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Seven-day capecitabine plus docetaxel and oxaliplatin regimen for the treatment of advanced gastric cancer: A phase-I clinical trial

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Abstract. Docetaxel, cisplatin and 5-fluorouracil (DCF regimen) are currently applied as an effective combination treatment for various human malignancies; however, the efficacy of this regimen is impaired by severe adverse events associated with it. Therefore, better-tolerated regimens with comparable efficiency are required for patients with gastric cancer. To explore such possibilities, a phase-I clinical trial was performed to evaluate the safety and tolerability of a modified regimen replacing cisplatin and 5-fluorouracil with oxaliplatin and capecitabine, respectively (DOX program). The maximum-tolerated dose (MTD) and dose-limited toxicity (DLT) of capecitabine in this regimen were determined and a dose for subsequent phase-II clinical trials was identified. A total of 24 patients with advanced gastric cancer were sequentially enrolled in the present capecitabine dose-escalation trial. The patients were treated with docetaxel and oxaliplatin at fixed doses [75 and 100 mg/m^2, respectively, intravenously, on day 1 (d_1)], and with capecitabine at increasing doses (1,500, 2,000 and 2,500 mg/m^2, per os, d_{1-7}). The MTD of capecitabine was 2,000 mg/m^2 (d_{1-7}), repeated every 21 days for at least two cycles. The most frequent DLTs for this regimen were leukopenia (15/24, 62.5%, all at grade-III/IV) and neutropenia (13/24, 54.2%, all at grade-III/IV), nausea (14/24, 58.3%, all at grade-III) and vomiting (13/24, 54.2%, all at grade-III). The effective rate of the DOX regimen was 75.0% (18/24). Based on the results, the combination of docetaxel (75 mg/m^2, d_1), oxaliplatin (100 mg/m^2, d_1) and capecitabine (2,000 mg/m^2, d_{1-7}) is recommended for a future phase-II trial. While these doses for the DOX regimen were generally well tolerated, the efficacy of this modified regimen in patients with advanced gastric cancer remains to be further evaluated in subsequent phase-II trials.

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Introduction

The combination of docetaxel, cisplatin and 5-fluorouracil (DCF regimen) is currently used to treat human malignant diseases, including various progressive head and neck squamous cell carcinomas and advanced gastric and esophageal cancers (1,2). However, a high incidence of grade III/IV adverse events (AEs) resulting from these compounds works against the therapeutic efficacy of the DCF program (3). Therefore, optimizing the conventional DCF program may lead to a comparable efficacy, but with lower toxicity.

The oral anti-cancer precursor molecule, capecitabine, is metabolized to 5-fluorouracil by thymidine phosphorylase (TP) in tumor cells, and its efficacy has been established in multiple clinical trials (4). It is more effective than (or at least not inferior to) 5-fluorouracil against a variety of malignant solid tumor types (5). Therefore, capecitabine may be ideal for replacing intravenous 5-fluorouracil. Oxaliplatin is a third-generation, platinum-containing anti-cancer drug and several clinical studies have reported that the one-year survival rate of patients who had received an anti-cancer regimen containing oxaliplatin was significantly higher than that of patients who had received cisplatin regimens, while less toxicity was documented (6). In addition, oxaliplatin and docetaxel can increase TP activity in tumor cells (7) and may have a synergistic anti-tumor effect when concurrently applied with capecitabine. Therefore, replacement of cisplatin and 5-fluorouracil in the traditional DCF regimen with oxaliplatin and capecitabine, respectively (DOX regimen) may offer better efficacy and fewer AEs.

In the present phase-I clinical trial, the safety and tolerability of this modified DOX regimen for treating advanced gastric cancer were estimated. Capecitabine was gradually increased from 1,500 mg/m^2 [day 1 (d_1)-d_7], while the dose of the other drugs was kept constant (docetaxel, 75 mg/m^2 and oxaliplatin, 100 mg/m^2, d_1). The present study aimed to determine the dose-limiting toxic dose and maximum tolerated dose (MTD) of the DOX regimen.

Materials and methods

Study design. The present study reported on a single-center, non-randomized, open-label, single-arm phase-I trial enrolling

patients (n=24) with advanced gastric cancer who were seen at the Affiliated Cancer Hospital of Guangxi Medical University (Nanning, China) between October 2009 and December 2012. All of the patients provided written informed consent and the trial was approved by the ethics committee of the Affiliated Cancer Hospital of Guangxi Medical University (Nanning, China). This trial was registered in the Chinese Clinical Trial Registry (ChiCTR-ONRC-13,004,023).

