Single-agent Capecitabine in Patients with Metastatic Colorectal Cancer Refractory to 5-Fluorouracil/Leucovorin Chemotherapy

Jae Jin Lee, Tae Min Kim, Su Jong Yu, Dong-Wan Kim, Yo-han Joh, Do-Youn Oh, Jung Hye Kwon, Tae You Kim, Dae Seog Heo, Yung-Jue Bang and Noe Kyeong Kim

Department of Internal Medicine, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

Received November 16, 2003; accepted April 20, 2004

Objective: The effectiveness of capecitabine, an oral fluoropyrimidine carbamate, is well documented in previously untreated metastatic colorectal cancer patients (overall response rate: 25%). However, its efficacy in patients with metastatic colorectal cancer refractory to 5-fluorouracil/leucovorin (5-FU/LV) has not been determined. This study was performed to evaluate the efficacy and to identify the side-effects of capecitabine in patients with metastatic colorectal cancer showing progression despite 5-FU/LV-based combination chemotherapy.

Methods: Fifty-one metastatic colorectal cancer patients who showed progressive disease in 5-FU/LV-containing regimens (median: two regimes) were treated with capecitabine 1250 mg/m² twice daily (days 1–14 repeated every 3 weeks).

Results: Only one partial response was observed (response rate: 2%). Twenty-seven patients (53%) showed stable disease after two cycles. The median time to disease progression of either a partial response or stable disease was 3.4 months. Hand–foot syndrome was the main toxicity of capecitabine and occurred in 35% of cases (grade 3 or 4 in 6%). The median number of cycles administered was two and the relative dose intensity of capecitabine was 80%.

Conclusion: The response rate to capecitabine was low in metastatic colorectal cancers that were refractory to 5-FU/LV-containing chemotherapy. However, disease stabilization was seen in a significant number of patients.

Key words: capecitabine – metastatic colorectal – cancer – second-line chemotherapy

INTRODUCTION

5-Fluorouracil (5-FU) is the most widely used agent in the treatment of metastatic colorectal cancer and has a response rate of 20% (1). The optimal dose schedule for 5-FU administration is controversial, but continuous infusion shows lower toxicity and a higher response rate than bolus injection (2–5). Therefore, 5-FU/leucovorin (LV) has become a standard regimen for advanced colon cancer (6–9), not only by intravenous infusion but also using oral fluoropyrimidine derivatives that allow sustained exposure of 5-FU to target cells (10). Capecitabine, an oral fluoropyrimidine carbamate, is converted to 5-FU selectively in tumors through a cascade of three enzymes. Specifically, after its rapid and extensive absorption as an intact molecule through the intestinal mucosa, it is finally converted to 5-FU by thymidine phosphorylase in tumor tissue (11,12). Capecitabine was compared with parenteral 5-FU/LV as a first-line treatment in metastatic colorectal cancer in two randomized phase III studies and achieved at least the efficacy of intravenous 5-FU/LV. The overall response rate was 18–24%, the median time to progression was 4.3–5.2 months and the median overall survival time was 12.5–13.2 months (13,14). Capecitabine, when used as second-line chemotherapy in a phase II study performed by Hoff et al., showed noticeable disease stabilization, but no clinical response (15).

The effect of capecitabine in metastatic colorectal cancer refractory to 5-FU/LV is not well known. Hence the objective of this study was to evaluate the efficacy and safety of capecitabine in metastatic colorectal cancer patients showing progression on 5-FU/LV-containing chemotherapy.

SUBJECTS AND METHODS

PATIENTS

Histological confirmation of colorectal adenocarcinoma was required, as was the presence of at least one two-dimensionally...
measurable lesion. Patients with metastatic colorectal cancer who had received prior 5-FU/LV-containing chemotherapy were eligible for this study. All patients were of disease progressive status and treatment-free intervals of all patients were less than 3 months. Six patients had shown tumor progression following partial response at the last chemotherapy before capecitabine single therapy. Patients were required to have an ECOG performance status of ≤2, adequate organ function and a life expectancy of at least 3 months. Patients had received previous chemotherapy with at least one or more 5-FU/LV-based regimen. All patients agreed with and signed an informed consent form.

Patients were not eligible if they were pregnant or lactating; hypersensitive to 5-FU or had suffered a previously severe reaction to fluoropyrimidines, had a history of another cancer or were not yet fully recovered from recent major surgery. Patients were also ineligible if they showed CNS involvement, neurological or psychiatric disorders that could interfere with their compliance, significant cardiac disease or myocardial infarction within the previous 12 months, serious uncontrolled infections or malabsorption syndrome.

