A Pilot Phase II Study of Capecitabine in Advanced or Recurrent Colorectal Cancer

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Background: A pilot phase II study was conducted to evaluate the Japanese intermittent regimen of capecitabine in patients with advanced/recurrent colorectal cancer.

Methods: Twenty-two patients received oral capecitabine in a dose of 828 mg/m² twice daily for 3 weeks every 4 weeks.

Results: In the 20 patients evaluable for efficacy, the overall response rate was 25.0% (95% CI, 8.7–49.1%), rising to 33.0% in the subset of patients previously untreated for metastatic disease (n = 9). A further nine patients had stable disease. The median duration of response was 7.0 months. Five patients (22.7%) experienced grade 3/4 treatment-related adverse events, the most common being a bullous rash observed in two patients (9.1%).

Conclusions: The 3 weeks out of 4 intermittent regimen of capecitabine demonstrated good antitumor activity and tolerability in patients with advanced/refractory colorectal cancer, providing a clear rationale for conducting a larger phase II study in patients with advanced disease.

Key words: capecitabine (Xeloda®) – colorectal cancer – phase II study

INTRODUCTION

5-Fluorouracil (5-FU), discovered by Heidelberger et al. in 1957 (1), is widely used for the treatment of gastrointestinal and breast cancers in Japan. However, the elimination half-life of 5-FU is short (2), and its efficacy varies according to dose and regimen. Continuous infusional regimens and bi modulation with leucovorin (LV) have been previously attempted to improve the antitumor efficacy of 5-FU (3–6). While both these approaches have led to superior response rates, survival benefits have been modest, and several studies and meta-analyses have failed to identify any clinically significant advantage (7,8). Compounding these issues is the fact that regimens based on continuous infusions of 5-FU impose significant inconvenience, higher costs and complications associated with indwelling central venous access lines and pumps. Consequently, patients receiving therapy for late-stage disease prefer oral rather than I.V. chemotherapy but are unwilling to accept a lower response rate or a shorter duration of response to their preferred choice of oral chemotherapy (9–11).

Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate that delivers 5-FU predominantly to tumor cells. The drug is rapidly and extensively absorbed through the gut as an intact molecule and is then metabolized to 5-FU in three steps (12–14). Firstly, it is converted to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxylesterase (primarily in the liver). Secondly, it is converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase (in tumor cells and in the liver). Finally, it is converted to 5-FU by thymidine phosphorylase (TP), which is significantly more active in the tumor tissue than in the adjacent healthy tissue (15). The increasing specificity for tumor cells that occurs with each successive conversion step potentially reduces the systemic 5-FU exposure while increasing the 5-FU dose within the tumor tissue. Preclinical studies have shown that capecitabine has superior antitumor efficacy compared with other 5-FU derivatives, including 5′-DFUR (16).

Based on the above preclinical data, a number of clinical studies on breast cancer were initiated in 1994. Since then, capecitabine has been approved in over 80 countries worldwide (including Japan, USA and the EU) as a monotherapy for the treatment of advanced or metastatic breast cancer patients who have failed previous anthracycline and taxane chemotherapy. In addition, the combination of capecitabine and docetaxel has been approved for the treatment of patients with advanced or metastatic breast cancer after failure of cytotoxic chemo-

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therapy including anthracycline (or when further anthracycline therapy is not possible). Capecitabine is also approved for the first-line treatment of patients with metastatic colorectal cancer.

In Japan, a phase I study conducted between November 1994 and March 1996 indicated that the maximum tolerated dose (MTD) of capecitabine administered continuously in cancer patients was 1255 mg/m² twice daily (17). Because of the occurrence of skin disorders following continuous treatment, an intermittent treatment regimen of 828 mg/m² administered twice daily for 3 weeks followed by a 1-week rest period was recommended for phase II studies. This dose/schedule, which has been evaluated in a number of Japanese phase I/II trials in advanced breast, gastric and colorectal cancer, differs from the more dose-intensive internationally approved intermittent capecitabine regimen, where patients receive a higher dose of 1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period. However, it is important to note that the total dose of capecitabine given over six cycles of treatment is similar in both the Japanese and Western schedules (208 656 mg and 210 000 mg, respectively). The open-labeled, multicenter trial presented in this study was conducted to evaluate the efficacy and safety of the Japanese intermittent capecitabine regimen in patients with advanced/recurrent colorectal cancer.

