Combination Chemotherapy of Oxaliplatin and Capecitabine in Patients with Metastatic Colorectal Cancer: a Pilot Study

Myung-Ju Ahn, M.D., Ho-Suck Oh, M.D., Jung-Hye Choi, M.D., Young-Yeul Lee, M.D., In-Soon Kim, M.D., Il-Young Choi, M.D., Oh Young Lee, M.D. and Heung-Woo Lee, M.D.

Departments of Internal Medicine and General Surgery, College of Medicine, Hanyang University, Seoul, Korea

Purpose: To evaluate the efficacy and toxicity of oxaliplatin and capecitabine in patients with metastatic colorectal cancer.

Materials and Methods: Between December 2001 and April 2003, fourteen patients were enrolled in this study. Oxaliplatin, 80 mg/m$^2$, was administered intravenously on day 1, and capecitabine, 1,250 mg/m$^2$ bid po (total daily dose 2,500 mg/m$^2$), was given on days 1–14 of 3 week cycles.

Results: The median age of the patients was 57 years (range: 41–74), and the most common sites of metastasis were liver, lung or lymph node. Of the 12 evaluable patients, the overall response rate was 41.7%, but with no complete response. The median response duration and median progression free survival of 12 patients were 42 and 24.4 weeks, respectively. The median overall survival was not reached. A median 6 (range: 1–9), and a total 80, cycles were administered to 14 patients. 80 cycles were evaluable for toxicity. The most common hematological toxicities were NCI grades I/II anemia (45%), leucopenia (33.75%) and thrombocytopenia (17.5%). The most common non-hematological toxicities were nausea/vomiting (28.75%) and neurotoxicity (8.75%). Hand and foot syndrome was noted in only 3.75%. There was no life-threatening toxicity.

Conclusion: Oxaliplatin and oral capecitabine combination chemotherapy showed significant activity and favorable toxicity in patients with metastatic colorectal cancer. Further studies, with larger numbers of patients and long-term follow-up will be needed. (Cancer Research and Treatment 2003;35:407-410)

Key Words: Colorectal neoplasm, Chemotherapy, Oxaliplatin, Capecitabine

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed malignancy, accounting for 10 to 15% of all newly diagnosed cancer cases in Europe and the United States (1). Approximately half of these patients develop a metastatic disease. The prognosis for these patients is poor, although palliative chemotherapy has been shown to prolong survival and improve the quality of life compared to those with just the best supportive care (2).

Capecitabine (Xeloda<sup>®</sup>), an oral fluoropyrimidine carbamate, was rationally designed to predominantly generate 5-FU within tumor cells (3). After rapid and extensive absorption as an intact molecule, capecitabine is converted to 5-FU, predominantly in tumor tissue, by exploiting the high activity of thymidine phosphorylase in malignant tissue (4). In a randomized phase II study, an intermittent regimen (twice daily treatment at 1,255 mg/m$^2$ for 14 days, followed by a 7 day rest period) produced a confirmed tumor response in 24% of patients, and a median time to disease progression of 7.7 months (5). In two recently published randomized trials, a superior therapeutic index was reported for capecitabine compared with a bolus of 5-FU/LV (6).

Oxaliplatin, a new cytotoxic agent form the diaminocyclohexane platinum family, has a mechanism of action similar to that of other platinum derivatives, but its spectrum of antitumor activity against tumor models differs from those of cisplatin and carboplatin (7). Its activity as a single agent in metastatic colorectal cancer patients was demonstrated in phase II trials, with response rates ranging between 10 and 24% (8–10). In a phase III trial, oxaliplatin plus 5-fluorouracil and leucovorin had significantly longer progression-free survival (median 9.0 months) and a better response rate (50.7%) (11).

Oral capecitabine can replace intravenous 5-FU/LV, with advantages in convenience, efficacy and patient preference. Since adding oxaliplatin to the infused 5-FU/LV improves its efficacy, substituting capecitabine for 5-FU/LV, in combination with oxaliplatin, should give an effective and convenient treatment (12,13). Based on this hypothesis, in this study, a phase II study was designed to evaluate the efficacy and safety
of capecitabine and oxaliplatin in advanced or metastatic colorectal cancer.