Inclusion criteria were as follows: i) Advanced gastric cancer confirmed histologically or cytologically; ii) no previous treatment with docetaxel, oxaliplatin or capecitabine, and the last chemotherapy cycle completed at least 4 weeks prior to enrollment; iii) an age of 18-70 years; iv) an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤1; v) estimated survival of at least 3 months; vi) blood parameters as follows: White blood cells $\geq 4.0 \times 10^9$/l, absolute neutrophil count $\geq 2.0 \times 10^9$/l, hemoglobin ≥100 g/l, platelets $\geq 100.0 \times 10^{12}$/l; vii) aspartate aminotransferase and alanine aminotransferase ≤2.5 times the upper limit of normal levels in liver function tests, and normal renal function; and viii) written informed consent.

Exclusion criteria were as follows: i) Allergies to docetaxel, oxaliplatin or capecitabine; ii) inability to receive oral capecitabine; iii) malabsorption syndromes; iv) serious heart and liver dysfunction; v) brain metastases; and vii) any other factor rendering the subject unsuitable for the trial. The trial protocol is illustrated in Fig. 1.

Safety evaluation. The medical history of each patient was reviewed and documented, and a physical examination, blood biochemistry, electrocardiograms and other tests were performed seven days prior to initiation of the DOX program. Routine blood examination was performed on d_1, d_{10} and d_{14} of every cycle, and liver and renal function tests were performed every week during treatment. AEs were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0) (8).

Treatment. Dose escalation was performed in cohorts of six patients beginning at an initial capecitabine dose of 1,500 mg/m^2 (750 mg/m^2, per os bidaily) for seven days, docetaxel [75 mg/m^2, intravenous (iv) infusion over 1 h] and oxaliplatin (100 mg/m^2 iv infusion over 2 h) on d_1, within a 21-day cycle. Each cohort was observed for 21 days at the set dose level. If no more than one-third of the patients experienced a dose-limiting toxicity (DLT), a subsequent cohort of nine additional patients was treated at the next higher dose level. Dosing regimens were as follows: Docetaxel, 75 mg/m^2 (d_1), oxaliplatin, 100 mg/m^2 (d_1) and capecitabine was dosed at increasing levels (1,500 mg/m^2 for level 1, 2,000 mg/m^2 for level 2, 2,500 mg/m^2 for level 3 and 3,000 mg/m^2 for level 4, d_{1-7}). DLT was defined as the occurrence of any grade-IV hematological toxicity during the first cycle or any non-hematological grade-III or -IV toxicity, excluding nausea and alopecia, over the 2-week delay prior to the next cycle. Skin toxicity, vomiting and diarrhea were only regarded as DLTs if they remained at grade III or above despite optimal treatment. After recovery from DLTs or other toxicities attributed to the study medication, the patients continued their chemotherapy treatment at a modified appropriate dose. The MTD was defined as the highest dose at which no more than one-third of the patients experienced DLTs. Chemotherapy was discontinued if disease progression or intolerable AEs occurred, or if the patients refused to continue the treatment.

Efficacy evaluation. Physical examination, X-ray and spiral computed tomography were performed to evaluate measurable lesions within 14 days after initiation of therapy. Treatment responses were assessed using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) every 6 weeks (9).

Results

Patient characteristics. Between October 2009 and December 2012, 24 patients with advanced gastric cancer were recruited at the Department of Medical Oncology of the Affiliated Cancer Hospital of Guangxi Medical University (Nanning, China). The demographic data and characteristics of the patients are shown in Table I. All patients completed at least two cycles of chemotherapy with the DOX regimen, and 13 patients completed at least six cycles. The median number of completed chemotherapy cycles was 4.7.

MTD. Table II lists the toxicities observed at each dosing level. No DLTs occurred in the first six-patient cohort (docetaxel, 75 mg/m^2, d_1; oxaliplatin, 100 mg/m^2, d_1; capecitabine, 1,500 mg/m^2, d_{1-7}). Of the nine patients who were treated at level 2 (docetaxel, 75 mg/m^2, d_1; oxaliplatin, 100 mg/m^2, d_1; capecitabine, 2,000 mg/m^2, d_{1-7}), two patients experienced DLTs with grade-IV leukopenia and/or neutropenia. At dose level 3 (docetaxel, 75 mg/m^2, d_1; oxaliplatin, 100 mg/m^2, d_1; capecitabine, 2,500 mg/m^2, d_{1-7}), three patients developed DLTs, which were grade-III nausea and vomiting in one patient and grade-IV leukopenia and neutropenia in the other two patients. Thus, the MTD of capecitabine had been reached and could not be increased further. Accordingly, the recommended dose for the DOX program was docetaxel, 75 mg/m^2, d_1; oxaliplatin, 100 mg/m^2, d_1; and capecitabine, 2,000 mg/m^2, d_{1-7}.

