A Phase II Study of the Global Dose and Schedule of Capecitabine in Japanese Patients with Metastatic Colorectal Cancer

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Background: Although the standard 3-week capecitabine regimen (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest) has shown superior activity and improved safety over bolus 5-fluorouracil/leucovorin in two large randomized phase III trials in Europe and in the United States, only a 4-week regimen of capecitabine (828 mg/m² twice daily for 3 weeks) has been studied in Japan. Therefore, we performed a phase II study to investigate the 3-week regimen of capecitabine in Japanese patients with metastatic colorectal cancer (MCRC).

Methods: Previously untreated patients with MCRC received oral capecitabine 1250 mg/m² twice daily for 2 weeks. Treatment was repeated every 3 weeks. Blood and urine samples were collected for pharmacokinetic analysis.

Results: Sixty patients were enrolled. The overall response rate was 35% [95% confidence interval (CI), 23–48%], and 52% of patients had stable disease. The median time to progression was 5.5 months (95% CI, 4.2–6.7 months). The median overall survival was 20.2 months (95% CI, 16.6–27.8 months). The most frequently occurring adverse drug reaction was hand-foot syndrome (all-grade 73%; grade 3 13%). Diarrhea, anorexia, nausea and stomatitis were each seen in 37% of patients. The pharmacokinetic profiles of capecitabine and its metabolites were similar to those reported in Caucasian patients.

Conclusions: The 3-week regimen of capecitabine was effective and well tolerated in Japanese patients with MCRC as well, and could be used as the basic regimen for future combination therapies.

Key words: capecitabine – colorectal cancer – phase II study

INTRODUCTION

For more than 40 years, 5-fluorouracil (5-FU) has been the mainstay of treatment for patients with metastatic colorectal cancer (MCRC). Many incremental improvements to 5-FU regimens, such as biomodulation with leucovorin (LV) and schedule modification, have been made. For example, infusional 5-FU offers not only improved response rates, but also a small survival benefit, compared with those of bolus 5-FU according to data from randomized trials and meta-analyses (1,2). However, continuous infusions require venous access lines and pumps with significant associated costs. Consequently, patients prefer to receive oral rather than intravenous chemotherapy (3,4).

Several new fluoropyrimidines, including uracil plus tegafur (UFT), capcitabine and S-1, have been developed and evaluated in the treatment of colorectal cancer. Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU predominantly to tumor cells. After oral administration, capecitabine is rapidly and extensively absorbed through the intestine as an intact molecule, and then metabolized to 5-FU in three steps. In the first step, capecitabine is hydrolyzed to 5’-deoxy-5-fluorocytidine (5’-DFCR) by carboxylesterase primarily in the liver. 5’-DFCR is then converted to 5’-deoxy-5-fluorouridine (5’-DFUR) by cytidine deaminase, which is highly active in...
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Written informed consent was obtained from all patients.

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All patients had to have histologically confirmed colorectal
adenocarcinoma with at least one measurable lesion according
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> 10 × 10^9/mm^3; serum creatinine < 1.5 × upper limit of normal
(ULN); serum bilirubin < 1.5 × ULN; ALT (GPT), AST
(GOT) ≤ 2.5 × ULN (or ≤ 5 × ULN in the case of liver meta-
stases); alkaline phosphatase ≥ 2.5 × ULN (or ≤ 5 × ULN in the
case of liver metastases or ≤ 10 × ULN in the case of bone
disease) and creatinine clearance > 50 ml/min. Patients had
received no chemotherapy for metastatic disease (excluding
adjuvant chemotherapy completed more than 6 months before
registration) and no radiotherapy to target lesions. Patients
were not included if they had received radiotherapy within
the previous 4 weeks, or had not fully recovered from the
major surgery within 4 weeks. Other eligibility criteria were
as follows: Eastern Cooperative Oncology Group (ECOG)
performance status of 0–2; expected survival time of more
than 3 months and age at enrollment of 20–74 years.

