patients (n = 48)</th>
<th>Number of cycles (n = 413)</th>
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<tbody>
<tr>
<td></td>
<td>NCI-CTC grade, version 3</td>
<td>NCI-CTC grade, version 3</td>
</tr>
<tr>
<td></td>
<td>1   2  3  4  3/4, %</td>
<td>1   2  3  4  3/4, %</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15  16  0  0  0</td>
<td>77  35  0  0  0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4   25  5  0  10</td>
<td>120 28  7  0  2</td>
</tr>
<tr>
<td>Anemia</td>
<td>31  15  3  0  6</td>
<td>287 63  3  0  1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10  12  5  1  13</td>
<td>101 57  5  1  2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>37  4   0  0  0</td>
<td>154 4   0  0  2</td>
</tr>
<tr>
<td>Nausea</td>
<td>30  5   0  0  0</td>
<td>112 7   0  0  0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11  5   0  0  0</td>
<td>41   7   0  0  0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8    2   0  0  0</td>
<td>16   3   0  0  0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13   1   0  0  0</td>
<td>19   2   0  0  0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8    1   0  0  0</td>
<td>19   4   0  0  0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6    0   0  0  0</td>
<td>9    0   0  0  0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>33   3   0  0  0</td>
<td>210  4   0  0  0</td>
</tr>
<tr>
<td>Abnormal AST/ALT</td>
<td>29   0   0  0  0</td>
<td>102  2   0  0  0</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>16   6   1  0  2</td>
<td>60   30  1  0  &lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>24   3   0  0  0</td>
<td>105  4   0  0  0</td>
</tr>
</tbody>
</table>

NCI-CTC, National Cancer Institute—Common Toxicity Criteria; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
grade 3 hyperbilirubinemia. Possible explanations for the reduced occurrence of severe non-hematologic toxic effects compared with other studies using the XELOX regimen include the younger patient population, greater dose reduction or delay, or real reduced toxicity of the OS regimen. In contrast, the median age was between 58 and 67 years in many other studies, while the median age in our study was 56 years due to the lower upper limit for patient inclusion. Perhaps, younger patients can better tolerate the treatment. In addition, treatment was interrupted in cases of grade 2 or higher toxicity. The dose of oxaliplatin was reduced by 25% or the dose of S-1 was reduced by 20 mg/day for a second occurrence of a given grade 2 toxicity. For a third occurrence of a given grade 2 toxicity, the oxaliplatin dose was reduced by 50% or that of S-1 by 40 mg/day. Treatment was discontinued if, despite dose reduction, a given grade 2 toxicity occurred for a fourth time. These dose modifications might have reduced the chance of developing more severe (grade 3/4) toxic effects in subsequent cycles following grade 2 toxic effects. Large comparative studies are needed to confirm the more favorable toxicity profiles of the OS regimen.

As expected, the administration of the OS regimen was convenient for the patients. Unlike the inconvenient, 2-day, continuous infusion of 5-FU in the FOLFOX regimen, the OS regimen requires only a 2-h infusion of oxaliplatin and oral administration of S-1 every 3 weeks. Thus, the OS regimen was as convenient as the XELOX regimen and required fewer clinic visits than the FOLFOX regimen [19].

In conclusion, the OS regimen can be an effective, well-tolerated, and convenient therapeutic strategy in patients with metastatic colorectal cancer. A comparative clinical trial with the XELOX regimen in advanced colorectal cancer is ongoing at our institute.

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references