Phase II study of capecitabine plus cisplatin in patients with gastric cancer

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A phase II study was conducted to assess the efficacy and toxicity of combination therapy with capecitabine and cisplatin in patients with de-novo advanced gastric cancer, and in patients with refractory/recurrent gastric cancer after previous nonplatinum-based therapy. Sixty-four patients were enrolled in the study. Of these, 50 patients had untreated gastric cancer, and 14 had received previous therapy with nonplatinum-based therapy. All patients received oral capecitabine 1250 mg/m^2 twice daily, days 1–14, and intravenous cisplatin 60 mg/m^2 on day 1. This cycle was repeated every 3 weeks. Among the 50 previously untreated patients, three achieved complete response, and 19 had partial response, giving a response rate of 44% in the intention-to-treat population. The median time to progression and median overall survival were 6 months [95% confidence interval (CI): 1.4–10.6] and 9 months (95% CI: 5.7–12.3), respectively. In patients who had received previous therapy, clinical usefulness was evaluated resulting in response rate of 14%, disease control rate of 28.5%, and median overall survival of 4 months (95% CI: 3.1–4.9). The principal grade 3/4 adverse events were neutropenia (20%), anemia (14%). No neutropenic fever or treatment-related deaths. Capecitabine in combination with cisplatin is effective and well tolerated as first-line treatment in patients with advanced gastric cancer. Unfortunately, we could not positively suggest the usefulness of the same combination regimen as salvage therapy in patients with progressive or recurrent disease after nonplatinum-based therapy.
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Introduction

Worldwide, gastric cancer is estimated to be the fourth most common type of cancer and the second most frequent cause of cancer-related mortality. The incidence of gastric cancer is particularly high in Asia, South America, and Eastern Europe. In Japan, gastric cancer is the most common cause of cancer death [1].

To date, palliative chemotherapy has been the only reasonable therapeutic option for patients with recurrent or unresectable advanced gastric cancer (AGC). Multiple single-agent chemotherapies have been shown to be only modestly effective in advanced disease, and the search for the best combination of therapy has been difficult. Small, randomized trials comparing chemotherapy with best supportive care in AGC provide consistent evidence that cytotoxic treatment is of some benefit [2–5]. Chemotherapy using the 5-fluorouracil (5-FU), epirubicin, and methotrexate (FEMTX); 5-FU, doxorubicin, and methotrexate (FAMTX); or etoposide, leucovorin, and 5-FU (ELF) regimens increased median survival to 7–10 months from 3–4 months with best supportive care.

Combinations of 5-FU and cisplatin (FP) have been tried extensively in AGC and suggested to be more effective than single agents or other drug combinations. In a phase III Korean trial, an FP regimen produced improved response rates (RRs) compared with 5-FU, doxorubicin, and mitomycin (FAM), or 5-FU monotherapy, although overall survival (OS) did not differ among the three groups [6]. This trend of superiority of the FP regimen was also suggested by a European phase III trial, which compared it with FAMTX or etoposide, leucovorin, and bolus 5-FU (ELF) [7].

In a randomized trial conducted in the United Kingdom, FAMTX, the accepted reference regimen, was compared with ECF [8]. ECF is a regimen that includes 5-FU, cisplatin, and epirubicin. Preclinical data suggest synergy between cisplatin and 5-FU, and higher RRs have been seen in colorectal cancer using infusional rather than bolus 5-FU, which may, in part, explain the improved results seen in ECF. ECF produced a higher RR (45 vs. 21%), a longer time to progression (TTP) (7.4 vs. 3.4 months), and a significantly longer median survival (8.9 vs. 5.8 months). However, catheters and pumps are necessary for the administration of protracted infusion 5-FU, requiring frequent outpatient visits or admission during which a schedule of short infusions is administered.

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These factors add to the cost, morbidity, and the inconvenience of treatment.

The oral fluoropyrimidine capecitabine (*N*4-pentoxylcarbonyl-5-deoxy-5-fluorocytidine; Xeloda; Hoffmann-La Roche Ltd, Basel, Switzerland) was designed to generate 5-FU preferentially in tumor tissue and to mimic continuously infused 5-FU without the complications and inconvenience associated with central venous access. With capecitabine, 5-FU is generated preferentially in tumor tissue through high intratumoral concentrations of thymidine phosphorylase [9,10].

