

First-line chemotherapy with capecitabine/oxaliplatin for advanced gastric cancer: A phase I study

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Abstract. Combination chemotherapy with capecitabine and oxaliplatin for gastric cancer (G-XELOX) is considered as a potentially promising regimen. However, the use of the G-XELOX regimen in Japanese patients has not been investigated to date, and recommended doses of G-XELOX for Japanese patients with metastatic gastric cancer have not been established. The aim of the present study was to determine the maximum tolerated dose (MTD) and recommended dose (RD) for systemic chemotherapy with G-XELOX for metastatic gastric cancer. The enrolled patients received systemic chemotherapy with oxaliplatin 130 mg/m² on day 1 and capecitabine 2,000 mg/m²/day, b.i.d. for 14 days, repeated every 3 weeks. A decrease in oxaliplatin dose was planned from start level 1 (130 mg/m²). A total of 6 patients were enrolled between January and July 2015. MTD was not reached at level 1. Oxaliplatin 130 mg/m² in combination with capecitabine 2,000 mg/m²/day b.i.d. could be administered with acceptable toxicity, and

all patients were treated at these doses. One case of grade 3 stomatitis was considered as a dose-limiting toxicity at level 1; however, excluding this case, no grade 3 or 4 non-hematological toxicity was observed. There were no treatment-related deaths. The median relative dose intensity was 71.3% for capecitabine and 92.1% for oxaliplatin. Of the 6 patients, 3 had measurable lesions according to the Response Evaluation Criteria In Solid Tumors; the response rate and disease control rate were both 67%. Therefore, systemic chemotherapy with G-XELOX was well-tolerated by patients with advanced gastric cancer. The RD was defined as oxaliplatin 130 mg/m² in combination with capecitabine 2,000 mg/m²/day b.i.d.

Introduction

Gastric cancer is the fifth most frequently diagnosed malignancy and the third leading cause of cancer-related mortality worldwide (1). Once the disease becomes inoperable, the prognosis for gastric cancer is exceptionally poor. The majority of the cases of inoperable advanced or metastatic gastric cancer (AGC) remain incurable, with a median survival of only 11-14 months, even for patients who undergo chemotherapy (2-4). The standard treatment for AGC currently consists of systemic chemotherapy; however, despite several randomized trials, a consensus standard chemotherapy regimen for AGC has not been established. The combination of fluoropyrimidine and platinum is used worldwide for the treatment of AGC (2,3), and cisplatin plus 5-fluorouracil (FU) or epirubicin plus cisplatin plus 5-FU (ECF) are widely used (5). However, the administration of cisplatin is limited by nephrotoxicity, which is the dose-limiting toxicity of this agent. In Japan, in order to reduce nephrotoxicity, a 24-h hydration period is recommended following administration of cisplatin.

Oxaliplatin, a non-nephrotoxic platinum analog, is reported to be as effective as cisplatin, with a favorable safety profile in patients with AGC (2,4). Furthermore, the oral fluoropyrimidines capecitabine and S-1 have been developed as substitutes for 5-FU, which is administered by continuous infusion via a central venous catheter. Capecitabine (Xeloda, Roche) has been shown to be effective in the treatment of gastric cancer, and is also administered as a combination treatment with

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Abbreviations: G-XELOX, combination chemotherapy with capecitabine and oxaliplatin for advanced gastric cancer; MTD, maximum tolerated dose; RD, recommended dose; b.i.d., twice per day; UMIN, university hospital medical network; RECIST, Response Evaluation Criteria In Solid Tumors; AGC, advanced or metastatic gastric cancer; ECF, epirubicin, cisplatin and 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; ANC, absolute neutrophil count; DLT, dose-limiting toxicity; CT, computed tomography; PFS, progression-free survival; OS, overall survival; RR, response rate; DCR, disease control rate; SOX, S-1 and oxaliplatin; CS, cisplatin plus S-1; REAL-2, randomized ECF for advanced and locally advanced esophagogastric cancer 2

Key words: gastric cancer, systemic chemotherapy, capecitabine, oxaliplatin, XELOX, CapeOx, phase I study

oxaliplatin (6). Capecitabine plus oxaliplatin (G-XELOX) is considered as a standard regimen for AGC. Globally, doses in the G-XELOX regimen consist of capecitabine (1,000 mg/m² twice daily on days 1-14) plus oxaliplatin (130 mg/m² on day 1) every 3 weeks.