SUBJECTS AND METHODS

STUDY DESIGN

An open-labeled trial was conducted to evaluate the efficacy and safety of capecitabine (828 mg/m² twice daily) administered according to the intermittent schedule of 3 weeks of treatment followed by a 1-week rest period per cycle. The trial was conducted in accordance with the Good Clinical Practice for Trials on Drugs (GCP), announced on October 2, 1989, by the Pharmaceutical Affairs Bureau (Notification No. 874). The institutional review board of each participating center approved the study, and all patients provided written informed consent before enrollment.

PATIENTS

Eligible patients had to have histologically confirmed colorectal cancer with measurable or assessable lesions according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th Edition) (18). Eligibility criteria also included an ECOG performance status (PS) of 0–2, an expected survival of ≥6 months and an age at enrollment between 20 and 74 years. Patients were required to have adequate renal, hepatic and hematological parameters (leukocytes 4000–12 000 cells/mm³; platelets ≥100 000 cells/mm³; hemoglobin concentration ≥9.0 g/dl; GOT [AST], GPT [ALT] and alkaline phosphatase ≤2.5 times the upper limit of normal [ULN] and total bilirubin and creatinine <1.5 × ULN). Patients had to have received no more than one prior chemotherapy regimen (excluding adjuvant chemotherapy completed ≥6 months before enrollment) and no radiotherapy for the lesions evaluated in the study. In addition, no patient was to have evidence of carry-over effects or toxicity associated with prior chemotherapeutic regimens (washout period of 4 weeks or more; 2 weeks or more for antimalabs and immunotherapy).

Patients with the following conditions were excluded from the study: a history of drug hypersensitivity; ascites or pleural effusions requiring treatment; clinically severe complications such as non-malignant liver, renal or lung disease or diabetes mellitus; electrocardiographic abnormalities; a possibility of pregnancy; peripheral neurologic signs and symptoms not associated with cancer; brain metastases; active peptic ulcer requiring treatment; ascites or pleural effusions as the only assessable lesions; evidence of HIV infection or a history of prior chemotherapy with an unapproved drug.

PLANNED SAMPLE SIZE

We adopted a two-step method with interim evaluation. An independent review committee was scheduled to perform an interim evaluation when the number of patients suitable for statistical analysis reached 20. The study was to be discontinued if four or more patients responded either completely or partially, and a late phase II study conducted in a larger population of patients. Alternatively, if less than four patients responded to treatment, a target number of 35 patients had to be enrolled to evaluate efficacy. The target number of patients was set at 35, and the interim evaluation planned with 20 patients was based on Fleming’s two-step method (19). The statistical power was 86%, meaning that with an expected response rate of 20%, the lower margin of efficacy and one-sided α-level were both 5%.

DOSAGE AND DOSE MODIFICATIONS

The dose of capecitabine was determined according to the patient’s body surface area based on the recommended phase I dose of 828 mg/m² twice daily (Table 1). Capecitabine was administered orally after breakfast and evening meals for 3 weeks followed by a 1-week rest period (no treatment), unless patients developed progressive disease (PD). Patients who did not develop PD during the first course of treatment could receive more courses of capecitabine. Other anti-cancer therapies such as immunotherapy, endocrine therapy and systemic steroid therapy, were prohibited during the course of the study.

In the event of patients developing drug-related grade 3 adverse events (excluding anorexia, nausea, vomiting, alopecia, malaise or skin reactions) or laboratory abnormalities (excluding grade 3/4 leukopenia, granulocytopenia and lymphopenia with a fever persisting for 3 days or less) or in patients in whom the investigator judged continuation of treatment unfeasible, treatment could be delayed for up to 4 weeks to allow patient recovery. If the investigator considered that continuation of treatment at the same dose would be intolerable due to adverse events, irrespective of grade, the administered dose could be reduced to approximately 75% of the initial dose. Treatment was permanently discontinued in patients who...
developed drug-related grade 4 adverse events or who could not tolerate treatment, even at a reduced dose.

