Cancer Chemother Pharmacol (2009) 63:213–218
DOI 10.1007/s00280-008-0728-4

ORIGINAL ARTICLE

Phase I dose-escalating study of 24-h continuous infusion of 5-fluorouracil in combination with weekly docetaxel and cisplatin in patients with advanced gastric cancer

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Received: 24 December 2007 / Accepted: 2 March 2008 / Published online: 15 March 2008

Abstract
Purpose To determine the maximum-tolerated dose (MTD) of a 24-h continuous infusion of 5-fluorouracil (5-FU) when administered in combination with a fixed weekly dose of docetaxel and cisplatin in patients with advanced gastric cancer.
Methods Patients with advanced gastric adenocarcinoma ($n = 21$) received a weekly regimen of docetaxel, cisplatin and 5-FU (DCF) for 3 consecutive weeks every 4 weeks. The doses of docetaxel and cisplatin were fixed at 33.3 and 30 mg/m^2, respectively. The dose of 5-FU was increased from a starting dose of 1,000 mg/m^2 to the MTD.
Results A total of 53 cycles of chemotherapy were administered (median = 3 cycles/patient). The MTD of 5-FU was 1,750 mg/m^2. All 21 patients were assessed for toxicity and 19 patients (90%) were evaluated for response. Both grade 3–4 hematologic and non-hematologic toxicities occurred in less than 10% of patients and there were no treatment-related deaths. Among the 19 patients, we observed 1 complete and 4 partial responses for an overall response rate of 26% (95% CI: 6–46%). This rate increased to 39% (95% CI: 12–66%) in 13 chemotherapy-naïve patients.
Conclusions A consecutive weekly DCF regimen at 4-week intervals appears feasible for advanced gastric cancer with a favorable toxicity profile. The recommended doses are 33.3 mg/m^2 of docetaxel, 30 mg/m^2 of cisplatin and 1,500 mg/m^2 of a 24-h continuous intravenous infusion of 5-FU. The response of this weekly regimen in our study was favorable and deserved further investigation in a phase II trial.

Keywords Gastric cancer · Phase I · 5-Fluorouracil · Docetaxel · Cisplatin

Introduction

Advanced gastric cancer remains an incurable disease with a median survival rate of 6–9 months [1]. Combination chemotherapy is largely acknowledged as an effective treatment for patients with unresectable or metastatic gastric cancer. The randomized studies showed that, compared to the best supportive care, chemotherapy improves survival and quality of life for the patients with good performance status [1–3]. Although a large number of combination regimens have been evaluated in clinical trials, it is still hard to determine which is best as a standard treatment protocol.

Recently, docetaxel showed strong anti-cancer activity against gastric cancer in both first- and second-line treatment settings [4–6]. In a multi-center, open-label, randomized, phase III study (V325), compared to the control arm of the CF regimen, a combination of docetaxel, cisplatin and 5-fluorouracil (5-FU) showed higher efficacy in terms of response rate, time to progression and overall survival [7]. According to this clinical trial, combination of docetaxel, cisplatin and 5-FU (DCF) is an effective treatment approach in patients with advanced gastric cancer. But,

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adding docetaxel increases the occurrence of grade 3–4 neutropenia (82 versus 57%) and febrile neutropenia infection (29 versus 12%). Other toxicities of DCF treatment regimen include effects on the gastrointestinal system, especially mucositis and diarrhea. In the V325 study, these two grade 3–4 toxic reactions developed in about 20% of patients in the DCF arm. Both mucositis and diarrhea are dose-limiting toxicities (DLT) of 5-FU (when given by continuous infusion) and are worsened by the addition of docetaxel.

One way of reducing the myelosuppressive toxicity of docetaxel is to administer it weekly. In studies of non-small-cell lung cancer patients, weekly use of docetaxel significantly reduced hematologic toxicity without compromising efficacy [8, 9]. Several studies on colorectal cancer reported low incidences of toxicities for weekly 5-FU administration [10, 11]. Based on those results, a weekly DCF (wDCF) regimen is considered optimal for treating metastatic gastric cancer, but a full-scale clinical assessment is needed. Due to the poor tolerability of the patients with gastric cancer to chemotherapy [7], we conducted a phase I dose-escalating study involving a 24-h continuous infusion of 5-FU in combination with a fixed dose of weekly docetaxel and cisplatin in patients with advanced gastric cancer. The purpose of this study was to determine the maximum-tolerated dose (MTD) of 5-FU and to evaluate the toxicity of the above-described weekly regimen.

