A phase II Japanese study of a modified capecitabine regimen for advanced or metastatic colorectal cancer

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This phase II study evaluated a modified Japanese capecitabine regimen as first-line treatment for advanced/metastatic colorectal cancer. Sixty patients received oral capecitabine 828 mg/m^2 twice daily for 3 weeks every 4 weeks. In the 56 efficacy-evaluable patients, the overall response rate was 26.8% (95% CI 15.8–40.3%) and 21 patients (37.5%) had stable disease. The median duration of response and overall survival times were 7.4 months (range 4.3–13.8) and 17.6 months (95% CI 14.1–20.5), respectively. The most frequent non-hematological treatment-related adverse events (all grades) were hand–foot syndrome (62.7%), anorexia (28.8%), diarrhea (22.0%) and fever (22.0%). There was no grade 3/4 diarrhea. The most common grade 3/4 laboratory abnormalities were lymphocytopenia (30.5%) and hyperbilirubinemia (35.6%). We conclude that the modified Japanese intermittent regimen of capecitabine is effective and well tolerated as first-line treatment for advanced colorectal cancer, and is worthy of further study in larger phase III studies. *Anti-Cancer Drugs* **15:137–143**

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Introduction

5-Fluorouracil (5-FU) has been used for the treatment of various malignancies for over 40 years, although conventional bolus 5-FU is associated with gastrointestinal disorders (e.g. diarrhea, stomatitis), neurotoxicity and myelosuppression. Attempts to improve the antitumor efficacy and tolerability of 5-FU have included biomodulation with agents such as leucovorin (LV) and schedule modification. Administering 5-FU by continuous infusion avoids some of the toxicities associated with bolus injection and can be effective in patients resistant to bolus 5-FU. However, several studies and meta-analyses have failed to identify any clinically significant survival advantage of infusional over bolus 5-FU [1–3]. Compounding these issues is the knowledge that regimens based on continuous infusions impose significant inconvenience, requiring regular hospital visits for treatment, and the associated traveling time and costs, and indwelling venous access lines and pumps increase the risk of local toxicity related to administration. 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 in order to receive their preferred route of administration [4–6].

Several new fluoropyrimidines, including uracil plus tegafur (UFT), doxifluridine [5′-deoxy-5-fluorouridine (5′-DFUR)], S-1 and eniluracil, have been developed and evaluated in the treatment of various carcinomas. Most of these agents have failed phase III evaluation due to inadequate efficacy [7,8] or, in the case of S-1, have not yet been evaluated in phase III trials. Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU predominantly to tumor cells, which, through its twice-daily oral administration, mimics continuous infusion of 5-FU and avoids the disadvantages of continuous i.v. access [9]. After oral administration, capecitabine is rapidly and extensively absorbed through the gut as an intact molecule, and is then metabolized to 5-FU in three steps. In the first step, capecitabine is hydrolyzed by carboxylesterase (primarily in the liver) to form 5′-deoxy-5-fluorocytidine (5′-DFCR). The next step is mediated by cytidine deaminase, which is highly active in tumor cells and in the liver, and converts 5′-DFCR to 5′-DFUR. Thymidine phosphorylase (TP), which is significantly more active in tumor tissue than in adjacent healthy tissue [10], finally converts 5′-DFUR to 5-FU. The increasing specificity for tumor cells occurring with each successive conversion step potentially reduces systemic 5-FU exposure while increasing the 5-FU dose within tumor tissue. Consequently, capecitabine avoids

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some of the gastrointestinal disorders (e.g. diarrhea) that are commonly observed following treatment with 5′-DFUR and UFT/LV [11].