MATERIALS AND METHODS

1) Eligibility and patient evaluation

Histologically, or cytologically, proven advanced, or metastatic, colorectal cancers were included. Other eligible criteria included: measurability of tumor lesions, age >18 years, ECOG performance 0–2, adequate organ function and a life expectancy of at least 3 months. Patients had received no prior chemotherapy for advanced disease or had completed adjuvant chemotherapy >6 months before study entry. Radiotherapy was permitted for palliation, but not when associated with a present measurable lesion. All patients were gave their written informed consent before enrollment.

2) Treatment schedule

Oxaliplatin, 80 mg/m², was administered in 500 ml of 5% dextrose as a 2-hour infusion on Day 1, which was repeated every 3 weeks. Capecitabine was given orally, at a dose of 1,250 mg/m² bid, as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by a 1-week rest period). For practical reasons, the capecitabine doses were rounded to the nearest dose that could be administered with 500 and 150 mg tablets. Capecitabine doses were given orally, approximately 12 hours apart, with water within 30 minutes of food ingestion, with the simultaneous intake of antacids to avoid potential interference with the absorption of the capecitabine. Treatment was continued until disease progression, unacceptable adverse effects or withdrawal of the patient’s consent.

3) Dose modification

Treatment was delayed after a maximum of 14 days. If there was a second episode of grade 2 toxicity, or any grade 3 toxicity, the treatment was reduced by 20%. If there was a third occurrence of grade 2 toxicity, second episode of grade 3 toxicity or any grade 4 toxicity, a 40% reduction was required. A fourth episode of grade 2 toxicity, third episode of grade 3 toxicity or a second episode of grade 4 toxicity, despite dose reduction, the treatment was discontinuation. In case of myelosuppression, treatment was postponed or adjusted according to the following instructions: in case of a WBC of <4,000/mm³ or platelets <100,000/mm³ at the start of a cycle, treatment was postponed for 1 week.

4) Response criteria and toxicity

The pretreatment evaluation included a complete medical history and physical examination, a complete blood count, chemistry profile and carcinoembryonic antigen (CEA) measurement, a chest X-ray and radiological tumor parameter assessment. Patients were assessed for their clinical response after 2 cycles of chemotherapy. The tumor response classification was derived from standard World Health Organization criteria. Toxicities were assessed according to the National Cancer Institute of Canada Clinical Trials Group expanded common toxicity grading. Hand-foot syndrome (palmar-planter erythrodysesthesia) was classified as grades 1 (numbness, dysesthesia, painless swelling, erythema not disrupting normal activities), 2 (painful swelling, disrupting daily activities) or 3 (moist desquamation, ulceration, blistering, severe pain, inability to work or perform activities of daily living).

RESULTS

1) Patients and treatment

From December 2001 until April 2003, a total of 14 patients were enrolled in this study. Table 1 lists the demographic data and baseline characteristics for all patients. The median age of the patients was 57 years (range: 41–74). The primary sites of disease were for the colon and rectum in 5 and 9 patients, respectively. Four patients had received adjuvant chemotherapy, with 5-FU/LV, and two adjuvant radiotherapy, for rectal cancer. The most common site of metastasis was the liver, followed by lung, lymph node and ovary. Seven patients had one metastatic site, and 3 had 3 or more involved organs. Two patients were excluded from an evaluation; one patient received chemotherapy without a measurable disease due to the resection of a metastatic lesion, and the other refused chemotherapy after one cycle of treatment.

2) Toxicity

A total of 80 cycles were evaluable for toxicity, and the incidence of toxicity are summarized in Table 2. The most common hematological toxicities were NCI grade I/II anemia (45%), leukopenia (33.75%) and thrombocytopenia (17.5%). The most common non-hematological toxicities were nausea/
Table 2. Toxocities

<table>
<thead>
<tr>
<th>No of cycles (n=80)</th>
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<tr>
<td>Grade I (%)</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Leukopenia</td>
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<td>Thrombocytopenia</td>
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<td>Gastrointestinal</td>
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<td>Nausea</td>
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<td>Diarrhea</td>
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<td>Hepatotoxicity</td>
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<td>Neurotoxicity</td>
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<td>Hand &amp; foot syndrome</td>
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CR+PR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