Exclusion criteria were as follows: pregnant or lactating
women; sexually active men/women unwilling to practice
contraception during the study; a history of hypersensitivity
to 5-FU; organ allografts; clinically significant cardiac disease
or myocardial infarction within the last 12 months; metastases
of the central nervous system; a history of epilepsy; psychiatric
disability precluding compliance with oral drug intake or
giving informed consent; history of another malignancy within
the last five years, except for cured basal cell carcinoma of
skin, cured carcinoma in situ of uterine cervix, or cured
esophago-gastric carcinoma removed by endoscopic proced-
ures; serious uncontrolled infection; malabsorption syndrome;
participation in any investigational drug study within 4 weeks
preceding the start of treatment.

PATIENTS AND METHODS

STUDY DESIGN
The primary endpoint of this open-label multicenter phase II
study was response rate. Secondary endpoints were safety,
time-to-tumor progression (TTP), survival and pharma-
okinetic analysis. This study was conducted in accordance
with the Good Clinical Practice guidelines for clinical trials
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esophago-gastric carcinoma removed by endoscopic proced-
ures; serious uncontrolled infection; malabsorption syndrome;
participation in any investigational drug study within 4 weeks
preceding the start of treatment.

EVALUATION OF RESPONSE AND SAFETY
Anti-tumor efficacy was evaluated by the investigators accord-
ing to RECIST guidelines (19). An Independent Review Com-
mittee (IRC) confirmed tumor responses. Adverse events were
assessed according to the National Cancer Institute—Common
Toxicity Criteria, Version 2.0 (20). Hand-foot syndrome (HFS)
was classified as follows: grade 1 (numbness, dysesthesia,
painless swelling or erythema not disrupting daily living activ-
ities); grade 2 (erythema with painful swelling or disruption of
daily living activities) or grade 3 (moist desquamation, ulcer-
ation, blistering or severe pain, or any symptoms leading to an
inability to work or to perform daily living activities).

STUDY ASSESSMENTS
Tumor responses were assessed every 2 cycles up to the
cycle 10, and then every 3 cycles. Tumor markers (CEA
and CA19-9) were also assessed at these times. Laboratory
tests were performed before treatment, on day 8 of cycle 1
and on day 22 of each cycle. Drug compliance was reviewed at
regular patient visits by checking unused tablets. Survival in all
patients was monitored for 2 years after the last patient was
enrolled.
DOSAGE AND DOSE MODIFICATIONS

Capecitabine (Xeloda®) 1250 mg/m² was taken orally twice daily within 30 min after breakfast and dinner. The actual dose of capecitabine administered was determined according to the patient’s body surface area (BSA) as follows: 3000 mg/day if BSA was <1.33; 3600 mg/day if BSA was between 1.33 and 1.56; 4200 mg/day if BSA was between 1.57 and 1.80; and 4800 mg/day if BSA was >1.80. Each cycle of therapy consisted of 2 weeks of capecitabine administration followed by a 1-week rest period. Patients received treatment unless they had disease progression or unacceptable toxicity, or withdrew consent.

Treatment interruption or dose reductions were made if patients experienced grade 2–4 toxicities, but not if the toxicity was considered unlikely to become serious or life-threatening. Treatment was interrupted in cases of grade 2 or grade 3 toxicities and was not resumed until adverse drug reactions improved to grade 1. The dose of capecitabine was not reduced for the subsequent treatment cycle in cases of the first appearance of grade 2 toxicity. Capecitabine dose was reduced by 25% when patients experienced any grade 2 toxicity for a second time or for any grade 3 toxicity. It was reduced by 50% when patients experienced any grade 2 toxicity three times, any grade 3 toxicity twice, or any grade 4 toxicity. Treatment was discontinued if such toxicities were observed despite dose reduction.

STATISTICAL METHODS

The target number of patients for accrual was 60. Given an expected response rate of 25%, a threshold response rate of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the analysis of response. The 95% confidence interval (CI) of the response rate was calculated by the exact method, assuming a binomial distribution of data. Treatment duration was defined as days from the first day of drug administration to the last regulated rest day of the final cycle. Dose intensity was calculated by dividing the cumulative dose/treatment duration by BSA. TTP was calculated as the time from the first administration of capecitabine to disease progression or death if the patient died before progression. Overall survival was defined as the time from study enrolment to death. These endpoints were calculated by the Kaplan–Meier method. Safety was evaluated in all patients who received capecitabine treatment.