A total of 54 patients were enrolled for capecitabine treatment at the Seoul National University Hospital during the 24-month period from September 2000 to August 2002. This study was a retrospective study and medical records of all patients were reviewed retrospectively. The patients were followed up until death or, for those still alive, to their last visit prior to 31 October 2003. Of the 54 patients enrolled, 51 were evaluable but three were unable to be followed up after one cycle of capecitabine (Table 1). Table 2 shows the previously administered 5-FU/LV-containing chemotherapy.

Evaluation of the patients’ retreatment evaluation included a complete medical history taking and a physical examination, a complete blood count, chemistry profile, chest X-ray and computed tomography (CT). A complete blood count was obtained before the start of each treatment cycle, together with a serum chemistry profile, physical examination and toxicity assessment. Patients had a radiological tumor parameter assessment every two cycles or if there were clinical signs of tumor progression. The tumor response evaluation was based on the standard World Health Organization criteria (16). Toxicities were assessed according to the National Cancer Institute of Canada Clinical Trials Group expanded toxicity grading (17). Hand–foot syndrome (palmar–plantar erythrodysesthesia) was classified as grade 1 (numbness, dysesthesia, painless swelling, erythema not disrupting normal activities), grade 2 (painful swelling, disrupting daily activities) or grade 3 (moist desquamation, ulceration, blistering, severe pain, inability to work or perform the activities of daily living).

**TREATMENT**

Capecitabine was administered orally at a dose of 1250 mg/m² twice daily as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by 1 week of rest). Capecitabine was given at approximately 12 h intervals orally with water within 30 min of ingesting food. Pyridoxine was administered orally at a dose of 100 mg twice daily to prevent hand–foot syndrome. Treatment was continued until disease progression, unacceptable adverse effects or the withdrawal of patient consent.

**TREATMENT MODIFICATION**

Treatment with capecitabine was interrupted in cases of grade 2 or worse toxicity and was not resumed until the toxicity had resolved or improved to grade 1. When treatment was resumed, capecitabine doses were reduced as follows: (1) by 25% for patients who experienced a second occurrence of a given grade 2 toxicity or any occurrence of grade 3 toxicity or (2) by 50% for patients who experienced a third occurrence of grade 2

---

**Table 1. Patients’ demographics and disease characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>31:20</td>
<td>54.4:45.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (32–73)</td>
<td>76.4</td>
</tr>
<tr>
<td>ECOG performance</td>
<td>0–1</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>31</td>
<td>60.7</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>20</td>
<td>39.3</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td>No.</td>
<td>22/17/9/2/1</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Bone</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 2. Prior chemotherapy at baseline**

<table>
<thead>
<tr>
<th>Prior chemotherapy</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2/3/4</td>
<td>15/11/18/7</td>
<td>76.4</td>
</tr>
<tr>
<td>Regimen</td>
<td>2 (1–4)</td>
<td>82.4</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>28</td>
<td>45.1</td>
</tr>
<tr>
<td>Oxaliplatin/5-FU/LV</td>
<td>42</td>
<td>31.3</td>
</tr>
<tr>
<td>Irinotecan/5-FU/LV</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>UFT-E/LV</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Response to chemotherapy</td>
<td>30</td>
<td>59.0</td>
</tr>
<tr>
<td>Response at any time</td>
<td>21</td>
<td>41.0</td>
</tr>
<tr>
<td>Progression after response*</td>
<td>6</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*At the last chemotherapy before capecitabine.
toxicity or a second occurrence of grade 3 toxicity or any occurrence of grade 4 toxicity. Treatment was discontinued if toxicity occurred, despite dose reduction, for a fourth time at grade 2, a third time at grade 3 or a second time at grade 4. Relative dose intensities were calculated. When patients were enrolled, we reduced the dose of capecitabine by 25% in case of ECOG performance status grade 2, neutropenia.

**STATISTICAL ANALYSIS**

Time to disease progression was calculated from the start date of capecitabine to the first recorded observation of progressive disease or death from any cause. Overall survival was calculated from the start date of capecitabine to the date of death from any cause. Survival was calculated by intent-to-treat. Time to progression and overall survival were analyzed according to Kaplan–Meier estimates.

Among adverse reactions, hematological side-effects were summarized as incidence rates and non-hematological side-effects were summarized as numbers of patients.

**RESULTS**

**PATIENTS AND TREATMENT**

The total number of cycles of capecitabine received by the 51 patients was 159 and the median cycle number was two (range, 1–14). For patients treated with capecitabine, the median relative dose intensity was 80%. Patients adhered reasonably well to the planned dosage regimen. The most frequent reasons for treatment discontinuation were disease progression (47 patients, 92%), adverse reaction (four patients, 8%). Adverse reactions encountered were hand–foot syndrome (two cases), infection (one case) and vomiting (one case).

The overall response rate was 2%, with no complete response, 2% (1/51) partial response, 53% (27/51) stable disease and 45% (23/51) progressive disease. Disease stabilization was seen in a significant number of patients (53%).