However, the use of the G-XELOX regimen in Japanese patients has not been described to date, and recommended doses for Japanese patients with AGC have not been established.

The aim of the present study was to determine the maximum tolerated dose (MTD) and recommended dose (RD) for chemotherapy with oxaliplatin combined with a fixed capecitabine dose in the treatment of AGC.

Patients and methods

Eligibility criteria and patients. The eligibility criteria for inclusion in the present study were as follows: Age ≥ 20 years; histologically confirmed human epidermal growth factor receptor type 2-negative unresectable or recurrent gastric cancer; Eastern Cooperative Oncology Group (ECOG) performance status < 2 ; estimated life expectancy ≥ 3 months; and adequate organ function, as defined by hemoglobin (Hb) ≥ 8 g/dl, absolute neutrophil count (ANC) $\geq 1,500$ /mm³, platelet count $\geq 100,000$ /mm³, total bilirubin ≤ 1.5 mg/dl, serum transaminase level ≤ 100 U/l and creatinine clearance ≥ 40 ml/min. The exclusion criteria were as follows: Contraindication to either drug included in the chemotherapy regimen; evidence of prior history of platinum administration; insufficient oral intake; synchronous or previous malignancy other than carcinoma *in situ*; or severe comorbidities.

This trial was conducted in accordance with the Helsinki Declaration and Good Clinical Practice guidelines, and was approved by the Institutional Review Board of Kobe City Medical Center General Hospital (Kobe, Japan). All the patients were required to provide written informed consent prior to enrolment.

Study design and treatment. Protocol treatment was defined as chemotherapy consisting of capecitabine and oxaliplatin. The patients received capecitabine 1,000 mg/m² b.i.d. on days 1-14 plus oxaliplatin 130 mg/m² every 3 weeks. The study was designed to determine the recommended dose (RD) of chemotherapy. A total of 6 patients were treated at dose level 1 (capecitabine 1,000 mg/m² b.i.d. on days 1-14 and oxaliplatin 130 mg/m² on day 1). If ≥ 3 of the 6 patients experienced a dose-limiting toxicity (DLT), an additional 6 patients were accrued at the next lower dose level (level 0; capecitabine 1,000 mg/m² twice daily on days 1-14 and oxaliplatin 100 mg/m² on day 1). The MTD was defined as the dose at which ≥ 3 of the 6 patients experienced a DLT. Treatment was repeated until disease progression, unacceptable toxicity, or withdrawal of consent. Treatment was delayed if, on the planned day of treatment, the laboratory results included any of the following: ANC $< 1,500$ /mm³, platelet count $< 75,000$ /mm³, Hb < 8 g/dl, serum transaminase > 100 U/l, total bilirubin > 2.0 mg/dl, or serum creatinine > 1.50 mg/dl, or if symptomatic toxicity was present. Patients who could not tolerate oxaliplatin continued to receive capecitabine monotherapy until disease progression or intolerable toxicity. The RD was defined as one dose

level below the MTD. If the MTD was not achieved, even at level 1, it was considered as the RD. DLT was defined as any of the following adverse events occurring in the first cycle: i) Grade 4 neutropenia lasting > 4 days; ii) grade 4 thrombocytopenia ($< 25,000$ /mm³); iii) febrile neutropenia; iv) grade 3 or 4 non-hematological toxicities; v) treatment discontinuation due to adverse events; or vi) treatment-related death. Protocol treatment was administered triweekly until disease progression, unacceptable toxicity, or withdrawal of consent. In patients with pharyngolaryngeal dysesthesia, the duration of oxaliplatin infusion was prolonged from 2-6 h. In the event of grade 4 non-hematological toxicities, treatment was definitively interrupted.

Study assessment. Pretreatment evaluation included a medical history, physical examination, complete blood cell count and serum chemistry tests, esophagogastroduodenoscopy, and chest, abdominal and pelvic computed tomography (CT) scans. Clinical examination and biochemical tests were required before and during each treatment cycle. All images for tumor responses were evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 (7). All adverse events during chemotherapy were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_Quick_Reference_5x7.pdf).

