Original article

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A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer

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Background: Capecitabine (Xeloda®) is a novel, oral, selectively tumor-activated fluoropyrimidine with proven activity in the treatment of advanced colorectal cancer. This trial was conducted to evaluate the efficacy, safety and feasibility of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer, with a view to replacing 5-fluorouracil (5-FU) in such patients.

Patients and methods: Forty-four patients received capecitabine 1250 mg/m^2 twice daily (2500 mg/m^2/day) for 14 days followed by 7 days of rest, for up to six cycles.

Results: Capecitabine produced an objective response rate of 34% (all partial responses) and stable disease in 14 patients (30%). The median time to disease progression (TTP) was 3.2 months [95% confidence interval (CI) 2.7–6.4 months] and median overall survival was 9.5 months (95% CI 6.9–13.2 months). Hand-foot syndrome (HFS), nausea, anorexia, diarrhea and vomiting were the most common adverse events. While HFS was the most frequent grade 3/4 toxicity (National Cancer Institute Common Toxicity Criteria), only 9% of patients experienced grade 3 HFS. Severe myelosuppression was not reported during the study.

Conclusions: Capecitabine monotherapy is active and well tolerated as first-line therapy in patients with advanced/metastatic gastric cancer. Larger comparative trials investigating capecitabine-based combination regimens in patients with advanced gastric cancer are warranted.

Key words: capecitabine, gastric cancer, metastatic, untreated

Introduction

Gastric cancer is the most frequently diagnosed cancer and one of the leading causes of cancer-related death in Korea [1]. While 5-fluorouracil (5-FU) is the most effective single agent, objective responses tend to be <20%, and of partial and short duration. Continuous infusions of 5-FU are more active than intravenous bolus administration, but impracticality limits their use. Capecitabine (Xeloda®) is a selective, oral fluoropyrimidine carbamate that generates 5-FU selectively in tumor tissues. This selectivity is achieved by the enzyme thymidine phosphorylase (TP), which is responsible for the final conversion of capecitabine to 5-FU and is found at much higher levels in gastric cancers than in normal tissues [2–5]. Capecitabine offers the possibility of continuous tumor exposure to 5-FU by preferential activation at the tumor site, while potentially minimizing the exposure of healthy body tissues to systemic 5-FU.

In a Japanese clinical trial of 60 patients with previously untreated advanced and metastatic gastric cancer, intermittent capecitabine (828 mg/m^2 twice daily for 3 weeks followed by 1 week of rest) led to a response rate of 25.5% and a median survival of 8.8 months [6]. A similar response rate (24%) has been observed following administration of capecitabine in combination with epirubicin and cisplatin in 29 patients with inoperable esophago-gastric adenocarcinoma [7]. In both studies, capecitabine-based therapy was well tolerated. To investigate further the potential of capecitabine in this setting, we evaluated the efficacy and safety of the global standard 3-weekly intermittent capecitabine regimen in an open-label, multicenter, non-comparative, phase II study of previously untreated patients with advanced and/or metastatic gastric cancer.

Patients and methods

Eligible patients were between 18 and 75 years of age, and had histologically or pathologically confirmed advanced or metastatic, bidimensionally measurable gastric cancer not amenable to curative surgery [World Health Organization (WHO) criteria]. Patients were required to have a Karnofsky performance status (KPS) ≥70%, adequate renal, hepatic

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and hematological functions, and a life expectancy of >3 months. All patients gave written informed consent to participate. The protocol was approved by the Korean Food and Drug Administration (FDA) and recognized institutional review boards of each participating institution, and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

A detailed medical history, physical and neurologic examinations, chest X-ray, spiral computed tomographic (CT) scan of the abdomen, electrocardiogram, and pregnancy test for women were performed within the 2 weeks before study commencement. Run-in procedures, including vital signs and clinical laboratory tests were performed within 7 days before the start of chemotherapy.

Patients received oral capecitabine 1250 mg/m^2 approximately every 12 h for 2 weeks, followed by 1 week of rest, every 3 weeks. Capecitabine was supplied as film-coated tablets in two dose strengths (150 and 500 mg tablets), which patients were instructed not to split. Patients with complete remission (CR), partial remission (PR) or stable disease (SD), and who were tolerating treatment well, were treated for up to six cycles. Those with clearly documented progressive disease (PD) were taken off treatment at the time of progression. Responding patients (CR or PR) or those with SD after 18 weeks were followed until PD, and were able to continue on capecitabine at the discretion of the investigator. Treatment doses were not interrupted or reduced because of toxicities considered by the investigator to be unlikely to become serious or life-threatening. The dosage was adjusted or interrupted for treatment-related adverse events of grade ≥2 based on a defined algorithm [8].

Tumor assessments, according to WHO criteria [9] were performed at 6-week intervals by the investigators and an Independent Review Committee (IRC). Tumor lesions were assessed by CT scan, X-rays or magnetic resonance imaging (MRI), and objective tumor response was based on the dimensions of measurable marker lesions, measured by the same radiologist throughout the study. TTP was calculated as the time from the first treatment to the time the patient was first recorded as having PD, or the date of death if the patient died before PD was demonstrated. Survival was monitored every 3 months after the patient completed treatment.