Patients and methods

Patients

Patients with histologically confirmed, unresectable, recurrent and/or metastatic gastric adenocarcinoma were eligible for inclusion in this study. Additional inclusion criteria included: age 18–70; ECOG performance status $\leq$2; adequate bone marrow function (absolute neutrophil count and platelet count $\geq 1.5 \times 10^9$ and 75×10^9 L^1, respectively); hepatic function (total serum bilirubin $\leq$1.5 mg/dL, transaminases $\leq$1.5 times upper normal limit) and adequate renal function (calculated creatinine clearance $\geq$60 mL/min). Measurable disease was not mandatory for inclusion in the study. Patients who had previously received chemotherapy were also eligible, except those with prior regimens that contained taxanes, or those who had received a 24-h continuous infusion of 5-FU. Patients were required to have fully recovered from the toxicity of previous chemotherapy treatments except alopecia. The study protocol was approved by the ethics and scientific committees of Cancer Hospital Fudan University and signed informed consent forms were obtained from all patients prior to their enrollment.

Study designs

The treatment regimen consisted of weekly administration of docetaxel and cisplatin, and 24-h continuous infusion of 5-FU on days 1, 8 and 15. This treatment was repeated every 4 weeks and continued until the disease progressed or until unacceptable toxicity developed. Docetaxel was administered at a dose of 33.3 mg/m^2 as an 1-h infusion. Dexamethasone (8 mg p.o. 12 h before docetaxel treatment, 30 min before the docetaxel treatment, and 12 h after docetaxel injection) was given to avoid hypersensitivity reactions and to prevent docetaxel-induced fluid retention. Cisplatin was infused at a dose of 30 mg/m^2 for 30 min after appropriate hydration. The starting dose of 5-FU was 1,000 mg/m^2 as a 24-h continuous infusion. In the absence of DLT, dose escalation in additional cohorts continued at a dose increase of 250 mg/(m^2 dose). All patients received 5-HT3 inhibitors prior to chemotherapy. A peripherally inserted central catheter (PICC) was recommended for intravenous access.

Only the first cycle of treatment was evaluated to determine DLT. DLTs were defined as follows: grade 4 neutropenia and/or thrombocytopenia, any episodes of febrile neutropenia, any grade 3 or 4 non-hematologic toxicities, excluding nausea/vomiting and alopecia. Patients were enrolled in cohorts of three to receive the combination chemotherapy. If one DLT occurred, three additional patients had to be treated at the same dose level. If two or more DLTs occurred at a given dose level, then that level was recorded as the MTD. The dose just below the MTD became the recommended dose for further evaluation. A minimum of six patients was required for establishing the MTD. For patients who had reached a DLT, treatment was resumed at the next lower dose after resolving symptoms of previous toxic reactions.

Patient evaluation

Baseline evaluations included complete medical history, physical examination, chest radiographs, complete blood cell count with differential and platelet counts, complete blood chemistry and an ECG. Computed tomography (CT) scans of the abdomen and pelvis were done at study entry. Additional imaging studies were done whenever clinically indicated. During treatment, complete blood cell counts were routinely done twice a week and performed daily in case of grade 3–4 neutropenia, thrombocytopenia or febrile neutropenia, until hematologic recovery. Blood chemistry analyses and physical examinations were done when clinically indicated. Toxicities were recorded according to the NCI common toxicity criteria (NCI-CTC Version 3.0).

When applicable, imaging studies were done after every two cycles of treatment to evaluate tumor response. Responses were documented according to the RECIST

criteria [12]. Time to progression (TTP) was defined as starting from the date of starting treatment and ending either on the date when disease progression was documented, or on the date of death or of last contact. Overall survival (OS) was defined as starting from the treatment start date and ending on the date of death. The Kaplan–Meier method was used for all survival analyses.

Results

Patient characteristics

Twenty-one patients (12 males and 9 females) with metastatic gastric cancer were enrolled. Patient characteristics are shown in Table 1. All patients were assessable for toxicity and the vast majority (90%) had an ECOG performance status of 0 to 1. Thirteen (62%) patients were initially diagnosed with metastatic disease and seven of eight patients received adjuvant chemotherapy after a curative gastrectomy. Prior to enrollment, palliative chemotherapy had been given to eight (38%) patients and each regimen included one type of fluoropyrimidine. The most common manifestations of disease were tumor at the primary site, lymph node involvement and peritoneal and liver metastases. Nineteen (90%) patients had measurable disease according to the RECIST criteria, whereas two other patients only presented with malignant ascites and pleural effusion.