PHARMACOKINETIC ANALYSIS

Blood sampling was performed in the first 20 patients who gave consent to participate in the pharmacokinetic study. On day 1, the evening dose of capecitabine was not administered in order to quantify urinary recovery of capecitabine and its metabolites over a 24 h collection period. On days 1 and 14, 5 ml blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 11 h after the morning dose using vacutainers containing EDTA as an anticoagulant. Blood samples were centrifuged at 1500 g and 4°C for 10 min, and supernatant plasma was removed and stored in plastic tubes below −20°C until analysis. Urine was collected and pooled during the following time intervals: 0, 0–11 and 11–24 h on day 1; and 0–11 h on day 14. At the end of each interval, the total volume and the pH of urine were recorded; and a 15 ml aliquot was removed and stored at −20°C until analysis.

Plasma and urine concentrations of capecitabine and its metabolites were determined by a validated liquid chromatography with mass-spectrometry detection (LC/MS-MS). The lower limits of quantification (LLOQ) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and α-fluoro-β-alanine (FBAL) in plasma were 0.01, 0.01, 0.05, 0.002 and 0.011 μg/ml, respectively. The LLOQ of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, α-fluoro-β-ureidopropionic acid and FBAL in urine were 0.02, 0.02, 0.02, 0.1, 0.02 and 0.1 μg/ml, respectively.

Pharmacokinetic parameters were assessed by standard non-compartment analysis, using WinNonlin® professional version 4.1 (Pharsight Corporation). Maximum plasma concentration (C_max) and the time to reach C_max (T_max) were determined. Apparent half-life (t1/2) was estimated from ln2/λ, where the apparent rate constant of elimination, λ, was estimated by linear regression on the logarithm of the plasma concentration versus time data. The area under the plasma concentration time curve from time 0 to infinity (AUC) was estimated from the sum of AUC0–t, and Clast/λ, where AUC0–t is the area under the curve from time 0 to the last sampling time (tlast) at which a concentration above the limit of quantification was measured (Clast). AUC0–t was estimated using the linear-log trapezoidal rule. Percentage of dose recovered in urine as capecitabine or one of its metabolites was calculated based on the dose administered, urinary concentration and volume of urine collected.

RESULTS

PATIENT CHARACTERISTICS

Sixty patients were enrolled at 11 centers between January 2003 and November 2003. All patients met the eligibility criteria and received at least one dose of capecitabine. Therefore, both tumor response and safety were assessed in 60 patients. The baseline characteristics of patients are shown in Table 1. Median age was 60 years (range 34–71 years). A total of 33 patients (55%) had colon cancer, and 26 (43%) had rectal cancer. Metastatic sites affected were liver (73%), lung (58%), lymph node (47%) and others (17%).

TREATMENT DURATION AND INTENSITY

The median duration of treatment was 186 days (range 8–508 days). The median cumulative dose of capecitabine was 370 g (range 27–1255 g). The planned dose intensity was 1667 mg/m²/day and the actual median dose intensity was 1420 mg/m²/day (range 940–2220 mg/m²/day). Approximately 57 and 35% of patients completed 8 and 10 cycles of therapy, respectively. The reasons for treatment discontinuation were progressive disease (54 patients), adverse reactions (5 patients) and salvage surgical therapy (1 patient).
The median dose per cycle was >75% of the planned dose up to 10 cycles.

**EFFICACY**

The objective response rate according to the IRC assessment was 35% (95% CI, 23–48%) (Table 2). Twenty-one patients had a partial response, and 31 (52%) had stable disease. Partial responses were observed in 11 out of 44 patients (25%) with liver metastases, 14 out of 35 patients (40%) with lung metastases and in 8 out of 28 patients (29%) with lymph nodes metastases. The median TTP was 5.5 months (95% CI, 4.2–6.7 months) (Fig. 1). Survival follow-up was performed at the cut-off date of October 2005. Thirty-five patients died of disease progression and there were no treatment-related deaths. The median overall survival was 20.2 months (95% CI, 16.6–27.8 months) and the 1-year survival rate was 70% (Fig. 1).