A program of clinical studies of capecitabine in colorectal cancer has been conducted worldwide. In Japanese phase I studies, the maximum tolerated dose (MTD) of capecitabine was 1255 mg/m^2 when administered continuously twice daily [12]. Because of the occurrence of skin disorders with a continuous treatment regimen, an intermittent treatment regimen of 828 mg/m^2 twice daily for 3 weeks followed by a 1-week rest period was recommended for phase II studies. This dose/schedule differs from the more dose-intensive internationally approved intermittent capecitabine regimen (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period). During the Japanese development of capecitabine, the 4-weekly intermittent schedule of capecitabine resulted in an overall response rate of 25.0% (five of 20) in a small pilot study in patients with colorectal cancer [13]. In the latter study, the median survival time following treatment with capecitabine in colorectal cancer patients was 13.3 months and tolerance of oral capecitabine was excellent.

In the present report, we describe the results of a larger phase II study conducted to evaluate the efficacy and safety of the Japanese capecitabine regimen as first-line treatment in patients with advanced or metastatic colorectal cancer.

Patients and methods

Study design

This open-label phase II study was designed to evaluate the efficacy and safety of intermittent capecitabine (828 mg/m^2 twice daily given orally for 3 weeks, followed by a 1-week rest period) in patients with previously untreated advanced/metastatic colorectal cancer. The trial was conducted in accordance with the Good Clinical Practice (GCP) guidelines for clinical trials. Written informed consent was obtained from all patients.

Patients

The target number of patients 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%. Eligible patients had to have histologically confirmed colon or rectal cancer with measurable lesions, and with laboratory data that met the standard criteria for renal, hepatic and hematological status, i.e. leukocytes 4000–12 000 cells/mm^3; platelets $\geq$ 100 000 cells/mm^3; hemoglobin $\geq$ 9.0 g/dl; GOT (AST), GPT (ALT) and alkaline phosphatase $\leq$ 2.5 times the upper limit of normal (ULN) for the center; and total bilirubin and creatinine $<$ 1.5 times the ULN. Patients were to have received no prior chemotherapy for metastatic disease (excluding adjuvant chemotherapy that had been completed more than 6 months before registration) or radiotherapy to target lesions. Eligibility criteria also included an ECOG performance status of 0–2, an expected survival time of 3 months or more and an age at enrollment of 20–74 years.

Patients with the following conditions were excluded from the study: pregnant or lactating women and sexually active males/females unwilling to practice contraception during the study; a history of hypersensitivity to 5-FU; organ allografts; current treatment with oral or parenteral steroids; evidence of central nervous system (CNS) metastases; peripheral neurologic signs and symptoms not associated with cancer; a history of uncontrolled seizures, CNS or psychiatric disabilities; serious uncontrolled concurrent infections; active peptic ulcer requiring treatment; clinically severe complications of non-malignant disease, such as liver, renal or lung disease, or uncontrolled diabetes mellitus; history of another malignancy within the last 5 years; ascites or pleural effusions or bone metastasis as the only measurable lesions; ascites or pleural effusions requiring treatment; severe abnormal ECG; severe clinical heart disease such as congestive heart failure, symptomatic coronary artery disease, uncontrolled arrhythmia, or myocardial infarction (grade III or VI by the New York Heart Association criteria, 1997) within 1 year; or a history of prior treatment with an unapproved drug.

Dosage and dose modifications

The dose of capecitabine was determined according to the patient's body surface area based on the recommended dose from a previous phase I study (828 mg/m^2 twice daily) (Table 1) [12]. Capecitabine was taken orally twice daily within 30 min after breakfast and dinner. Each course of therapy comprised of 3 weeks of treatment followed by a 1-week rest period. Patients were scheduled to receive at least two courses of treatment, except in cases of disease progression, request from patient/family or adverse events. Throughout the study, chemotherapy (other than capecitabine), immunotherapy, hormonal therapy and systemic steroids were prohibited.

