Phase II study of a 4-week capecitabine regimen in advanced or recurrent gastric cancer

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Our objective was to evaluate the efficacy and safety of capecitabine in chemotherapy-naive patients with unresectable advanced or metastatic gastric cancer. An open-label multicenter phase II study was conducted for previously untreated patients with advanced or metastatic gastric cancer. Oral capecitabine 828 mg/m^2 twice daily was given on days 1–21 every 4 weeks. Baseline characteristics of 60 enrolled patients were: male/female 49/11, median age 64 years (range 28–74), good performance status (ECOG 0–1) in 98% of patients and 27 patients had prior gastrectomy (45%). A median of 4 treatment cycles were administered (range 1–37). Five patients were excluded from the efficacy analysis because they did not meet eligibility criteria. The overall response rate (RR) in the evaluable patient population ($n=55$) was 26% [95% confidence interval (95% CI) 15–39%] and a further 29% of patients had stable disease. The overall RR in the intent-to-treat population ($n=60$) was 23% (95% CI 13–36.0%). Median time to progression in the evaluable patient population was 3.4 months (95% CI 1.8–6.1) and overall survival time in the intent-to-treat population was 10.0 months (95% CI 6.4–13.6). The most frequent grade 3/4 drug-related adverse event was hand–foot syndrome (13%), but this was readily managed by treatment interruption and dose reduction. No patients developed grade 3/4 drug-related diarrhea, vomiting, leukopenia or thrombocytopenia. We conclude that this 4-week regimen of capecitabine showed promising activity and was well tolerated as first-line therapy for advanced/metastatic gastric cancer. Further investigation of this regimen is warranted. *Anti-Cancer Drugs* **17:231–236 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Since 5-fluorouracil (5-FU)-based chemotherapy prolongs survival compared with best supportive care alone [1], many phase III studies involving 5-FU-based combination regimens for advanced gastric cancer have been reported [2–4]. However, the definitive standard regimen has not yet been established and 5-FU monotherapy remains as one of the reference control regimens. The results of the randomized JCOG9205 phase III study comparing 5-FU continuous infusion (5-FUci) with 5-FU–cisplatin, and uracil/tegafur–mitomycin C have recently become available [4]. These show that median overall survival does not differ between 5-FUci and 5-FU–cisplatin, despite a significant difference in response rate (RR) and progression-free survival (PFS) favoring 5-FU–cisplatin [4].

Capecitabine (Xeloda) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU preferentially to tumor cells. After oral administration, capecitabine is rapidly and extensively absorbed through the intestine 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′-deoxy-5-fluorouridine (5′-DFUR). Thymidine phosphorylase (TP), which is significantly more active in tumor tissue than in adjacent healthy tissue, finally converts 5′-DFUR to 5-FU. With each successive conversion step, capecitabine potentially reduces the systemic exposure to 5-FU, while increasing 5-FU delivery to tumor tissues [5]. Consequently, capecitabine avoids some of the gastrointestinal toxicities (e.g. diarrhea) that are commonly observed with 5-FU.

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Based on preliminary clinical studies [6–8], capecitabine 1255 mg/m^2 twice daily administered for 2 weeks followed by a 1-week rest period was adopted globally in many subsequent trials. However, in a Japanese phase I study using continuous administration of capecitabine [9], the maximum tolerated dose (MTD) was 1255 mg/m^2 twice daily, with skin fissures and gastric ulcers noted as the dose-limiting toxicities. Consequently, a 4-week intermittent regimen (3 weeks of drug administration and 1 week of rest) of capecitabine 828 mg/m^2 twice daily was recommended by the investigators as a Japanese regimen for phase II studies [9]. This lower dose and prolonged administration period was selected to sustain both safety and dose intensity. In a small pilot study in patients with advanced gastric cancer [10], this 4-week regimen of capecitabine yielded a RR of 24% in chemotherapy-naive patients and showed a good safety profile without severe diarrhea.

On the basis of these findings, we conducted a larger phase II study with capecitabine to confirm the activity and safety of this 4-week regimen in patients with advanced gastric cancer.

Patients and methods

Study design

This study was designed as an open-label multicenter phase II study in accordance with the Good Clinical Practice guidelines for clinical trials in Japan and the Declaration of Helsinki. The study protocol was approved by the ethics committee of each institution. Written informed consent was obtained from all patients.