**STUDY ASSESSMENT**

Demographic characteristics, the presence of symptoms, laboratory values, electrocardiograms and tumor characteristics were assessed before treatment. If available, tumor markers were recorded as an index of response to treatment. For evaluation of response, tumors were assessed by CT, MRI or X-ray every fourth week of each course of treatment. Laboratory examinations were performed every second and fourth week of each course, and electrocardiograms were taken after completion of treatment. Symptoms were followed throughout treatment, and patients were monitored for 4 weeks after completion of treatment. All empty drug boxes and tablets were collected at the end of the study to evaluate treatment compliance.

**EVALUATION OF RESPONSE AND SAFETY**

Complete response (CR), partial response (PR), no change (NC) and PD were defined by the investigator according to The General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th Edition) (18). These criteria differ slightly from the WHO criteria since five evaluations of response were employed: CR, PR, MR (minor response), NC and PD. However, in the present study, MR and NC were grouped together as NC so that the tumor response criteria could be compared with other studies using the WHO criteria. Responses were confirmed 4 weeks after the initial classification, and an independent response evaluation committee was responsible for evaluating and confirming tumor responses at the end of the study. Although time to disease progression (TTP) was not evaluated during the study, survival follow-up [ITT] population). All patients were included in the safety analysis, although two were excluded from the efficacy evaluation: one patient with simultaneous colorectal and gastric cancer did not meet the eligibility criteria; the other patient’s tumor was not adequately assessed at the beginning of the treatment. The baseline demographic characteristics of the ITT population are shown in Table 2. The median age was 60 years (range, 46–72 years). The majority, 13 patients (59.1%), had cancer of the rectum and the remaining nine patients (40.9%) had colon cancer. The lungs and the liver were the most common sites of metastases. All patients had undergone prior surgical resection, and 12 (54.5%) had received prior chemotherapy, including eight treated with adjuvant chemotherapy. All of these had received 5-FU derivatives and four had received 5-FU-based combination chemotherapy. None of the patients had received prior radiotherapy.

**TREATMENT DURATION**

The median duration of treatment was 3.9 months (range, 1.0–13.6 months and 1–12 courses). Although treatment was scheduled for two or more courses, one patient withdrew at the completion of the first course because of PD; a second patient withdrew during the second course because of adverse events (bowel obstruction, anorexia, nausea and vomiting). Two other patients also met the protocol criteria for withdrawal (grade 4 raised alkaline phosphatase and hyperglycemia). However, because the investigator considered that these were not true grade 4 events and had little or no clinical impact on the patient, both the patients continued on the study.

Of the 20 patients who received two or more courses of capecitabine, 16 (72.7%) were eventually withdrawn due to PD, two (9.1%) were transferred to a maintenance study, one (4.5%) was withdrawn because of adverse events and one (4.5%) went off therapy for other reasons. Patients with CR, PR or SD (stable disease) were eligible to receive capecitabine therapy, and patients were monitored for 4 weeks after completion of treatment. All empty drug boxes and tablets were collected at the end of the study to evaluate treatment compliance.

**STATISTICAL METHODS**

Patients with a CR or PR were considered responders, and the response rate was calculated. The 95% confidence interval (CI) of the response rate was calculated by the exact method, based on a binomial distribution of data. The duration of response and the number of days until the onset of response were expressed by the minimum value, median value and maximum value. Overall survival was defined as the number of days from study enrollment until death and was calculated by the Kaplan–Meier method. Time to disease progression (TTP) was not recorded during the study. Safety was evaluated in all patients who received capecitabine treatment. Adverse event frequencies were recorded.

**RESULTS**

**PATIENT CHARACTERISTICS**

Twenty-two patients were enrolled between August 1996 and December 1997 and received capecitabine (intent-to-treat [ITT] population). All patients were included in the safety analysis, although two were excluded from the efficacy evaluation: one patient with simultaneous colorectal and gastric cancer did not meet the eligibility criteria; the other patient’s tumor was not adequately assessed at the beginning of the treatment. The baseline demographic characteristics of the ITT population are shown in Table 2. The median age was 60 years (range, 46–72 years). The majority, 13 patients (59.1%), had cancer of the rectum and the remaining nine patients (40.9%) had colon cancer. The lungs and the liver were the most common sites of metastases. All patients had undergone prior surgical resection, and 12 (54.5%) had received prior chemotherapy, including eight treated with adjuvant chemotherapy. All of these had received 5-FU derivatives and four had received 5-FU-based combination chemotherapy. None of the patients had received prior radiotherapy.