In the event of any drug-related grade 3 adverse events (excluding anorexia, nausea, vomiting, alopecia, malaise or skin reactions) or grade 3 drug-related laboratory

Table 1 Determination of capecitabine dose according to patient's body surface area

Body surface area (m^2)	Recommended dose (mg, twice daily)[a]
(For dose modification only)	600
$<$1.31	900
1.31 to $<$1.64	1200
$\geq$ 1.64	1500

[a]Based on recommended dose of 828 mg/m^2 twice daily.

abnormalities (excluding leucopenia of < 2000 cells/mm^3, granulocytopenia of < 1000 cells/mm^3 and lymphocytopenia of < 1000 cells/mm^3 associated with a fever persisting for ≤ 3 days), or if the investigator judged continuation of treatment unfeasible, medication was interrupted for up to 4 weeks or until all adverse events had resolved. Treatment was permanently discontinued in patients who developed grade 4 adverse events. If the investigator judged that the adverse events precluded continuation of treatment at the same dose, the administered dose could be reduced by 30% in the subsequent cycle except in cases of grade 3 alopecia, malaise, taste abnormality, anorexia, nausea, vomiting, lymphocytopenia, and increased bilirubin (≤ 2.0 mg/dl).

Study assessments

Before enrollment, patients were evaluated to determine demographic characteristics and the presence or absence of signs and symptoms; laboratory, electrocardiograph and imaging studies of all lesions were also performed. The results served as baseline data for the assessment of efficacy and safety. If feasible, tumor markers were measured and used as an auxiliary index of response. Lesions were examined at week 4 during each course of therapy to evaluate response. Laboratory tests were performed at weeks 2 and 4 during each course of treatment until the completion of the second course, and at week 4 during subsequent courses. Signs and symptoms were observed at appropriate intervals during treatment. Drug compliance was reviewed regularly, and confirmed by retrieving all empty drug boxes and unused tablets. Patients were followed-up for symptoms/adverse events for 4 weeks after completion of treatment, unless other therapy had been assigned. Survival follow-up was also performed at the cut-off date.

Evaluation of response and safety

Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were defined by the investigator according to the *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus* [14]. These criteria differ slightly from the WHO criteria as there are five evaluations of response: CR, PR, MR (minor response), NC (no change) and PD. However, in the current study MR and NC were grouped together as SD so that the tumor response criteria could be compared with other studies using the WHO criteria. The final determination of tumor response was confirmed by a response evaluation committee, which comprised independent reviewers not participating in the study.

Adverse effects and symptoms were assessed according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC) Grading System [15]. Adverse events not listed on the NCIC-CTC grading system were graded as mild (grade 1), moderate (grade 2), severe (grade 3) or life threatening (grade 4). Hand–foot syndrome (HFS or palmar–plantar erythrodysesthesia), was classified as grade 1, 2 or 3, as reported previously [16].

Statistical methods

All eligible patients were included in the analysis of response. Patients with a CR or PR were considered responders, and the response rate calculated. The 95% confidence interval (CI) of the response rate was calculated by the exact method, assuming a binomial distribution of data. The duration of response and the number of days until the onset of response in responders were expressed with minimum value, median value and maximum value. Overall survival was defined as the number of days from study enrollment until death and calculated by the Kaplan–Meier method. Safety was evaluated in all patients who received capecitabine treatment.

Results

Patient characteristics

Sixty patients were enrolled from 17 centers between April 1999 and October 2000. Of these, three did not meet the eligibility criteria following registration: two patients had received previous cytotoxic chemotherapy for metastatic disease and one patient violated the study entry criteria (enrolled with high AST level). An additional patient did not receive any study medication because of fever and pneumonia following registration. Therefore, tumor response was evaluated in 56 patients. Safety was assessed in all 59 patients treated with capecitabine.

The demographic characteristics of treated patients are shown in Table 2. The median age was 63 years (range 28–74 years), 28 (47.5%) presented with colon cancer, 29 (49.2%) had rectal cancer, and the remainder (3.4%) were diagnosed as having both colon and rectal cancer. The most common sites of metastases were the liver (38 patients), followed by the lung (28 patients) and lymph nodes (12 patients).