Table 3. Treatment efficacy

<table>
<thead>
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<th>No of patients (n=12) (%)</th>
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<tr>
<td>CR+PR</td>
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<tr>
<td>SD</td>
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<tr>
<td>PD</td>
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<td>Progression free survival</td>
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<td>Response duration</td>
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DISCUSSION

In this study, the combined capecitabine/oxaliplatin regimen in advanced colorectal cancer was shown to be highly effective and safe. The 41.7% response rate in the non-pretreated patients compared well with the 50.7 to 53% objective responses observed with oxaliplatin plus infusional fluorouracil and leucovorin (5-FU/LV) in first-line treatment. 41.7% of the patients were also observed to achieve stabilization, and only two showed a progression. Mature results from a recent multinational phase II trial of capecitabine plus oxaliplatin showed a 55% of response rate, 31% of stabilization, with a 19.5 month of overall survival, suggesting that capecitabine plus oxaliplatin to be a highly active first-line therapy for patients with metastatic colorectal cancer (14). The response rate in our study was inferior to other study (14), which might be attributable to the lower dose of oxaliplatin (80 mg/m² versus 130 mg/m³) administered in this study. The treatment dose and schedule for each capecitabine and oxaliplatin regimen still remains to be established. The combination regimen of oxaliplatin, 130 mg/m³/day, plus capecitabine, 2,000 mg/m³/day, every 3 weeks, is the commonly used regimen (12). Other study (15) reported that a dose-intensified, bimonthly regimen (capecitabine 3,500 mg/m³/day, on days 1 ~ 7, plus oxaliplatin 85 mg/m² on day 1, every 2 weeks) had superior therapeutic activity than conventional regimens, as described above. Further randomized study will be required to confirm the optimal dose and schedule of capecitabine and oxaliplatin in the treatment of metastatic colorectal cancer.

The capecitabine/oxaliplatin combination toxicity profiles were not serious. The most common hematological toxicities were NCI grade I/II anemia (45%), leukopenia (33.75%) and thrombocytopenia (17.5%). The most common non-hematological toxicities were nausea/vomiting (28.75/5%) and neurotoxicity (8.75%). Hand and foot syndrome was noted in only 3.75%, and limited to low-grade intensity. There was no life-threatening toxicity.

3) Efficacy

The results of the response evaluation, assessed by independent radiology reviews, are summarized in Table 3. A median of 6 (range: 1 ~ 9), and a total 80, cycles were administered to 14 patients. Of the 12 evaluable patients, 5 achieved a partial response, but no complete response was noted. The overall response rate was 41.7%. The median response duration of the five responders was 42 weeks (range: 14 ~ 54). The median progression free survival of all 12 patients was 24.4 weeks (range: 8.9 ~ 70.4)(Fig. 1). The median follow-up for the surviving patients was 48 weeks, but the median overall survival was not reached (range: 29.0 ~ 70.4+ weeks).
pathic pain were noted 16, 9 and 6%, respectively. In our study, neurological toxicity from oxaliplatin was noted in only 8.75%, and was limited to grades 1/2. This discrepant result of this study might be explained by the low dose of oxaliplatin administered. The overall treatment tolerance seems acceptable and comparable with other clinically well established 5-FU/LV plus oxaliplatin combination regimens.

Since most of the patients were able to be administered with outpatient-based treatment, as it requires only one clinic visit for oxaliplatin administration, capecitabine plus oxaliplatin offers substantially improved convenience, with less disruptive effects on patients’ lives, than regimens incorporating infused 5-FU/LV. We also noted that the incidence of hand and foot syndrome or diarrhea was very low in this study; no dose modification of capecitabine was needed. Recent study performed an economic analysis of the potential medical cost savings of capecitabine and oxaliplatin combination, and projected medical cost savings over infusional 5-FU/LV (18).

CONCLUSION

Despite the small numbers of patients and short-term follow-up, the overall results of this study have demonstrated that the combination of an oral capecitabine and oxaliplatin regimen has substantial antitumor activity in patients with previously untreated advanced colorectal cancer. An ongoing phase III trial, with capecitabine plus oxaliplatin versus oxaliplatin plus 5-FU/LV regimens, in first- and second-line metastatic colorectal cancer, will provide more definitive results in terms of their effectiveness and convenience.

REFERENCES