Toxicity. The most common toxicities observed in the present trial were leukopenia (62.5%), and other hematological AEs included neutropenia (13/24, 54.2%) and anemia (5/24, 20.8%). The AEs of the digestive tract included nausea (14/24, 58.3%), vomiting (13/24, 54.2%), anorexia (4/24, 16.7%) and diarrhea (1/24, 4.2%). The majority of the gastrointestinal side effects were grade I/II, although the occurrence of grade-III nausea and vomiting required intravenous nutrition therapy in one patient. Grade-IV leukopenia and neutropenia were observed in two patients treated with capecitabine at 2,500 mg/m^2 (d_{1-7}). After treatment with granulocyte colony-stimulating factor, the symptoms improved, and the patients completed the next chemotherapy cycle with 20% less capecitabine, which prevented additional AEs. Other non-hematological toxicities are listed in Table II.

Efficacy. All of the patients enrolled in the present trial were available for efficacy evaluation after two cycles of chemotherapy. While none of the patients had complete remission, two patients had partial remission (PR), 16 had stable disease and six had progressive disease. Accordingly, the effective rate of the DOX program was 75.0% (18/24).

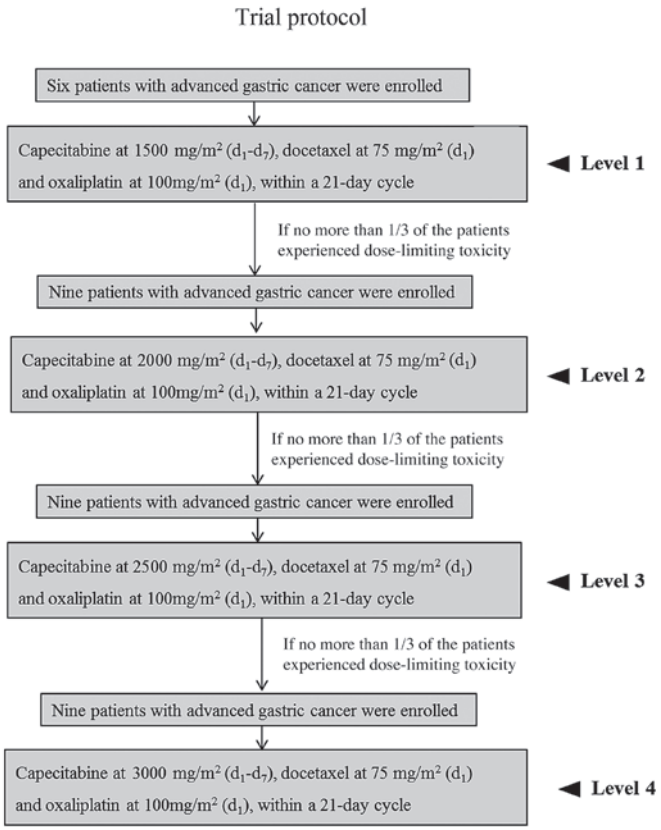

Figure 1. Trial protocol. The design of the present capecitabine dose-escalation trial is illustrated.

Table I. Characteristics of the patients with advanced gastric cancer.

Patient ID[a]	Age (years)	Gender	TNM Stage[b]	ECOG PS[c]	Completed cycles (n)
1-01	62	F	IV (T4N1M1)	1	6
1-02	61	M	III (T4N2M0)	1	6
1-03	48	M	IV (T4N1M1)	1	2
1-04	42	M	IV (T3N1M1)	1	6
1-05	64	M	III (T3N2M0)	0	2
1-06	59	M	III (T3N2M0)	1	5
2-07	59	M	IV (T2N2M1)	1	2
2-08	52	M	III (T2N3M0)	0	6
2-09	64	M	IV (T3N2M1)	1	6
2-10	54	M	III (T4N1M0)	1	4
2-11	69	M	IV (T3N1M1)	1	6
2-12	31	M	III (T4N1M0)	1	8
2-13	54	M	IV (T4N1M1)	1	2
2-14	62	F	IV (T2N2M1)	1	4
2-15	50	M	IV (T4N2M1)	1	4
3-16	45	F	IV (T3N2M1)	1	6
3-17	41	F	IV (T4N1M1)	0	2
3-18	49	M	IV (T3N1M1)	1	2
3-19	62	M	III (T2N3M0)	0	6
3-20	57	M	III (T2N3M0)	0	6
3-21	36	M	IV (T4N1M1)	1	6
3-22	48	F	IV (T3N3M1)	1	6
3-23	41	F	IV (T3N1M1)	1	4
3-24	46	M	IV (T4N1M1)	1	6