Safety was monitored throughout the study and for 28 days after the last study treatment. Adverse events were graded according to the National Cancer Institute of Common Toxicity Criteria. Hand-foot syndrome (HFS) was graded as in previous capecitabine studies [10]. Patients were educated to recognize grade ≥2 toxicity and to interrupt capecitabine until further instructed by their physician.

The response rate was expected to be ∼25% based on data from a previous Japanese phase II trial [6]. A sample size of 38 was calculated by Fleming's single-stage design [11] to ensure at least 80% power for proving lack of efficacy if the true response rate was <25%. Estimating a drop-out rate of 15%, a total of 44 patients were recruited to ensure that at least 38 patients were evaluable. TTP and survival were analyzed by the Kaplan–Meier product limit method. Patients who received at least one dose of study medication were included in the intention-to-treat (ITT) analysis. Those who did not receive at least one dose of study medication or for whom no follow-up safety information was available were excluded from the safety analysis.

Results

Patient characteristics

Of the 45 patients who were enrolled at four centers, 44 patients (35 men, nine women) received at least one dose of capecitabine and were evaluable for efficacy and safety (ITT population). One patient withdrew consent during the screening period and did not receive capecitabine. As shown in Table 1, the majority of patients (93%) had stage IV disease and 59% had two or more metastatic sites, the most commonly affected sites being the lymph nodes (86%) and the liver (45%). Twenty-three percent of patients had undergone one or more type of surgery.

Table 1. Patient characteristics

	n (%)[a]
Total number of patients treated	44
Age (years)	
Median	62
Range	25–72
Sex	
Male	35 (80)
Female	9 (20)
Karnofsky performance status (%)	
Median	90
Range	70–100
Disease stage	
IIIB	3 (7)
IV	41 (93)
Disease site	
Lymph node	38 (86)
Liver	20 (45)
Peritoneum	12 (27)
Lung	3 (7)
Number of metastatic sites	
0	0 (0)
1	18 (41)
2	17 (39)
≥3	9 (20)
Patients with one or more surgical intervention	10 (23)

[a]Unless otherwise stated.

Efficacy

Fifteen of the 44 patients [34%; 95% confidence interval (CI) 20%–50%] had a PR and 13 patients (30%) had SD (investigator-determined responses; Table 2). The IRC determined that 14 patients (32%; 95% CI 19%–48%) had PR and 14 (32%) had SD (Table 2). The median TTP was 3.1 months (95% CI 2.7–6.3 months) and the median overall survival was 9.5 months (95% CI 6.9–13.2 months) (Figure 1).

The median duration of treatment for all patients entered in the study was 61 days (range 7–196 days). Sixteen (36%) patients were treated for at least 18 weeks; of these, eight (18%) were treated for >18 weeks in the continuation phase. The median dose-intensity was 3541.5 mg/day and the median cumulative dose of capecitabine was 182.5 g.

Table 2. Efficacy data (intention-to-treat population, $n = 44$)

	n (%)[a]	95% CI (%)
Investigator-assessed response		
Overall best response (CR+PR)[b]	15 (34)	20–50
Complete response	0 (0)	–
Stable disease	13 (30)	17–45
Progressive disease	12 (27)	15–43
Median TTP (months)	3.1	2.7–6.3
IRC-assessed response		
Overall best response (CR+PR)[b]	14 (32)	19–48
Stable disease	14 (32)	19–48

[a]Unless otherwise stated.
[b]World Health Organization criteria.
CI, confidence interval; CR, complete remission; PR, partial remission; TTP, time to disease progression; IRC, Independent Review Committee.

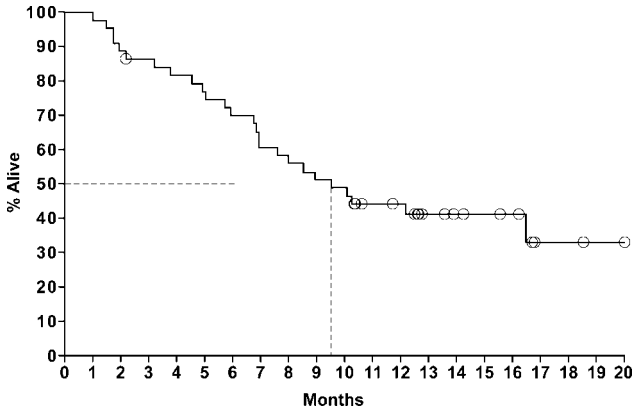

Figure 1. Survival curve for all patients. Open circles indicate censored observations.

Safety

The most common treatment-related clinical adverse events were HFS (68%), nausea (27%), diarrhea (27%) and anorexia (21%). Most events were mild to moderate in severity and did not exceed grade 2 (Figure 2). The predominant grade 3 toxicities were HFS, diarrhea and anorexia. One patient experienced a grade 4 genital rash, although no other grade 4 toxicity or toxicity-related deaths were reported. The most common events leading to treatment modification were HFS, nausea, vomiting, diarrhea, leukopenia and pyrexia.