Treatment duration

The median duration of treatment was 5.3 months (6 cycles), ranging from 0.7 (1 cycle) to 19.0 months (21 cycles). Although the protocol required that all patients receive two or more courses of capecitabine, treatment was discontinued before completing two courses in five patients. The reasons for study withdrawal were adverse events ($n = 1$, due to jaundice unrelated to drug), PD ($n = 2$), patient request ($n = 1$) and protocol violation ($n = 1$). The reasons for stopping treatment in the patients who received two or more courses of capecitabine were as follows: PD ($n = 47$, 79.7%), enrolled on a separate long-term study ($n = 4$, 6.8%), adverse events ($n = 2$, 3.4%) and surgical resection ($n = 1$, 1.7%). The

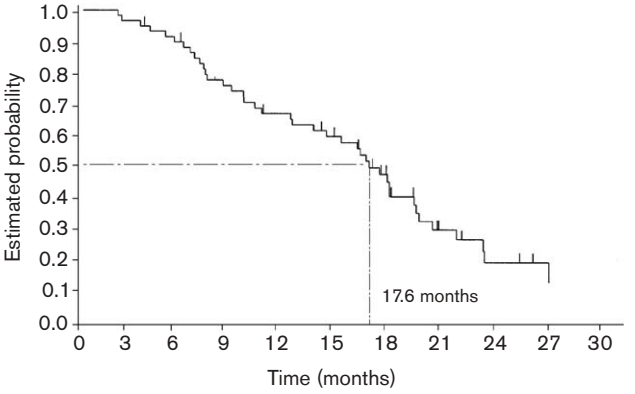
Table 2 Patient demographics (all treated patients)

Parameters	No.	%
Sex		
male	40	67.8
female	19	32.2
Age (years)		
median	63	
range	28–74	
Body surface area (m^2)		
median	1.56	
range	1.18–1.91	
Primary site		
colon	28	47.5
rectum	29	49.2
colon/rectum	2	3.4
Performance status		
0	47	79.7
1	12	20.3
Disease stage at diagnosis		
I	1	1.7
II	4	6.8
IIIa	10	16.9
IIIb	4	6.8
IV	40	67.8
No. of metastatic sites	multiple	solitary
liver	32	6
lung	21	7
lymph node	2	10
pelvis/peritoneal	0	10

Table 3 Tumor responses

No. of patients (%)					Total
CR	PR	SD	PD	NE	
0	15 (26.8)	21 (37.5)	20 (35.7)	0	56

Fig. 1



Overall survival.

Table 4 Responses according to sites of metastasis

	No. of patients					Total
	CR	PR	SD	PD	NE	
Lung	0	7	11	8	0	26
Pelvis/peritoneum	0	2	6	2	0	10
Liver	1	9	15	10	1	36
Lymph nodes	0	4	7	0	1	12

treatment compliance rate (taken tablets/prescribed tablets) was more than 90%.

Efficacy

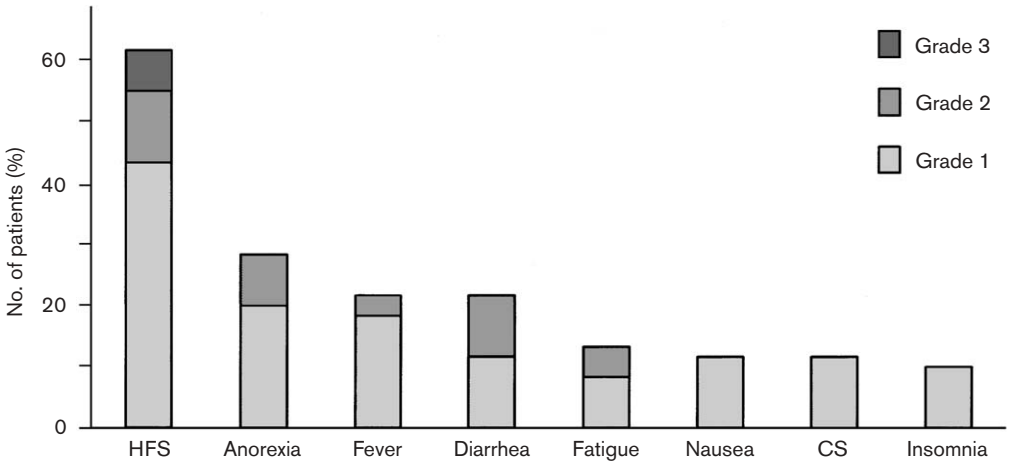
The overall response rate in the 56 patients evaluable for efficacy was 26.8%. (95% CI 15.8–40.3%, Table 3), based on 15 PRs, which was comparable with the response rate of 25.0% seen in an earlier phase II study of the same dose/schedule in a smaller population of patients [13]. In addition, 21 (37.5%) patients had SD. The median duration of response in responding patients was 7.4 months (range 4.3–13.8 months) and the median overall survival was 17.6 months (95% CI 14.1–20.5 months) (Fig. 1). Among the 36 sites of liver metastasis, there was one CR and nine PRs (response rate 27.8%); seven PRs (26.9%) were achieved in 26 pulmonary lesions; four PRs (33.3%) in 12 sites of lymph node metastasis; and two PRs (20.0%) in 10 sites of peritoneal/pelvic metastasis (Table 4).