Several phase II trials [11–13] have evaluated the efficacy and safety of capecitabine as a single agent for the treatment of gastric cancer. Hong *et al.* [11] treated patients with oral capecitabine 1250 mg/m^2 twice daily for 2 weeks on and 1 week off, whereas Sakamoto *et al.* [14] treated patients with a reduced dose of capecitabine 828 mg/m^2 twice daily for 3 weeks on and 1 week off. In both trials, capecitabine was active as well as well tolerated. In addition, capecitabine showed activity in a preclinical xenograft model of a 5-FU-resistant tumor [15].

As oral capecitabine is a highly active single agent and its safety profile differs from that of cisplatin with little overlap of key toxicities, capecitabine combined with cisplatin is an appealing and convenient alternative to 5-FU/cisplatin. Several phase II trials have used the labeled dose of capecitabine (1250 mg/m^2 twice daily for 2 weeks on and 1 week off) with cisplatin 60 mg/m^2 on day 1 in 3-week cycles for untreated patients with AGC [16–18]. The combination was active, with RRs ranging from 28 to 55%. The results of these trials suggest that capecitabine and cisplatin showed a very promising preliminary antitumor activity, well tolerated, and have good feasibility and toxicity profile, with convenient administration as a first-line treatment.

In view of these beneficial effects, we conducted a phase II study to evaluate the efficacy and toxicity of combined capecitabine and cisplatin in patients with previously untreated AGC, and patients with resistant/recurrent gastric cancer who had received no prior treatment with platinum compounds.

Patients and methods

Patient characteristics

Patients were eligible, if they had histologically confirmed advanced or metastatic gastric adenocarcinoma with at least one unidimensionally measurable lesion (i.e. with at least one diameter ≥ 2 cm, as assessed by physical or radiographic examination including chest radiograph or computed tomography scan). Patients were ≥ 18 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group scale. Patients had untreated disease, or disease recurring or progressing after prior therapy that contained no platinum compounds. Adequate hematological (hemoglobin ≥ 9 g/dl, absolute neutrophil count $\geq 2 \times 10^9$/l, and platelet count $\geq 100 \times 10^9$/l), hepatic (total bilirubin ≤ 1.5 mg/dl, serum transaminases $\leq 3 \times$ upper normal limit or $\leq 5 \times$ upper normal limit in cases of hepatic metastases), and renal (serum creatinine ≤ 1.5 mg/dl) functions were required. Patients with unresolved bowel obstruction or malabsorption syndrome were excluded. The protocol was approved by the institutional review board.

Treatment schedule and toxicity assessment

Capecitabine was administered orally at a dose of 1250 mg/m^2 twice daily according to the standard intermittent schedule (14 days of treatment followed by a 7-day rest period). Cisplatin was administered intravenously at a dose of 60 mg/m^2 for 1 h (before the first dose of capecitabine) with a standard hydration method on day 1, and repeated every 3 weeks. Ondansetron and dexamethasone were routinely used for the prevention of emesis before the administration of cisplatin. In addition, intravenous furosemide (20 mg) was given 30 min before infusing cisplatin. Treatment was continued until disease progression or unacceptable toxicity, or if the patient chose to discontinue treatment. Toxicity was evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Pretreatment, follow-up, and response evaluation

Physical examination, chest radiographs, complete blood counts, and biochemical tests were performed before each chemotherapy cycle. Computed tomography scans were performed every two to three cycles until the tumor progressed. Tumor response was classified on the basis of the response evaluation criteria in solid tumors guidelines [19].

Statistical analysis

Data were analyzed on a personal computer running SPSS for windows (Statistical Package for Social Scientists, release 15; SPSS Inc., Chicago, Illinois, USA). All tests are considered significant if ($P < 0.05$), all the tests were two-sided tests.

For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables the mean, range, and standard deviation were used to describe central tendency and dispersion. OS and TTP analysis was calculated by the Kaplan–Meier product-limit estimator. Comparison of the survival was performed by the log-rank test. TTP was calculated from the date of entry to the study to the date of progressive disease; OS was measured from the date of entry to the date of last follow-up or death.