<table>
<thead>
<tr>
<th>Body surface area (m²)</th>
<th>Recommended dose’ (mg, twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.1</td>
<td>800</td>
</tr>
<tr>
<td>1.1 to &lt;1.3</td>
<td>1000</td>
</tr>
<tr>
<td>1.3 to &lt;1.5</td>
<td>1150</td>
</tr>
<tr>
<td>1.5 to &lt;1.7</td>
<td>1300</td>
</tr>
<tr>
<td>≥1.7</td>
<td>1500</td>
</tr>
</tbody>
</table>

’Based on recommended dose of 828 mg/m² twice daily.
in a maintenance study designed to observe the safety of long-term capecitabine treatment. In the present study, compliance with capecitabine therapy (received dose versus planned dose in each patient) was measured at 84% or more during the study period, and there were no episodes of clinically relevant non-compliance.

Efficacy

The response to capecitabine in the 20 evaluable patients assessed by the response evaluation committee is shown in Table 3. Five patients had PR, although no CRs were reported. Of the remaining patients, nine had NC and six had PD. The overall response rate of 25.0% (95% CI, 8.7–49.1%) was superior to the expected response rate of 20.0% and was higher (33.3%) in the subset of patients previously untreated for metastatic disease ($n = 9$). Furthermore, a higher response rate (28.6%) was obtained in the subset of patients who were previously untreated ($n = 9$) or had completed adjuvant chemotherapy before enrollment ($n = 5$). Patients with lung metastases at baseline had a response rate of 28.6% (one CR and three PRs in 14 patients), while that of 11 patients with liver metastases was 27.3% (three PRs) (Table 3).

In the five patients with PR, the median time to onset of response was 0.9 months (range, 0.9–4.6 months) and the median duration of response was 7.0 months (range, 6.4–14.0 months). Median overall survival was 13.3 months (95% CI, 9.2–18.0 months) (Fig. 1).

Adverse Events

All adverse events, excluding those clearly unrelated to the study drug, were defined as treatment-related adverse events. Twenty patients (90.9%) experienced at least one adverse event during the study, the majority of which were not higher than grade 1. The most common adverse events (all grades) were as follows: hand–foot syndrome in seven patients (31.8%); increase in total bilirubin in six patients (27.3%); nausea, anorexia and decreased erythrocyte count in five patients each (22.7%); and vomiting, diarrhea, glycosuria, raised alkaline phosphatase, decreased hematocrit and thrombocytopenia in four patients each (18.2%, Table 4).

![Figure 1. Overall survival.](image-url)
Overall, five patients (22.7%) experienced grade 3/4 treatment-related adverse events (Table 4). The most common grade 3/4 drug-related adverse events were hand–foot syndrome (9.1%); bowel obstruction, increase in total bilirubin, lymphopenia and prolonged activated partial thromboplastin time (APTT) were also reported in one patient each. While two grade 4 drug-related adverse events (prolonged APTT and hyperglycemia in one patient each) were reported, there were no treatment-related adverse events, the most common being grade 3 hand–foot syndrome in two patients (9.1%). Grade 4 drug-related adverse events occurred in only two patients, including prolonged APTT and hyperglycemia in one patient each. These findings suggest that the oral capecitabine regimen tested in the current study might be better tolerated compared with intravenous 5-FU/LV and have similar tolerability to 5′-DFUR (30), although a larger phase II trial is required to confirm these findings.

**DISCUSSION**

Capecitabine has demonstrated consistently high single-agent activity and a favorable safety profile in taxane and anthracycline pre-treated metastatic breast cancer (21–24) and improved overall survival when added to docetaxel in the anthracycline-failure setting (25). In addition, in randomized phase III trials, comparing the efficacy and tolerability of 3-weekly intermittent capecitabine with i.v. bolus 5-FU/LV as first-line treatment of advanced colorectal cancer, capecitabine was more active than 5-FU/LV in the induction of tumor response and at least equivalent in terms of TTP and overall survival (26). Furthermore, a combined analysis of these randomized phase III studies in colorectal cancer revealed that capecitabine offers a clinically meaningful advantage over 5-FU/LV in terms of safety (27).