Safety

All patients reported at least one adverse event during treatment with capecitabine. The most frequent treatment-related adverse events (all grades) were HFS (62.7%), anorexia (28.8%), diarrhea (22.0%), fever (22.0%) and fatigue (13.6%) (Fig. 2). Importantly, no grade 3/4 diarrhea was observed and only four grade 3 events (all HFS) were reported. Hyperbilirubinemia (35.6%) and lymphocytopenia (30.5%) were the most frequently reported grade 3/4 laboratory abnormality. Importantly, there was no grade 3/4 leucopenia and no withdrawals, hospitalizations or blood transfusions because of hematological adverse events.

Treatment was interrupted in 20 patients during the course of the study. The most common events leading to interruption were HFS and increased serum bilirubin levels. The median number of cycles before the first interruption was 9 (range 1–12). Three patients discontinued treatment because of jaundice (unrelated, stopped at cycle 2), acute renal failure (related, cycle 9) and HFS (related, cycle 9). One patient required dose adjustment due to HFS (after starting cycle 4). Grade 4 treatment-related adverse events were: hyperbilirubinemia (3.4%), lymphocytopenia (3.4%), increases of BUN (1.7%), acute cardiac failure (1.7%) and acute renal failure (1.7%). Fourteen patients experienced serious adverse events and three patients were withdrawn as a result. There were three deaths reported within 4 weeks after the end of treatment. Two of these were classified as being unrelated to treatment. The cause of death in the

Fig. 2



Summary of frequently reported treatment-related symptomatic adverse events (≥10% of patients). CS=constipation.

remaining patient was acute cardiac failure, which occurred 3 days after withdrawal from the study and was thought to be due to PD, rather than being treatment related.

Discussion

Colorectal cancer is currently the third most commonly diagnosed malignancy in Japan after lung cancer and gastric cancer, but is estimated to become the most common cancer type, as in Western countries, by the year 2015. Capecitabine was developed to improve on the efficacy and safety of 5-FU derivatives on the market by delivering 5-FU predominantly to tumor cells. In Western countries, capecitabine has demonstrated consistently high single-agent activity and a favorable safety profile in taxane and anthracycline pre-treated metastatic breast cancer [16–19], and improved overall survival when added to docetaxel in the anthracycline-failure setting [20]. In addition, randomized phase III trials comparing the efficacy and tolerability of capecitabine with i.v. bolus 5-FU/LV as first-line treatment of advanced colorectal cancer showed that capecitabine was more active than 5-FU/LV in the induction of tumor response (26 versus 17%), and at least equivalent in terms of time to progression and overall survival [21]. Furthermore, a combined analysis of these randomized phase III studies revealed that capecitabine offers a clinically meaningful advantage over 5-FU/LV in terms of safety [22].