[a]Patient identifiers are indicated by the prefix *x-yy*, where *x* denotes the dose level from 1-3 and *yy* denotes the patient number from 01 to 24. [b]According to the American Joint Committee on Cancer TNM staging classification for carcinoma of the stomach (7th edition, 2010). ECOG PS, Eastern Cooperative Oncology Group performance status; M, male; F, female; TNM, tumor-nodes-metastasis.

Discussion

The DCF program has been used as an effective regimen for diverse solid tumor types, including advanced gastric, esophageal as well as head and neck cancers. However, a high incidence (82%) of grade-III-IV neutropenia has been documented with this regimen (1). In addition, cycle delays occurred in 64% of the patients treated with a standard DCF program, and dose reductions were required for 41% of the patients (1). As many as 29.3% of the patients refused to continue the DCF program, and so only 12.2% of the subjects completed eight cycles (10). The prescribed implementation of the DCF regimen was therefore obstructed by its toxicity, particularly in elderly patients (age, ≥65 years) (1). Thus, an alternative chemotherapeutic regimen with a broad spectrum of anti-tumor action, but lacking overlapping mechanisms associated with AEs, is urgently required. In the present study, the DCF protocol was modified by replacing cisplatin and 5-fluorouracil with oxaliplatin and capecitabine, respectively, and the tolerability, treatment-associated toxicity, as well as efficacy of this regimen were then examined.

Oxaliplatin is a third-generation platinum compound, which is as effective as cisplatin, but causes less gastrointestinal reactions and nephrotoxicity (6). Gu *et al* (11) have reported a synergistic effect of oxaliplatin with taxanes. Neurotoxicity is typically responsible for the DLT attributable to oxaliplatin, which manifests as peripheral sensory nerve abnormalities (12). It is well known that the incidence and severity of neurotoxicity induced by oxaliplatin increases in a dose-dependent manner (12). Due to the high incidence rate of neurotoxicity previously observed at doses of 130-200 mg/m^2 (11) the dose of oxaliplatin used in the present study was fixed at 100 mg/m^2. Indeed, in the present study, none of the patients experienced any obvious neurotoxicity at the set oxaliplatin dose.

By contrast, neutropenia is the most frequent AE of docetaxel at 70-75 mg/m^2 as part of combination regimens (13). A prospective randomized trial confirmed that there were no significant differences with regard to survival for patients who received docetaxel at 75 and 100 mg/m^2 as second-line treatments of non-small cell lung cancer (14). In another randomized phase-II clinical trial, docetaxel was reduced from 85 to 75 mg/m^2 due to AEs (10). Thus, in the present study, the dose of docetaxel was fixed at 75 mg/m^2. In the present study, neutropenia was identified in 54.2% of the patients, and was mild and temporary in most patients; however, one patient in the second dose-level cohort, and two patients in the third dose-level cohort, developed grade-IV neutropenia, which required treatment with granulocyte colony-stimulating factor.

Table II. Adverse events according to the NCI-CTC.

Adverse event	Level 1 (n=6) All grades, n (%)	Level 2 (n=9) All grades, n (%)	Level 3 (n=9) All grades, n (%)	Total (n=24) n (%)
Hematological				
Leukopenia	4 (66.7)	5 (55.6)	6 (66.7)	15 (62.5)
Neutropenia	3 (50.0)	5 (55.6)	5 (55.6)	13 (54.2)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	1 (16.7)	3 (33.3)	1 (11.1)	5 (20.8)
Non-hematological				
Nausea	3 (50.0)	4 (44.4)	7 (77.8)	14 (58.3)
Vomiting	3 (50.0)	4 (44.4)	6 (66.7)	13 (54.2)
Anorexia	1 (16.7)	3 (33.3)	0 (0.0)	4 (16.7)
Peripheral neuritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hand-foot syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	1 (11.1)	0 (0.0)	1 (4.2)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	5 (55.6)	5 (20.8)
Impaired hepatic function	0 (0.0)	0 (0.0)	2 (22.2)	2 (8.3)
Mucositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NCI-CTC, common terminology criteria for adverse events established by the National Cancer Institute.