Table 1 Patient characteristics

Characteristics	*n* (%)
No. of patients	21
Age	
Median	54
Range	22–68
Sex	
Male	12 (57)
Female	9 (43)
ECOG performance status	
0–1	19 (90)
2	2 (10)
Prior surgery	
None	11 (52)
Curative gastrectomy	8 (38)
Palliative gastrectomy	2 (10)
Prior adjuvant chemotherapy	7 (33)
Prior adjuvant radiotherapy	0
Prior palliative chemotherapy	8 (38)
Disease extent	
Locally advanced	0
Metastatic disease	21 (100)
No. of disease sites involved	
1	1 (5)
2	6 (28)
3	10 (48)
≥4	4 (19)
Disease sites	
Stomach	13 (62)
Lymph nodes	18 (86)
Peritoneum	3 (14)
Liver	3 (14)
Lung	2 (10)
Pancreas	2 (10)
Bone	1 (5)
Measurable disease	19 (90)

Toxicity

In total, 53 cycles of chemotherapy were given, with a median of three cycles per patient (range 1–6). Table 2 presents patient accrual and tolerance per dose level. Of three patients enrolled on dose level 1 (5-FU 1,000 mg/m^2), none experienced DLTs. At dose level 2 (5-FU 1,250 mg/m^2) and dose level 3 (5-FU 1,500 mg/m^2), one DLT (grade 3 diarrhea and grade 4 neutropenia) was observed at each dose level (involving 12 patients). Dose escalation thus continued to dose level 4 (5-FU 1,750 mg/m^2). At this level, a heavily treated patient had grade 3 mucositis. Of the three additional patients enrolled, a 43-year-old male developed moderate angina pectoris and palpitations on the third week of treatment. ECG changes suggested inferior myocardial ischemia and echocardiograms and cardiac enzymes were normal. The symptoms resolved spontaneously without medical intervention. Subsequently, the patient received a docetaxel and cisplatin combination regimen and no cardiac events occurred. Since this young patient had no prior history of cardiac disease, the cardiac ischemia was probably due to having reached a DLT of 5-FU. As a result of the two DLTs that occurred at dose level 4, the MTD was considered to have been reached and dose escalation was stopped. Therefore, the recommended dose for further phase II studies of this chemotherapeutic combination was defined as 33.3 mg/m^2 of weekly docetaxel, 30 mg/m^2 of cisplatin and 1,500 mg/m^2 of 24-h continuous 5-FU infusion.

Table 3 shows the incidence rate of major toxic reactions in all treatment cycles. There was no treatment-related mortality. Hematologic toxicity was mild. Grade 3–4 neutropenia and anemia occurred in two patients. No patient experienced febrile neutropenia or neutropenic infection. Non-hematologic toxicity was manageable and grade 3–4 toxicity was uncommon. Two patients with grade 3 muco-

Table 2 Dose-limiting toxicities (DLTs) according to dose level

Dose level	5-FU (mg/m^2)	No. of patients		DLTs	
		Total	With DLT	Event	Grade
1	1,000	3	0	Diarrhea	3
2	1,250	6	1	Neutropenia	4
3	1,500	6	1	Mucositis	3
4	1,750	6	2	Cardiac ischemia	3

Table 4 Tumor response

Response	No. of patients (%)	
	All patients (n = 19)	Chemo-naïve (n = 13)
CR	1 (5)	1 (8)
PR	4 (21)	4 (31)
SD	5 (26)	3 (23)
PD	4 (21)	2 (15)
Not available	5 (26)	3 (23)

sitis or diarrhea recovered fully after appropriate medical management. The docetaxel-related toxic reactions of hyperlacrimation and fluid retention were not observed in all patients. As previously mentioned, one patient developed cardiac ischemia.

Response

Tumor responses are summarized in Table 4. Among the 19 patients with measurable disease, there was one complete response (CR) and there were four partial responses (PR), with an overall response rate of 26% (95% CI: 6–46%). These five patients were all chemo-naïve. When six previously treated patients were excluded, the overall response rate increased to 39% (95% CI: 12–66%). Moreover, five (26%) patients had stable disease (SD) and four had progressive disease (PD).

Five patients (26%) did not undergo a response assessment and three of them developed DLT and dropped out of the protocol treatment process, either due to the patients' refusal to continue or the physician's discretion. Another two patients did not receive further chemotherapy after one cycle; one stopped treatment because of deteriorated performance status and for unknown reasons, the other patient never returned to complete his or her role in the experiment. At the time of this analysis, the median time to progression (TTP) and median overall survival (OS) had not yet been determined.

Discussion

The results of the present phase I study clearly demonstrate that a DCF regimen can be safely and relatively comfortably administered on a weekly basis for 3 consecutive weeks at 4-week intervals. Combined with a fixed dose of docetaxel [33.3 mg/(m^2 week)] and cisplatin [30 mg/(m^2 week)], the recommended dose of 5-FU for further phase II studies is 1,500 mg/(m^2 week). The dose intensity of 5-FU at this level is comparable to that of the standard 5-FU schedule [750 mg/(m^2 day), days 1–5] used in the V325 study [7].