In a pilot phase II study of a modified Japanese dosing regimen (828 mg/m^2 twice daily for 3 weeks every 4 weeks), the response rate was 25.0%, which compares favorably with responses reported previously for 5-FU/LV therapy as first-line treatment [2] and also confirmed the safety profile of the drug [13]. In the current study, the response rate was 26.8% (95% CI 15.8–40.3%), which is comparable to that observed with capecitabine as first-line treatment for metastatic colorectal cancer in the above-mentioned randomized studies conducted in the EU and USA (25.7%) [21]. In addition, the overall survival rate in the current study (17.6 months) is robust compared to that observed in the above studies (12.9 months) [21].

With regard to the safety of this modified capecitabine regimen, the majority of adverse events were reversible and manageable, leading us to conclude that this regimen is well tolerated in patients with advanced/metastatic colorectal cancer. Table 5 compares the most common adverse events in the current Japanese study with those from the above-mentioned randomized studies conducted with the standard intermittent capecitabine regimen [22]. The proportion of patients experiencing these adverse events was almost identical, with the exception of gastrointestinal events, in particular grade 3/4 diarrhea, which appeared to occur in fewer patients receiving the Japanese regimen compared with the standard intermittent capecitabine regimen. HFS, the most frequently reported adverse effect of capecitabine, has also been reported following treatment with continuous infusions of 5-FU, 5-FU/LV, doxorubicin, cytarabine, docetaxel, and also continuous infusions of vinorelbine and other agents. While the mechanisms of this effect have not yet been clearly determined, interrupting medication and dose reduction when necessary, as well as application of emollients, is sufficient to control the symptoms in most patients.

In conclusion, this study demonstrates that the Japanese intermittent regimen of capecitabine is convenient, effective and well tolerated in patients with advanced

Table 5. Proportion of patients experiencing common adverse events (Japanese and standard intermittent capecitabine regimens)

Event	Japanese regimen ($n=59$) [current study]		Standard regimen ($n=596$) [22]	
	Total	Grade 3/4	Total	Grade 3/4
HFS	37 (62.7%)	4 (6.8%)	318 (53.4%)	102 (17.1%)
Diarrhea	13 (22.0%)	0 (0%)	284 (47.7%)	78 (13.1%)
Nausea	5 (8.5%)	0 (0%)	225 (37.8%)	15 (2.5%)
Vomiting	5 (8.5%)	0 (0%)	139 (23.3%)	17 (2.9%)
Stomatitis	3 (5.1%)	0 (0%)	144 (24.2%)	13 (2.2%)

Japanese regimen: 828 mg/m^2 twice daily for 3 weeks, every 4 weeks. Standard regimen: 1250 mg/m^2 twice daily for 2 weeks, every 3 weeks.

colorectal cancer. The potential advantages of this modified regimen over the more dose-intensive regimen used in Western countries are a reduction in adverse events and better tolerability. However, it is important to note that the total dose of capecitabine given over 6 cycles is similar with both schedules (208 656 versus 210 000 mg, respectively). Furthermore, the impact of population selection means that it is difficult to compare the results of our relatively small phase II study with the pooled phase III data from the two registration trials of the standard capecitabine regimen. Consequently, our findings require confirmation in a larger randomized phase III trial before any firm conclusions can be made. Capecitabine is already prescribed as one of the principal treatments for advanced/metastatic colorectal cancer, where its oral administration provides the option of managing advanced colorectal cancer effectively in an outpatient setting and therefore improving patients' quality of life. Capecitabine has also displayed high activity when combined with other highly active anticancer agents, particularly irinotecan [23,24] and oxaliplatin [25,26], and is expected to show efficacy in the adjuvant setting in the near future. Chemoradiation for rectal cancer is another area where the advantages of oral capecitabine are proving to be of benefit [27,28]. The results from these and larger phase III trials of the Japanese intermittent regimen are expected to confirm the potential of capecitabine to replace 5-FU as the backbone of colorectal cancer treatment in both Japan and in the Western world.

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