Endpoints and statistical analysis. The primary endpoint in the present study was the MTD and RD of the G-XELOX regimen. Secondary endpoints included toxicities, response rate (RR), progression-free survival (PFS) and overall survival (OS). Safety and efficacy analyses were both conducted in an intention-to-treat population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. All statistical analyses were conducted using the SPSS software package (SPSS 22.0 Inc., IBM Corp., Armonk, NY, USA).

This trial was registered with the University Hospital Medical Information Network (UMIN no 000015951).

Results

Patients. Between January and July 2015, 6 patients were enrolled. The characteristics of the enrolled patients are listed in Table I. The median age was 72 years, 67% of the patients had diffuse-type disease, 50% had multiple organ metastases, and all patients were chemo-naïve. One patient had undergone distal gastrectomy for resection of the primary tumor.

Treatment administration and DLT. A total of 6 patients were enrolled at dose level 1 (capecitabine 1,000 mg/m² b.i.d. on days 1-14 and oxaliplatin 130 mg/m² on day 1). Of the 6 patients administered level 1, 1 patient developed a DLT (grade 3 stomatitis) and, hence, the RD for phase II studies was determined to be capecitabine 1,000 mg/m² b.i.d. on days 1-14 and oxaliplatin 130 mg/m² on day 1.

Toxicity and dose intensity. Toxicity was assessable in all 6 patients. The most severe toxicities throughout the protocol treatment period are listed in Table II. Grade ≥ 3

Table I. Patient characteristics (n=6).

Variables	n	%
Age, years		
Median	72	
Range	65-77	
Sex		
Male	3	50
Female	3	50
ECOG PS		
0	3	50
1	3	50
Primary tumor location		
Upper	3	50
Middle	3	50
Lower	0	0
Histology		
Intestinal	2	33
Diffuse	4	67
Surgery for primary tumor		
Yes	1	17
No	5	83
Prior adjuvant chemotherapy		
Yes	0	0
No	6	100
Metastatic site		
Single	3	50
Multiple	3	50
Peritoneal metastasis		
Yes	1	17
No	5	83
HER2 status		
IHC 0	3	50
IHC 1	2	33
IHC 2/FISH	1	17

ECOG, Eastern Cooperative Oncology Group; PS, performance status; HER2, human epidermal growth factor receptor type 2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization.

thrombocytopenia and febrile neutropenia occurred in 17 and 0% of the patients, respectively. Grade ≥ 3 non-hematological toxicity (stomatitis) only occurred in 1 patient (17%), but it subsided with conservative treatment. Peripheral neuropathy was observed in all patients, but without functional disorders. The median percentage of relative dose intensity delivered during protocol treatment was 71.3% (range, 12.4-100%) for capecitabine and 92.1% (range, 68.3-100%) for oxaliplatin.

Efficacy and treatment continuation. Response was assessable in 5 patients. Of the 6 patients, 3 had measurable lesions according to RECIST; of those 3 patients, 2 had a partial response and 1 had progressive disease, with an RR of 67%

Table II. Maximum toxicity per patient during protocol treatment (n=6).

Adverse events	NCI-CTC grade					
	1	2	3	4	All, %	3/4, %
Hematological						
Leukopenia	3	0	0	0	50	0
Neutropenia	2	1	0	0	50	0
Anemia	6	0	0	0	100	0
Thrombocytopenia	4	0	1	0	83	17
Non-hematological						
Anorexia	3	2	0	0	83	0
Ascites	1	0	0	0	17	0
Cheilitis	0	1	0	0	17	0
Conjunctivitis	0	1	0	0	17	0
Constipation	1	0	0	0	17	0
Diarrhea	2	1	0	0	50	0
Dizziness	1	0	0	0	17	0
Edema	1	0	0	0	17	0
Fatigue	5	1	0	0	100	0
Febrile neutropenia	-	-	0	0	0	0
Hand-foot syndrome	1	0	0	0	17	0
Nausea/vomiting	3	1	0	0	67	0
Neurotoxicity	5	1	0	0	100	0
Pain	2	0	0	0	33	0
Stomatitis	0	0	1	0	17	17

NCI-CTC, national cancer institute common toxicity criteria.

and a disease control rate (DCR) of 67%. The median time to the first dose reduction was 2 cycles (range, 2-3 cycles) in 4 of the 6 patients, commonly due to gastrointestinal toxicities or myelosuppression. Of the 6 patients, 4 discontinued the protocol treatment due to disease progression and 1 due to toxicities. One patient underwent curative resection for primary disease after 11 cycles of protocol treatment and remained alive without disease at the time of writing, >2 years after the initiation of the protocol treatment (last follow-up, April 2017). The median PFS and OS in all the patients were 3.6 and 5.7 months, respectively.