The median time to disease progression was 102 days (3.4 months) in patients with either a partial response or stable disease (Fig. 1A). Overall, the median time to disease progression was 61 days (2.0 months) (Fig. 1B) and overall survival for all patients was 267 days (8.9 months).

**TOXICITY PROFILE**

Table 3 lists the incidences of hematological and non-hematological toxicities to capecitabine. Grade 3 or 4 hematological toxicities were reported in 1% of patients. The most common non-hematological toxicity of capecitabine was hand–foot syndrome (35%). Grade 3 or 4 adverse non-hematological toxicities were observed for hand–foot syndrome (6%), stomatitis (4%), nausea and vomiting (2%) and diarrhea (2%). The most frequent adverse reactions leading to discontinuation were hand–foot syndrome, nausea and vomiting and infection. No treatment-related adverse reactions were fatal.

**DISCUSSION**

In terms of first-line chemotherapy, fluorouracil and folinic acid are better than supportive care for improved survival and higher quality of life (18). When the tumor progresses after first-line treatment with fluorouracil, survival is short and associated with a poor quality of life (19). Several clinical trials for second-line chemotherapy in metastatic colorectal cancer have been reported. In a phase III study of irinotecan versus best supportive care in patients with metastatic colorectal cancer who failed 5-FU therapy, overall survival was significantly improved in those patients receiving the irinotecan treatment (1 year survival, 36% vs 14%: irinotecan vs supportive care), thus demonstrating a survival advantage and clinical benefit from second-line chemotherapy in patients with metastatic colorectal cancer no longer responding to fluorouracil (20).

Oral agents allow home-based treatment and offer economic benefits through reduced nursing activities. The need for new agents with improved efficacy, tolerability and ease of admin-
irinotecan in terms of survival without pain, performance status and weight (26). In a multi-center, prospective study of 107 patients with metastatic colorectal cancer who had failed treatment with intravenous 5-FU bolus showed no objective responses but reported disease stabilization (32%) in a significant number of patients (15). A phase I/II study of capecitabine in advanced colorectal cancer patients known not to derive survival benefits from combination therapy with 5-FU and irinotecan is ongoing (23).

A few studies have evaluated the effect of capecitabine in metastatic colorectal cancer refractory to 5-FU/LV. Our study found that capecitabine achieved a 2% partial response and 53% disease stabilization in previously treated metastatic colorectal cancer patients and that the median time to progression in partial response and stable disease was 3.4 months.

The toxicity of capecitabine as a first-line therapy was significantly lower, but hand-foot syndrome was found to be significantly more common with capecitabine (13,14,24). The present study shows an incidence of hand-foot syndrome of 35.3% and a grade 3 incidence of 5.9%. The incidences of grade 3 neutropenia, stomatitis, nausea and diarrhea were less than 5%.

A few studies have evaluated the quality of life of patients who have stabilized after palliative first-line chemotherapy for metastatic colorectal cancer. In a multi-center phase II study, 107 patients with colorectal cancer resistant to 5-FU were treated with irinotecan. The response rate was 13.7% and the rate of disease stabilization was 44.2%. The health status of the patients had improved in many respects, weight stabilization or gain was observed in 81% of patients and pain relief in 54% (25). Another phase III trial compared irinotecan with best supportive care in patients with metastatic colorectal cancer. Statistically significant differences were found in favor of irinotecan in terms of survival without pain, performance status and weight (26). In a multi-center, prospective study in 80 metastatic colorectal cancer patients who were receiving second-line chemotherapy, the results showed that, in comparison with responders, patients who stabilize on treatment have a very similar profile, in terms of health-related quality of life, the length of hospital admissions and corresponding costs. Therefore, it is reasonable to include stabilization as a clinically and economically beneficial result in the second-line treatment of metastatic colorectal cancer (27). In the present study, disease stabilization with capecitabine in 53% of patients for 3.4 months demonstrated the value of the disease stabilization. Also, the performance status of patients who stabilized on capecitabine single therapy tended to improve in ~50% of patients.

The low response rate of capecitabine may be because heavily treated patients with refractory disease were enrolled and a monotherapy regimen was adopted. These limitations may be addressed by combining capecitabine with oxaliplatin or irinotecan. In the future, further study is required to improve the lower response rate of combination chemotherapy with capecitabine.

Based on the results of the present study, we conclude that capecitabine monotherapy in previously treated metastatic colorectal cancer patients showed a low response rate, but a high level of disease stabilization and favorable toxicity profiles.

References


Table 3. Treatment-related adverse reactions of capecitabine

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>No. (%)</th>
<th>≥Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (11.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (11.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (3.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Non-hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>18 (35.3)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>10 (19.6)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9 (17.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (15.7)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Infection</td>
<td>4 (7.8)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>