**SAFETY**

The common adverse drug reactions (all grades) were HFS (73%), pigmentation (38%), diarrhea (37%), anorexia (37%), nausea (37%) and stomatitis (37%) (Fig. 2). The most frequent grade 3/4 adverse drug reaction was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. No grade 4 diarrhea was observed, and grade 3 diarrhea was seen in only one patient. Ileus occurred in one patient. As for grade 3/4 laboratory abnormalities, the common events were elevated total bilirubin (12%) and elevated AST (10%). One patient had grade 3 leucopenia, and 5 patients had grade 3 neutropenia. One patient had grade 4 hyperglycemia.

Treatment was interrupted due to adverse drug reactions in 48 patients (80%). The median time to the first interruption was 43 days. The major cause of treatment interruption was HFS (25 patients). Dose reduction was needed in 32 patients (53%), and 10 patients had the second dose reduction. The median time to the first dose reduction was 162 days. Nineteen patients had dose reductions due to HFS. Five patients discontinued treatment because of adverse events: ileus (grade 4, treatment related); hepatitis C (grade 3, not related, an accidental acute infection); liver function abnormality (grade 2, not related, due to the progression of liver metastasis); hydronephrosis (grade 4, not related) and HFS (grade 3, treatment related).

**PHARMACOKINETICS**

Plasma concentrations for capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU and FBAL) are shown in Fig. 3. The pharmacokinetic parameters are summarized in Table 3. Peak plasma concentrations of capecitabine and its metabolites
were reached rapidly at approximately 1.5–4 h after oral administration. Plasma concentrations of capecitabine, 5'-DFCR, 5'-DFUR and 5-FU were below the LLOQ at 8, 11, 8 and 8 h on day 1, respectively, and at 6, 11, 6 and 8 h on day 14, respectively. $T_{1/2}$ were generally short at $<1$ h, except for FBAL (around 2.5 h). After a single dose of capecitabine 1250 mg/m², the AUC for 5-FU was almost 30 times lower than its precursor 5'-DFUR on day 1. Comparing day 1 versus day 14, there was no significant accumulation of capecitabine and its metabolites except for 5-FU. The AUC for 5-FU on day 14 was 1.6 times higher than that on day 1.

The mean urinary excretion ratio of capecitabine and its metabolites are presented in Table 4. The mean proportions for the urinary recovery of capecitabine and its metabolites were 78% on day 1 and 80% on day 14. FBAL was the main urinary metabolite accounting for 50% on day 1 and 50% on day 14. The urinary excretion ratio of unmetabolized capecitabine was low at around 3%.

**DISCUSSION**

Two large randomized phase III studies have shown that capecitabine is more active than bolus 5-FU/LV in terms of tumor response (26 versus 17%), and equivalent to 5-FU/LV in terms of TTP and overall survival time in the first-line treatment of MCRC (11,13). Furthermore, a combined analysis of these randomized phase III studies revealed that capecitabine conferred a clinically meaningful advantage over 5-FU/LV in terms of safety (12). On the basis of these data, capecitabine was approved for the treatment of MCRC in Europe and in the US as an alternative to 5-FU/LV.

The results of the present study are similar to those observed in the pivotal phase III trials. The response rate in our study...
the number of patients who had more than 3 metastatic sites in this study was less than that in the phase III studies (18 versus 52%) (12), and our patients had better PS (PS 0, 70%). These better backgrounds might bring out slightly higher response rate in our study. The rate of stable disease was 52% in the current study and 38% with the 4-week regimen (10). Consequently, the disease control rate was superior in the present study than with the 4-week regimen (87 versus 64%). Moreover, the median TTP was similar to that reported in the phase III studies (5.5 months versus 4.6 months) using the same 3-week schedule, and was longer than that in the previous Japanese phase II study (2.2 months, unpublished data) using the 4-week regimen. Notwithstanding the limitations of comparing data between trials, these data strongly suggest that the capecitabine 3-week regimen is superior to the 4-week regimen. One of the reasons for these better results might be attributed to the higher dose intensity of the 3-week regimen than that of the 4-week regimen.