Discussion

To the best of our knowledge, this is the first report of the feasibility and activity of systemic chemotherapy consisting of capecitabine plus oxaliplatin (G-XELOX) in Japanese patients with metastatic gastric cancer. RDs of systemic chemotherapy with capecitabine plus oxaliplatin were defined as oxaliplatin at 130 mg/m² in combination with capecitabine at 2,000 mg/m²/day b.i.d.

Allowing for the small number of patients in this study, the safety of G-XELOX appeared to be promising. The most frequent adverse events were anemia, fatigue and peripheral neurotoxicity. In addition, all 6 patients developed grade 1 anemia. Several patients with advanced gastric cancer experience some degree of anemia, and all 6 patients in this study had the equivalent of grade 1 anemia (<lower limit of

normal, 10.0 g/dl) at enrollment (median, 12.0 g/dl). Grade ≥ 3 toxicities (thrombocytopenia and stomatitis) occurred in 17% of the cases ($n=2$), but both cases resolved. In this study of G-XELOX, all-grade thrombocytopenia occurred in 83% of the cases, and grade 3 thrombocytopenia occurred after 3 cycles of chemotherapy. A phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 (CS) as first-line chemotherapy for AGC, reported that thrombocytopenia at any grade was more frequently observed in the oxaliplatin group (4). Thrombocytopenia is considered to be a characteristic toxicity of oxaliplatin-based regimens compared with cisplatin-based regimens.

A recent phase III study of epirubicin/fluoropyrimidine/platinum triplet (REAL-2) and a phase III study comparing SOX with CS, indicated that oxaliplatin is superior to cisplatin in terms of efficacy as well as tolerability (2,4). The G-XELOX regimen requires only one clinical visit per 3-week cycle for a 2-h infusion of oxaliplatin, conferring a marked advantage regarding disruption of daily life over regimens containing cisplatin, which require hospitalization to ensure hydration.

Although efficacy was not the primary endpoint of the present study, antitumor activity (RR=67% and DCR=67%) was highly promising. A phase II study of G-XELOX achieved an overall RR of 63%, a median PFS of 5.8 months, and a median OS of 11.9 months (8). Although only 3 of our 6 patients had measurable lesions according to RECIST, these results may confirm the efficacy of the G-XELOX regimen in the treatment of gastric cancer. The survival results were unsatisfactory, but may have been affected by the small study size and relatively advanced age of the enrolled patients. Furthermore, proton pump inhibitors (PPIs) may have impaired capecitabine efficacy. A recent analysis of the TRIO-013/LOGiC trial, a phase III randomized trial comparing capecitabine and oxaliplatin, with or without lapatinib, in metastatic gastroesophageal cancer, reported that PPIs negatively affect capecitabine efficacy by possibly raising gastric pH levels, leading to altered dissolution and absorption (9). In the present study, 5 of the 6 patients received PPIs and the remaining patient received a histamine receptor antagonist as gastric acid suppressant at the time of enrolment.

A limitation associated with the study design should also be discussed. Although a de-escalation design was initially planned for this study, the dose of oxaliplatin did not reach the MTD. Therefore, there remains the question whether oxaliplatin doses may be further increased in Japanese patients with advanced gastric cancer.

In conclusion, systemic chemotherapy with the G-XELOX regimen was found to be well-tolerated by patients with AGC. This phase I study demonstrated that the RDs of systemic chemotherapy with oxaliplatin and capecitabine

was oxaliplatin 130 mg/m² in combination with capecitabine 2,000 mg/m²/day b.i.d.. This regimen demonstrated sufficient activity to warrant further phase II studies.

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