In the current phase II trial using the 4-weekly Japanese intermittent capecitabine regimen, the overall response rate was 25.0% as second-line treatment, rising to 33.0% as first-line treatment. In comparison, the response rate of intravenous 5-FU/LV therapy in the first-line treatment setting is recognized to be in the range of 17–33% based on the results of four randomized studies (6,26,28,29). These findings regarding capecitabine and 5-FU/LV compare very favorably with those reported previously for 5′-DFUR in a multicenter phase II study, where the response rate in 76 previously treated colorectal cancer patients was only 9.2% (30). Interpretation of overall survival data in such a small group of patients is difficult due to selection bias. However, the median survival time for patients receiving capecitabine in the present study is comparable to those previously reported for 5-FU/LV (12.6–14.3 months) and 5′-DFUR (15.4 months) (6,26,28–30); a larger phase II trial is required to confirm these findings. In addition to other trials, a trial of this type has since been conducted in patients with advanced breast cancer, and findings are expected to be published later in 2004.

In terms of safety, grade 3/4 adverse events such as diarrhea and neutropenia have been reported relatively frequently following 5-FU/LV therapy in the studies mentioned above. In the present study, five patients (22.7%) had grade 3/4 drug-related adverse events, the most common being grade 3 hand–foot syndrome in two patients (9.1%). Grade 4 drug-related adverse events occurred in only two patients, including prolonged APTT and hyperglycemia in one patient each. These findings suggest that the oral capecitabine regimen tested in the current study might be better tolerated compared with intravenous 5-FU/LV and have similar tolerability to 5′-DFUR (30), although a larger phase II trial is required to confirm these findings.

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**Table 4. Summary of treatment-related adverse events (occurring in ≥10% of the intent-to-treat population)**

<table>
<thead>
<tr>
<th>Body system/event</th>
<th>Grade</th>
<th>No. of patients (total)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Skin/appendages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Liver/biliary system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOT increased</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GPT increased</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>–</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/nutritional system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycosuria</td>
<td>2</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Alkaline phosphatase raised</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocytes decreased</td>
<td>4</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Hematocrit decreased</td>
<td>3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*NCIC-CTC grade.*
It is also interesting to compare the results of the current study with the responses reported in phase II and III studies of the internationally approved intermittent capecitabine regimen (1250 mg/m² twice daily for 2 weeks every 3 weeks). In a phase II study, first-line treatment of 34 colorectal cancer patients with capecitabine was associated with a response rate of 24% (31). The response rate of capecitabine vs 5-FU/LV in the large phase III studies conducted in the EU and in the USA was 26% vs 17% (26). Based on our limited data, the Japanese intermittent regimen appears to be associated with a lower incidence of grade 3/4 adverse events than the standard 3-weekly intermittent capecitabine regimen (27): grade 3 HFS (4.5% vs 17%); grade 3/4 diarrhea (0% vs 13%); grade 3/4 hyperbilirubinemia (4.5% vs 23%). In addition, the rate of dose reductions because of adverse events was lower (9%) compared with the EU and the USA phase III studies (34%) (26). This type of cross-study comparison is feasible because the total dose of capecitabine given over six cycles is similar in both the Japanese and Western schedules (208-266 mg vs. 210 000 mg, respectively), and the difference in tumor response assessment times (every 4 weeks vs every 6 weeks) is unlikely to have a major impact on response rates. However, the usual limitations of cross-study comparisons should be taken into account when interpreting the current results.

Previous studies have shown that in patients with metastatic colorectal cancer, oral capecitabine provides a more convenient alternative to the commonly used protracted i.v. infusions of 5-FU that are known to impose significant inconvenience, costs and complications associated with indwelling central venous access lines and pumps. In terms of tolerability, capecitabine has a different adverse event profile compared with 5-FU and its derivatives, including a lower frequency of commonly observed adverse events such as myelosuppression and gastrointestinal disorders, the latter of which tends to impact the patients’ quality of life. Consequently, capecitabine provides an effective, convenient and well-tolerated therapy for use in the outpatient setting. The results from our small phase II study indicate that the Japanese intermittent capecitabine regimen is active and well tolerated in patients with advanced/refractory colorectal cancer. Nevertheless, these promising findings require confirmation in larger phase II/III trials before any firm conclusions can be arrived at.

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