Capecitabine is activated through its conversion into 5-fluorouracil by TP in malignant tissues. In tumor cells, TP is present at higher concentrations compared with normal cells, which enables capecitabine to exert a high anti-tumor efficacy, while exhibiting low toxicity to normal cells. A meta-analysis based on the REAL-2 and ML 17,032 trials compared the efficacy of capecitabine- and 5-fluorouracil-containing regimens in treating advanced stomach and esophageal cancer, revealing a significant superiority of capecitabine in terms of increasing overall survival (OS) and the objective response rate (ORR), whereas no significant difference was identified regarding progression-free survival (15). Capecitabine is an oral drug, and its dose can therefore be adjusted to avert toxicity, rendering it a safer and more convenient therapy. For example, the two patients in the third dose-level cohort who had suffered grade-IV neutropenia were able to complete the next chemotherapy cycle with a reduction of capecitabine by 20%, and this adjustment prevented the reoccurrence of similar AEs. The observations of the present study also suggested that the incidence and severity of neutropenia were associated with the dosage of capecitabine. Of note, docetaxel and oxaliplatin are able to lead to an upregulation of TP expression to enhance the anti-cancer activity of capecitabine, therefore exerting synergic effects (16,17).

The main AEs induced by capecitabine have been identified as gastrointestinal reactions and hand-foot syndrome (7), a finding that was confirmed by the observations of the present study. The standard dosing regimen for capecitabine comprised two doses (1,000 mg/m^2) administered on a daily basis for 14 days, followed by a seven-day interval; this was repeated every 21 days. However, as the majority of the patients treated with capecitabine were not able to complete 14 consecutive days of therapy due to AEs (7), this dosing regimen remains controversial. Previous pre-clinical studies have indicated that continuous administration of capecitabine for approximately seven days offered maximal anti-cancer efficacy, whereas administration beyond this duration only produced more toxicity while not increasing efficacy (18). Amarantidis *et al* (19) used a combination of docetaxel, oxaliplatin and capecitabine as a first-line treatment for advanced gastric cancer. Capecitabine (2,750 mg/m^2) was administered orally, divided into two daily doses given on d_{1-7}. Cycles were repeated every two weeks and this regimen was efficacious and safe. However, a retrospective analysis by Hennessy *et al* (20) suggested that this dose was too high for patients to tolerate. Therefore, in the present phase-I clinical trial, the initial dose of capecitabine was set at 1,500 mg/m^2, divided into two daily doses given at d_{1-7}.

In the present study, none of the patients at dose level 1 (capecitabine, 1,500 mg/m^2) and two of the nine patients at dose level 2 (capecitabine, 2,000 mg/m^2) experienced DLTs. Furthermore, of the nine patients who were treated with capecitabine at 2,500 mg/m^2 (dose level 3), one patient experienced severe nausea and vomiting (grade III) and two developed severe leukopenia and neutropenia (grade IV). Accordingly, the MTD of capecitabine was established at 2,000 mg/m^2. Therefore, the following regimen is recommended for a phase-II trial: Docetaxel (75 mg/m^2, d_1), oxaliplatin (100 mg/m^2, d_1) and capecitabine (2,000 mg/m^2, d_{1-7}).

The combination of docetaxel (25 mg/m^2, d_1 and d_8), oxaliplatin (50 mg/m^2, d_1 and d_8) and capecitabine (1,250 mg/m^2, d_{1-14}) has been demonstrated to be a tolerable and potent day-care regimen for advanced gastroesophageal cancer (21). In addition, a recent study has reported that combination chemotherapy comprising docetaxel (60 mg/m^2, d_1), oxaliplatin (100 mg/m^2, d_1) and capecitabine (1,000 mg/m^2, d_{1-21}) was effective as a first-line treatment for metastatic gastric cancer (22). The present study has revealed that a reduced duration of capecitabine treatment

(from 14 to 7 days) plus docetaxel and oxaliplatin offered comparable efficacy against advanced gastric cancer with tolerable side-effects. In the present study, the effective rate of the DOX regimen was 75%, an outcome similar to that of earlier clinical trials using these drug combinations (23-26), in which the median time to progression and median OS were not inferior to those achieved by the DCF regimen. However, overall clinical outcome for patients treated with the DOX regimen determined by the present study should be evaluated in a phase-II trial to compare it with that for patients treated with other DOX regimens or the conventional DCF regimen.

In conclusion, the recommended doses for the DOX regimen were docetaxel at 75 mg/m^2 (d_1), oxaliplatin at 100 mg/m^2 (d_1) and capecitabine at 2,000 mg/m^2 (d_{1-7}). These doses were generally well tolerated, and the efficacy of this regimen should be evaluated in a phase-II study.

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