Results

Patient characteristics

A total of 64 patients were enrolled between January 2006 and September 2007. Baseline characteristics, which are shown in Table 1, show a relatively standard gastric cancer population (with more males than females). Fifty patients had untreated disease, nine had developed progressive disease while receiving nonplatinum-based therapy in the first-line setting, whereas five had relapsed early after adjuvant treatment with nonplatinum-based therapy. Palliative surgery was carried out in six patients with locally advanced disease and in five patients with metastatic disease. At baseline, 92% of patients had clinical signs and symptoms. The doses of capecitabine and cisplatin were reduced in 22.8% of cycles, in line with the dose reduction criteria. Treatment administration was also delayed for a median of 7 days (range 1–14) in 32 of 292 (11%) cycles.

Efficacy

A total of 58 patients were eligible for efficacy (Table 2), six were excluded from the efficacy analysis because they did not meet eligibility criteria. Among the 50 untreated patients, overall confirmed response was seen in 22 patients, with three patients achieving complete response and 19 patients showing partial response (total RR 44%). Six patients (12%) remained stable, whereas 16 patients (32%) progressed. The median TTP in 28 patients (responsive and stable disease) was 6 months [range: 2–19, SE: 2.4, 95% confidence interval (CI): 1.4–10.6] (Fig. 1), and median OS for all patients was 9 months (range: 2–22, SE: 1.7, 95% CI: 5.7–12.3) (Fig. 2a). The median OS was 19, 9, and 6 months for responsive, stable, and progressive disease, respectively, and the difference was statistically significant ($P < 0.001$) (Fig. 2b).

Evaluation of response in patients who received previous therapy, showed that the objective RR was 14% (2 of 14), two patients (14%) remained stable; TTP was 3 and 4 months among those with responsive disease. One patient with stable disease died after the third cycle as a result of an attack of upper gastrointestinal bleeding, whereas the other had progressed 4 months after completion of six cycles of therapy. Ten patients (71%) progressed and disease control rate (partial response + stable disease) was 28.5% (4 of 14) (Table 2). Median OS was 4 months (range: 2–9 months, 95% CI: 3.4–4.7) (Fig. 3).

Table 1 Patient characteristics

Characteristic	Number	Percentage
Age (years)		
Mean (SD)	53 (11)	
Range	27–70	
Sex		
Male	40	62.5
Female	24	37.5
Performance status (ECOG)		
0	4	6
1	52	81
2	8	13
Location of primary tumor		
Gastroesophageal	14	22
Upper part	5	8
Body	8	13
Antrum	24	38
Diffuse	4	6
Not defined	9	14
Prior therapy ($n=14$)		
5-FU alone	4	28.5
5-FU + MTX	6	43
Others	4	28.5
Disease status		
Locally advanced	20	31
Metastatic	39	61
Recurrent	5	8
Metastatic sites		
Abdominal LN	46	92
Peritoneum	3	6
Liver	18	36
Lung	4	8
Ovary	4	8
Bone	3	6
Cervical LN	2	4
Abdominal wall	1	2
Number of metastatic sites		
Single	23	36
Two sites	19	30
Multiple	22	34

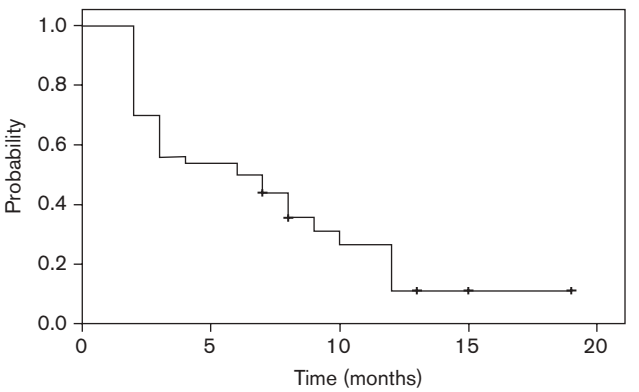
5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; MTX, methotrexate.