Most clinical hematological and laboratory values were stable or worsened by only one grade. Importantly, grade 3/4 myelosuppression (neutropenia, lymphocytopenia or anemia) was not observed in any of the patients. The most common grade 3 laboratory abnormality was a change in serum sodium level (5%). No patient discontinued treatment because of abnormal laboratory values.

There were 23 deaths reported during the study, the majority of which occurred >28 days after the end of the planned treatment schedule. All of the deaths were related to PD.

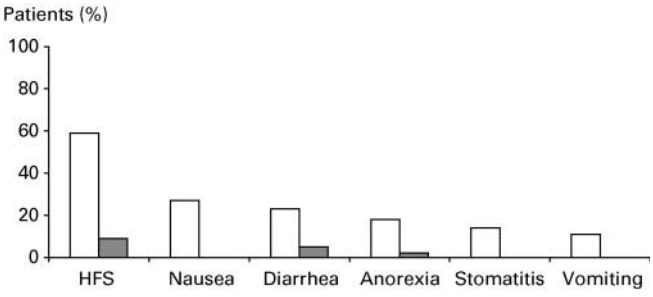

Figure 2. Most common treatment-related adverse events (>10% of patients). Open bars, grade 1/2 events; filled bars, grade 3/4 events.

Discussion

The current findings show that capecitabine is active and well tolerated as first-line treatment in patients with advanced and/or metastatic gastric cancer. Despite overlapping confidence intervals, our objective response rate of 34% compares well with rates reported previously for other single agents in patients with gastric cancer [12], including a less dose-intensive Japanese regimen of capecitabine (828 mg/m^2 twice daily on days 1–21 of a 4-week cycle) [6]. While the usual limitations of cross-study comparisons should be taken into account when interpreting efficacy results, it is interesting to note that the response rate is also comparable to the 28% observed in 30 patients receiving docetaxel and 5-FU/LV (leucovorin) for locally advanced and/or metastatic gastric cancer in a recent Spanish phase II trial [13], and the 47% response rate achieved with infusional 5-FU, cisplatin and mitomycin C in 45 patients with advanced/metastatic gastric cancer in a recent Italian phase II study [14]. While interpretation of survival data in such a small group of patients is difficult because of selection bias, the median survival time for patients receiving capecitabine in the current study (9.5 months) is comparable to the times previously reported for docetaxel and 5-FU/LV (7.7 months) and infusional 5-FU/cisplatin/mitomycin C (11.0 months) in the first-line setting [13, 14]. However, larger, randomized trials are required to confirm these findings.

The median treatment duration was 61 days (range 7–196 days) and the mean relative dose intensity was 91%, which is higher than that reported in previous studies in colon cancer [15] and gastric cancer [6, 7]. The higher dose intensity in the current study might be one of the possible explanations for our higher response rate compared with the previous Japanese trial reported by Kondo, in which patients received a lower dose 4-weekly regimen [6]. It is also important to acknowledge that 10 patients (23%) had undergone one or more surgical intervention for gastric cancer, which could impact on the absorption of orally administered drugs. While there are no pharmacokinetic data on the use of capecitabine in patients following gastric surgery [16], neither our findings nor those from previous studies of capecitabine suggest that previous surgery impacts on the efficacy of capecitabine in this setting.

The safety profile of capecitabine in this trial is similar to that observed with a 4-weekly capecitabine regimen in

patients with advanced/metastatic gastric cancer [6], capecitabine plus epirubicin, and cisplatin in patients with inoperable esophago-gastric adenocarcinoma [7], and compares favorably with that of 5-FU-based regimens in similar patient populations [13, 14]. Importantly, very few patients (5%) experienced grade 3 diarrhea, and capecitabine was minimally myelosuppressive and did not cause significant hair loss. The predominant treatment-related grade 3 adverse event was HFS (9%), which is a well known adverse event related to chronic fluoropyrimidine exposure, and is one of the most commonly reported adverse events following treatment with capecitabine [17]. HFS is manageable with therapy interruption and, if necessary, dose reduction, and is never life threatening.

These efficacy and safety findings, together with the striking 9:1 patient preference for oral rather than i.v. chemotherapy as treatment for late-stage disease [18–20], indicate that capecitabine is unique among currently available treatments for gastric cancer in that it is compatible with oral, patient-oriented, home-based therapy. Larger, randomized trials of capecitabine, either as a single agent or in combination with other highly active drugs, possibly incorporating pharmacoeconomic and quality of life end points, are clearly warranted in the first-line setting. Ongoing phase III trials include a Korean study of capecitabine/cisplatin versus 5-FU/cisplatin in patients with previously untreated advanced/metastatic gastric cancer, and a UK, four-arm trial evaluating capecitabine plus 5-FU and oxaliplatin plus cisplatin in patients with advanced esophago-gastric cancer [21].

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