In terms of safety, most adverse events were reversible and manageable, and the tolerability of this regimen in a Japanese patient population seemed similar to that observed in Western patient populations. Compared with the randomized phase III studies (12), the rate of HFS, the most frequently reported adverse drug reaction, was higher in the present study (73 versus 54%), but grade 3 HFS appeared a little lower (13 versus 17%). However, HFS was controlled easily by anti-emergent medications only. One patient withdrew from the study due to this adverse reaction (2%), but none of the patients required hospitalization for the treatment of HFS. In the phase III studies (12), 2% of patients withdrew because of HFS, a rate that was similar to our study. The rate of diarrhea (all-grade and grade 3/4) was less frequent in the present study than that reported in the corresponding control arms (12). The rate of grade 3/4 diarrhea was 35%, which compares favorably with the combined response rate reported in the phase III studies (26%) (11,13) and in a previous Japanese phase II study (27%) using the 4-week regimen (10). Comparing the patients’ background, the number of patients who had more than 3 metastatic sites in this study was less than that in the phase III studies (18 versus 52%) (12), and our patients had better PS (PS 0, 70%). These better backgrounds might bring out slightly higher response rate in our study. The rate of stable disease was 52% in the current study and 38% with the 4-week regimen (10). Consequently, the disease control rate was superior in the present study than with the 4-week regimen (87 versus 64%). Moreover, the median TTP was similar to that reported in the phase III studies (5.5 months versus 4.6 months) using the same 3-week schedule, and was longer than that in the previous Japanese phase II study (2.2 months, unpublished data) using the 4-week regimen. Notwithstanding the limitations of comparing data between trials, these data strongly suggest that the capecitabine 3-week regimen is superior to the 4-week regimen. One of the reasons for these better results might be attributed to the higher dose intensity of the 3-week regimen than that of the 4-week regimen.

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2 versus 13%) (12). Though pigmentation, which was not reported more than 5% in the phase III trials, was frequently observed in this study (38%), all events of pigmentation were grade 1 and did not lead to interruption or reduction. The rate of other adverse drug reactions in our study was almost identical to that reported in the phase III trials (12). With regard to severe abnormalities in laboratory parameters, AST elevation was more frequently observed in the present study (10 versus 1%), although the rate of hyperbilirubinemia was similar to phase III observations (12 versus 23%) (12). Dose reduction was executed more frequently than the phase III trials (53 versus 34%), but the rate of dose reduction to second level was almost similar (17 versus 12%). Median time to reduction to the first level was similar to phase III trials (2.6 months versus 2.5 months), and median time to reduction to the second level was longer in our study (5.3 months versus 3.6 months). From these results, the current 3-week regimen seems quite feasible for the treatment of MCRC in Japan.

The pharmacokinetic findings in the present study were basically similar to those reported in Caucasian patients (8,21). Pharmacokinetic analysis of plasma concentrations and urinary excretion showed rapid gastrointestinal absorption of capecitabine and efficient conversion to its metabolites. Peak concentrations of capecitabine and its metabolites, including 5-FU, were reached shortly after drug administration and declined exponentially with a half-life of approximately 1 h. Pharmacokinetic data obtained on days 1 and 14 showed no difference in pharmacokinetics over time and there was no clinically significant accumulation of capecitabine and its metabolites, except for 5-FU. The AUC of 5-FU on day 14 was 1.6 times higher than on day 1. A similar increase of 5-FU with multiple administration has been also reported in other clinical studies of capecitabine (7,8,21).

From these results, we conclude that the 3-week regimen of capecitabine is effective and well tolerated in Japanese patients with MCRC. Capecitabine has been reported to show good activity when combined with irinotecan (14,15) and oxaliplatin (16,17). Further investigation of this 3-week schedule is warranted in Japan.

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References


**APPENDIX**

List of participating centers: NHO Shikoku Cancer Center, National Cancer Center Hospital, National Cancer Center Hospital East, Cancer Institute Hospital, Aichi Cancer Center, Saitama Cancer Center, Kobe University Graduate School of Medicine, Kanagawa Cancer Center, Osaka Medical College, Kinki University, NHO Osaka National Hospital.