Table 2 Tumor response[a]

	No previous therapy ($n=50$)		Prior therapy ($n=14$)	
	Number	Percentage	Number	Percentage
Overall confirmed response	22	44	2	14
Complete response	3	6	0	0
Partial response	19	38	2	14
Stable disease	6	12	2	14
Progressive disease	16	32	10	71
Not assessable	6	12	0	0

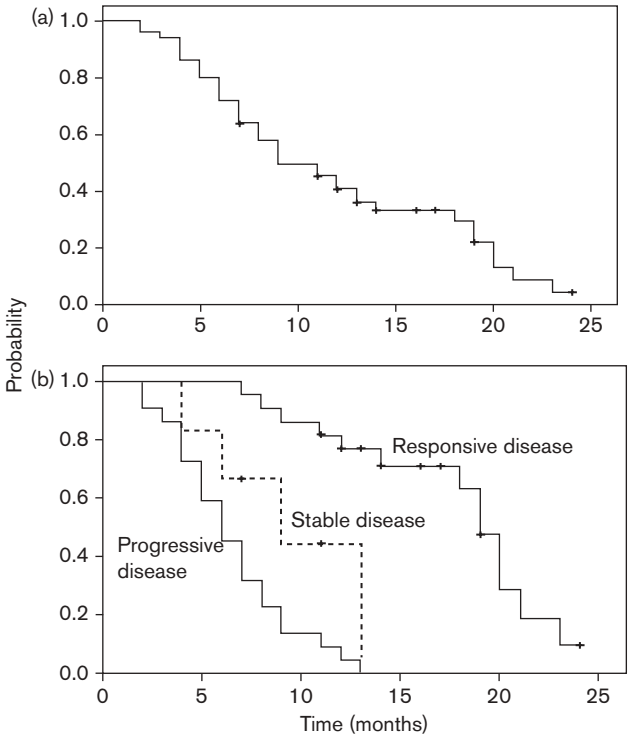
[a]Intention-to-treat analysis.

Fig. 1



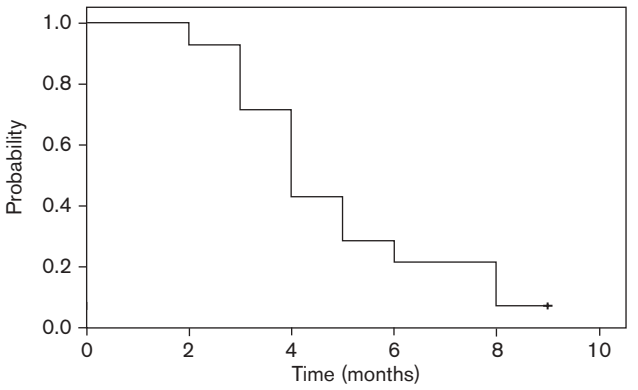
Median time to progression ($n=28$).

Fig. 2



(a) Median overall survival for all patients with no prior therapy ($n=50$). (b) Median overall survival for patients with responsive disease versus stable and progressive disease.

Fig. 3



Median overall survival for patients received previous therapy ($n=14$).

Toxicity

A total of 292 treatment cycles (median 6, range 1–10 cycles) were administered. All patients were evaluable for toxicity (Table 3). The most common treatment-related hematological adverse event was neutropenia, which occurred at grade 3/4 intensity in 13 patients (20%). No patient experienced febrile neutropenia. Grade 3/4 anemia occurred in 14% of patients. Hand–foot syndrome and asthenia were relatively common occurring in 36 (56%), 35 (55%) patients respectively. Hand–foot syndrome was noticed mainly after the second (33%) and third (28%) cycles of therapy. Frequent gastrointestinal toxicities [anorexia (53%), nausea and vomiting (47%), mucositis (33%), and constipation (28%)] were recorded. However, grade 3/4 nonhematological toxicities were infrequent. There were no treatment-related deaths.