Patients

All patients had to have histologically confirmed gastric cancer with measurable lesions. Eligibility criteria were as follows: ECOG performance status 0–2, an expected survival time of $\geq$ 3 months and an age at enrolment of 20–75 years. Patients were required to meet standard criteria for hematologic, hepatic and renal status: 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 Al-p $\leq 2.5 \times$ upper limit of normal (ULN) for the center; total bilirubin and creatinine $< 1.5 \times$ ULN. Patients were required to be chemotherapy-naive (including post-operative adjuvant chemotherapy) for gastric cancer and to have received no radiotherapy to target lesions. Surgery and/or immunotherapy was to have been completed 4 and 2 weeks prior to the initiation qof capecitabine, respectively. Major exclusion criteria were as follows: active peptic ulcer, pregnant or lactating women, central nervous system metastases, inability to take meals due to underlying disease and blood transfusion within 2 weeks of the screening blood test.

Dosage and dose modifications

Capecitabine 828 mg/m^2 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: BSA < 1.31 m^2 = 900 mg/dose, 1.31 m$^2 \leq$ BSA < 1.64 m^2 = 1200 mg/dose and BSA ≥ 1.64 m^2 = 1500 mg/dose. A dose of 600 mg twice daily was used when patients who were treated initially at the lowest dose level needed dose reduction. Each cycle of therapy consisted of 3 weeks of administration of capecitabine and a 1-week rest period. Patients were scheduled to receive at least 2 cycles of treatment unless they had disease progression, severe and uncontrollable adverse events or withdrew consent. Throughout the study, chemotherapy (other than capecitabine), immunotherapy, hormonal therapy and administration of systemic steroids were prohibited.

When drug-related grade 3 adverse events (excluding anorexia, nausea, vomiting, alopecia, malaise, taste abnormality, lymphopenia and increased bilirubin) occurred, capecitabine administration should be interrupted until the events had resolved to grade 0 or 1. Treatment could be restarted at the same dose after the first interruption. After the second interruption, the dose of capecitabine should be reduced to one level below the starting dose (i.e. 600, 900 or 1200 mg/dose as appropriate). Study treatment was discontinued in patients who developed grade 4 drug-related adverse events, except for lymphopenia.

Study assessments

Before enrollment, demographic characteristics, symptoms and signs of disease were evaluated in each patient. Laboratory, electrocardiography and imaging studies of all lesions were also performed. The results served as baseline data for the assessment of efficacy and safety. Toxicities were evaluated every 2 weeks during the first 2 cycles and every 4 weeks thereafter. Drug compliance was reviewed at the patients' regular visits by retrieving drug boxes and checking unused tablets. Survival in all patients was monitored for 1 year after the last patient was enrolled.

Evaluation of response and safety

Tumor responses were assessed every 4 weeks and evaluated according to WHO response criteria [11]. Evaluation was performed by the investigators and an Independent Review Committee (IRC).

Adverse events were assessed according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC) grading system [12]. Safety was evaluated in all patients who received capecitabine treatment. Hand–foot syndrome (HFS; palmar–plantar erythrodysesthesia) was classified based on clinical and functional domains as outlined in Table 1.

Table 1 Grading scale of HFS

Grade	Clinical domain	Functional domain
1	numbness, dysesthesia/paresthesia, tingling, painless	discomfort that does not disrupt normal activities
2	painful erythema, with swelling	discomfort that affects activities of daily living
3	moist desquamation, ulceration, blistering, severe pain	severe discomfort, unable to work or perform activities of daily living

Statistical methods

The target number of patients for accrual was 60. Given an expected RR of 25%, a threshold RR of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the efficacy analysis. The 95% confidence interval (CI) of the RR was calculated by the exact method, assuming a binomial distribution of data.

Treatment duration was defined as days from the initial to the last administration of capecitabine. Dose intensity was calculated by cumulative dose/treatment duration. Time to tumor progression (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 were calculated by the Kaplan–Meier method.

Table 2 Patient characteristics at baseline ($n=60$)

	No. patients	%
Median age [years (range)]	64 (28–74)	
Male/female	49/11	82/18
ECOG performance status		
0	44	73
1	15	25
2	1	2
Gastrectomy		
Yes	27	45
No	33	55
Histology		
Differentiated	31	52
Undifferentiated	29	48
No. metastatic sites		
1	45	75
≥ 2	15	25
Sites of metastasis		
lung	2	3
liver	27	45
lymph node	41	68
others	6	10

Results

Patient characteristics

A total of 60 patients were enrolled between February 1999 and April 2001. Their baseline characteristics are shown in Table 2. Median age was 64 years (range 28–74 years). The majority of patients had a good performance status (0 or 1). The major metastatic sites were lymph nodes and liver. All 60 patients received at least one dose of capecitabine and were included in the safety analysis. Although the investigators evaluated response in all patients, five patients did not meet the eligibility criteria (blood transfusion within 2 weeks preceding screening test, and elevated white blood cell count, bilirubin and AST at screening) and were excluded by the IRC.