Our study used a fixed dose of weekly docetaxel [33.3 mg/(m^2 week)]. This dose was chosen according to a randomized phase III study which showed that, compared with administering Docetaxel three times per week, a weekly dose of docetaxel, as a second-line treatment for advanced NSCLC, is associated with significantly less

Table 3 Toxicity (worst grade per patient in all cycles)

	Grade																			
	Dose level 1 (n = 3)					Dose level 2 (n = 6)					Dose level 3 (n = 6)					Dose level 4 (n = 6)				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Neutropenia	1	0	2	0	0	3	1	1	1	0	4	0	1	0	1	2	2	2	0	0
Anemi	0	2	0	1	0	2	3	1	0	0	5	0	1	0	0	1	4	0	1	0
Thrombocytopenia	2	1	0	0	0	6	0	0	0	0	5	0	1	0	0	5	1	0	0	0
Mucositis	3	0	0	0	0	6	0	0	0	0	5	0	1	0	0	5	0	0	1	0
Diarrhea	1	1	1	0	0	5	0	0	1	0	2	3	1	0	0	6	0	0	0	0
Nausea	1	1	1	0	0	3	3	0	0	0	2	1	1	1	1	5	0	1	0	0
Vomiting	1	1	1	0	0	5	1	0	0	0	3	0	0	2	1	5	0	1	0	0
Fatigue	3	0	0	0	0	3	2	1	0	0	3	2	1	0	0	5	0	0	1	0
Fluid retention	3	0	0	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0
Hyperlacrimation	3	0	0	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0
Cardiac ischemia	3	0	0	0	0	6	0	0	0	0	6	0	0	0	0	5	0	0	1	0

hematologic toxicity and does not compromise treatment efficacy or quality of life [8]. Two other phase I studies of patients with advanced gastric cancer found that the MTD of docetaxel was 40 mg/m^2 per week [10, 13]. However, both studies showed a much higher incidence of grade 3–4 neutropenia than our study. Furthermore, in the later study, febrile neutropenia occurred in 4 of 19 patients and 1 patient died from septic shock [13]. The dose intensity of docetaxel that was used in our protocol was equivalent to 75 mg/m^2 every 3 weeks, which is typically used in a standard DCF regimen. Only 2 of 21 patients in our study developed grade 3–4 neutropenia and there was no apparent febrile neutropenia.

Another goal of our experimental medication protocol was to alleviate gastrointestinal toxicity by changing the 5-FU administration schedule. In V325 study, 5-FU is administered at the dose of 750 mg/(m^2 day) as a continuous intravenous infusion on day 1 through 5 and grade 3–4 mucositis or diarrhea was reported in about one-fifth of the patients. Based on the experience of treating colorectal cancer with chemotherapy, alteration of the 5-FU infusion level may lead to a different toxicity profile. At least two studies reported mild hematologic and non-hematologic toxicities when 5-FU was used as a 24-h infusion combined with leucovorin (AIO regimen), which may increase both the efficacy of 5-FU and its toxicity [10, 11]. In both studies, less than 10% of patients with colorectal cancer had grade 3–4 mucositis and diarrhea, when they received weekly 5-FU administration. Our results show that, among all 21 patients, only 2 of them developed grade 3 mucositis or diarrhea, which are dose-limiting toxicities from the continuous infusion of 5-FU. Obviously, a modified weekly 5-FU schedule may have contributed to such a low proportion of these two toxicities in our study. Another phase I study with a similar design also concurred with our findings [14]. That study used a weekly DFLP chemotherapy regimen (docetaxel, 5-FU/leucovorin and cisplatin) for 2 consecutive weeks every 3 weeks in patients with advanced gastric cancer. None of the patients in this study developed mucositis or diarrhea of grade 3–4. But the study also showed a high incidence of grade 3–4 neutropenia, occurring in 45% of the patients, which was much higher than our study.

Since 19 (90%) patients had measurable disease levels, a response evaluation could be performed in this patient population. The 26% overall response rate achieved by our weekly DCF regimen is somewhat lower than the response rate (37%) in the V325 study, possibly because patient characteristics in these studies were a bit different [7]. The V325 study only enrolled chemo-naïve patients, while nearly one-third of the patients in the present study had already been receiving prior chemotherapy at the onset of the study. When six previously treated patients were excluded from the analysis, the response rate became 39%, which is in line with the rate in the V325 study. However, due to the small sample size of this phase I trial, we need to confirm the efficacy of this particular weekly DCF regimen in a subsequent phase II study.

In conclusion, the results of this trial indicate that treatment with three consecutive weekly DCF treatments, repeated every 28 days, is a feasible chemotherapy regimen with a favorable toxicity profile. The recommended doses are 33.3 mg/m^2 of docetaxel, 30 mg/m^2 of cisplatin and 1,500 mg/m^2 of a 24-h continuous infusion of 5-FU. The response of this weekly regimen in our study was favorable and deserved further investigation in a phase II trial.

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