Table 3 Hematological and nonhematological toxicities (National Cancer Institute Common Toxicity Criteria, version 3)

	All grades		Grades 3–4	
Adverse events ($n=64$)	Number	Percentage	Number	Percentage
Hematological				
Anemia	26	41	9	14
Neutropenia	24	38	13	20
Thrompocytopenia	8	13	3	5
Nonhematological				
Asthenia	35	55	3	5
Anorexia	34	53	5	8
Nausea/Vomiting	30	47	0	0
Diarrhea	11	17	2	3
Constipation	18	28	0	0
Mucositis	21	33	3	5
Hyperbilirubinemia	11	17	0	0
Elevated transaminases	12	19	0	0
Alopecia	13	20	0	0
Hand–foot syndrome	36	56	2	3
Renal	10	16	0	0

The complication rate was relatively high in patients who received previous therapy; anemia and neutropenia were found in 50% of patients (7 of 14); hand–foot syndrome in 10 patients (71%). Eight patients suffered nausea and vomiting (57%), whereas diarrhea and constipation were recorded in five and eight patients, respectively. Mucositis was found in nine patients (64%); increased bilirubin in four patients (29%); alopecia in three patients (21%), and elevated serum creatinine in four patients (29%).

Discussion

Patients with advanced or metastatic gastric cancer usually show poor general condition, undernourishment, advanced age, and comorbidity. These features can worsen prognosis, lower RR and survival, and increase toxicity, although these factors do not formally contraindicate chemotherapy.

The combination of capecitabine and cisplatin has been tested in several malignancies, including gastric [16–18], biliary [20], and head and neck cancer [21,22]. Using this combination as first-line chemotherapy in patients with AGC, we observed RR of 44%, median TTP of 6 months, and an OS of 9 months, findings within the range of results of other clinical trials [16–18]. In these previous phase II studies, the RR ranged from 28 to 54.8%, and the OS ranged from 10.1 to 11.1 months.

Our results also compares favorably with the reported efficacy of high-dose infusional 5-FU/cisplatin, which was reported to achieve a RR of 37%, median progression-free survival of 6 months and median OS of 9.7 months [23]. The efficacy demonstrated in this study might be a function of additive or synergistic antitumor activity between the two agents also observed in other studies in a variety of gastrointestinal cancers [17,20,24].

This study also showed that using the combination of capecitabine and cisplatin as salvage therapy in patients who progressed or recurred after previous therapy with nonplatinum compounds achieved tumor RR of 14%, disease control rate of 28.5%, and an estimated median OS of 4 months. These results were below the threshold obtained from Kang *et al.* [25], they studied the same regimen in patients with gastric cancer recurrent after fluoropyrimidine-based adjuvant chemotherapy. In their study, the overall RR was 28%, the median TTP and median OS were 5.8 and 11.2 months, respectively. Nevertheless, considering that most of the patients in our study group (eight patients) failed first-line chemotherapy, and had progressive disease, we would not have expected to observe greater RR, and the inferior results obtained in this group of patients could be explained. However, further studies are required to verify these conclusions.

The objective RR with new anticancer agents (irinotecan or docetaxel), used as second-line therapies in AGC, was recorded in the range of 5–27%, and OS times ranging from 3.5 to 10.2 months [26–28]; whereas weekly high-dose infusional 5-FU/leucovorin has been reported to achieve a RR of 18% and a median OS of 5 months [29], which seem to be within the range of results obtained in our study.

In this study, adverse events were generally mild and manageable without the need for hospitalization. There were no treatment-related deaths. The main grade 3/4 adverse event associated with the capecitabine/cisplatin regimen was neutropenia in 20% of patients, which occurs only rarely with single-agent capecitabine [11–14]. Therefore, the incidence of this side effect with the combination may be attributable to cisplatin. Nevertheless, neutropenia was an isolated event, was not associated with fever or infection.

Hand–foot syndrome was common (56%), but severe cases were successfully prevented through strict adherence to dose-modification schedule. Our findings were similar to those observed previously in AGC [6,18]. These data suggest that capecitabine in combination with cisplatin can be administered safely in an outpatient clinic setting.

On the basis of the study results, it can be concluded that the combination of capecitabine and cisplatin is safe, effective, and well tolerated as first-line therapy in patients with local AGC. Unfortunately, we could not positively suggest the usefulness of the same combination regimen as salvage therapy in patients with progressive or recurrent disease after nonplatinum-based therapy.

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