Treatment duration

A median of 4 treatment cycles were administered (range 1–37). The median duration of treatment was 3.1 months (range 0.1–35.8 months). The median cumulative dose of capecitabine was 190 g (range 12–1629 g). Median dose intensity was 1870 mg/day (range 1198–3000 mg/day). Twenty-one of 60 patients (35%) were treated for at least 20 weeks and 10 patients (17%) were treated for more than 40 weeks. Reasons for treatment discontinuation were progressive disease (72%), drug-related adverse events (13%), adverse events not related to capecitabine (8%) and other (ineligible patient, salvage surgical therapy and withdrawal of consent). Compliance with capecitabine was maintained over 90% in all patients.

Efficacy

The anti-tumor efficacy of capecitabine is shown in Table 3. The overall RR confirmed by the IRC in 55 evaluable patients was 26% (95% CI 15–39.0%), including 7% of patients who showed a complete response. The median duration of response in patients with a complete or partial response was 8.8 months (range 2.7–29.6 months). The median TTP was 3.4 months (95% CI 1.8–6.1 months). On the other hand, the overall RR in the intent-to-treat population was 23% (95% CI 13–36.0%). Median overall survival calculated in all 60 patients was 10.0 months (95% CI 6.4–13.6 months) and the 1-year survival rate was 42%. The Kaplan–Meier plot of overall survival is shown in Fig. 1.

Safety

Common drug-related adverse events were HFS (57%), anorexia (28%), nausea (27%) and diarrhea (20%). The majority were grade 1 or 2 (Fig. 2). The most frequent drug-related grade 3/4 adverse event was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. There were no episodes of grade 3/4 vomiting or diarrhea, which were defined as dose-limiting toxicities in preliminary studies conducted in the US and Europe [6,7].

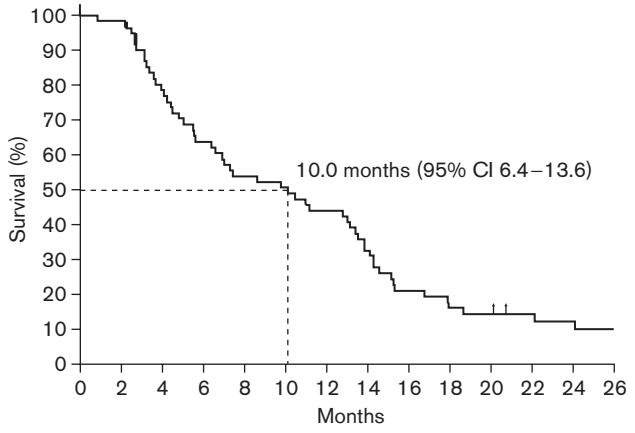
Frequently reported drug-related laboratory abnormalities were: lymphopenia (63%), decreased erythrocytes (55%),

Table 3 Anti-tumor response of capecitabine

	No. patients (%)	
	Assessed by investigators ($n=60$; ITT population)	Confirmed by IRC ($n=55$; evaluable population)
Response		
complete response (CR)	3 (5)	4 (7)
partial response (PR)	11 (18)	10 (18)
stable disease (SD)	20 (33)	16 (29)
progressive disease	21 (35)	19 (35)
Not evaluable[a]	5 (8)	6 (11)
Overall RR [% (95% CI)]	23 (13–36)	26 (15–39)
Disease control (CR/PR + SD) rate (%)	57	55 (41–68)

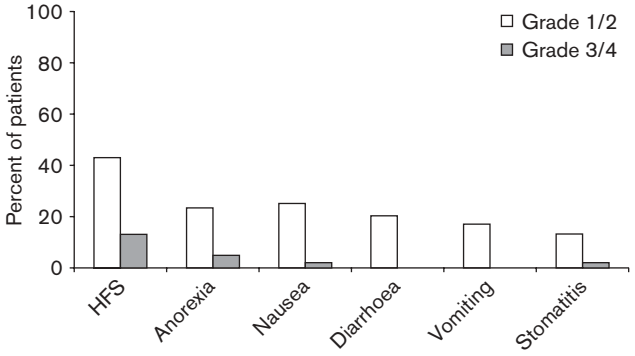
[a]Inadequate post-baseline observation.

Fig. 1



Overall survival ($n=60$).

Fig. 2



Common treatment-related clinical adverse events (more than 15% of patients).

decreased hemoglobin (50%), increased AST (GOT) (38%), hyperbilirubinemia (37%), hyperglycemia (37%), decreased hematocrit (37%), leukopenia (32%) and granulocytopenia (30%). Common grade 3/4 drug-related laboratory abnormalities were lymphopenia (43%) and hyperbilirubinemia (23%).

Treatment was discontinued in eight patients due to drug-related adverse events (increased bilirubin levels in three patients, HFS in two patients, and anorexia, rupture of abdominal aortic aneurysm and gastric perforation in one patient each). Dose reduction was needed in three patients with HFS, and one patient with grade 2 leukopenia and granulocytopenia. One patient died from rupture of an abdominal aortic aneurysm after the third cycle of treatment and this case was considered to be a treatment-related death.

Discussion

Capecitabine has shown consistently good efficacy and tolerability in solid tumors, especially in colorectal cancer [13,14] and breast cancer [15–17]. In addition, capecitabine offers the convenience of oral administration and has an improved tolerability profile compared with i.v. bolus 5-FU, resulting in less resource utilization in metastatic colorectal cancer [18,19]. There are also several promising reports of capecitabine monotherapy [20,21] and combination therapy [22,23] in advanced gastric cancer. Currently, a couple of phase III trials including capecitabine combination regimens are ongoing in Korea and the UK [24]. Most of these trials are based on a 3-week capecitabine schedule (2 weeks on and 1 week off).

We conducted a phase II study with a 4-week regimen of capecitabine (given on days 1–21) according to the recommendation of a Japanese phase I study [9], and showed that this regimen was active and well tolerated in advanced gastric cancer. The RR was 26%, median TTP was 3.4 months and median overall survival was 10.0 months. These efficacy results seem to be similar to those reported with the 3-week regimen of capecitabine in Korea ($n=44$, RR 32%, median TTP 3.1 months and median overall survival 9.5 months) [20] and Mexico ($n=18$, RR 25%, median TTP 21 weeks, and median overall survival 6.5 months) [21]. Although the dose intensity of capecitabine was lower in this study (median 1870 mg/day) than in the Korean study (median 3542 mg/day) which used the 3-week schedule [20], the median cumulative dose in our study (190 g) was almost equivalent to that in Korean study (183 g). This would account for the similar efficacy observed in both studies.

In terms of safety, the majority of treatment-related adverse events were grade 1 or 2. The predominant treatment-related grade 3/4 adverse event was HFS (13%) – a well-known adverse event associated with chronic fluoropyrimidine exposure and one of the most common adverse events associated with capecitabine treatment [19]. The prevalence and degree of HFS in this study were similar to those reported with the 3-week

regimen [20,21]. HFS was, however, never life threatening, and was managed relatively easily with therapy interruption and dose reduction. It is noteworthy that no patients experienced grade 3/4 diarrhea or vomiting in the present study with the 4-week regimen. This could be due to the different dose and schedule used or ethnic differences. The prevalence of severe diarrhea with capecitabine was lower in Japanese than in Caucasians in previous studies [6,7,9,10].

Although various laboratory abnormalities were observed, frequently occurring (more than 10%) treatment-related grade 3/4 abnormalities were limited to only two events, i.e. lymphopenia (43%) and hyperbilirubinemia (23%). In the current study, lymphocyte count was not specified in the inclusion criteria and most patients already had grade 1 or greater lymphopenia at baseline. However, grade 3/4 leukopenia was not observed and grade 3/4 granulocytopenia was seen in only one patient. The reason for the high incidence of hyperbilirubinemia observed in the present study was due to the toxicity criteria used. Specifically, the definition of grade 3 hyperbilirubinemia according to NCIC-CTC criteria is 1.5–3 × ULN. On the other hand, the grade 3 criterion according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 [25] is more than 3–10 × ULN. If this study was reviewed according to NCI-CTC criteria, the incidence of grade 3/4 hyperbilirubinemia would have been 8% and it is similar to that reported with other oral fluoropyrimidines [26]. From these results, the current regimen seems quite feasible in the treatment of advanced gastric cancer, although the data are not yet adequate to compare the safety profiles of the 3- and 4-week regimens.

Consequently, the efficacy and safety findings of the present study suggest that a 4-week regimen of capecitabine is a suitable alternative to the standard 3-week regimen. Further investigation of this regimen in advanced gastric cancer is warranted.

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