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ORIGINAL PAPER

Dose-dense biweekly docetaxel combined with 5-fluorouracil as first-line treatment in advanced gastric cancer: a phase II trial

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Abstract This study evaluated the efficacy, safety and impact on quality of life (QoL) of a dose-dense biweekly regimen of docetaxel and 5-fluorouracil in first-line treatment of advanced gastric cancer (AGC). Eligible patients received docetaxel 60 mg/m^2 and 5-fluorouracil (400 mg/m^2 bolus followed by 2,400 mg/m^2 46-h infusion), fortnightly. Prophylactic use of G-CSF was adopted in all patients. The primary end point was response rate (RR). Secondary end points were progression-free survival (PFS), overall survival (OS), toxicity and QoL. Thirty-nine patients with a median age of 55 (28–80) were included. The RR was 51.3 %. Median PFS and OS were 6.7 and 14.0 months, respectively. The most common adverse events (all grades) were anemia (34, 87.2 %), fatigue (29, 74.4 %), neutropenia (26, 66.7 %), nail change (19, 48.7 %) and liver dysfunction (15, 38.5 %). In QoL analysis, improvements were obtained in seven scales, whereas drops were seen in three scales. Common Grade 3/4 toxicities included anemia (28.2 %), liver dysfunction (7.7 %) and fatigue (7.7 %). This novel regimen is a promising option for AGC, showing high RR, improvement on QoL and acceptable toxicity.

Keywords Advanced gastric cancer · Docetaxel · 5-Fluorouracil · Dose-dense · Quality of life

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Introduction

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer-related death. About 1 million new cases of gastric cancer were diagnosed in 2008, 74 % of which were in Asia and 47 % in China [1]. Patients are most commonly diagnosed with locally advanced or metastatic gastric cancer and are not eligible for curative surgical resection, which was defined as advanced gastric cancer (AGC). Even after surgical resection, about half of patients will relapse [2].

The overall outlook for AGC is still dismal, with a median overall survival (OS) of 9–12 months [3–6]. The mainstay treatment for AGC is chemotherapy, hoping to prolong survival and palliate symptoms. However, benefit from cytotoxic chemotherapy was unsatisfactory, for either the low efficacy or the poor tolerability. Thus, a well-designed chemotherapy regimen with high response rate (RR) and low toxicity is desperately needed in order to

improve the poor prognosis and quality of life (QoL) of AGC.

5-Fluorouracil (5-FU) is the key agent for gastrointestinal malignancies. Prolonged 5-FU infusion significantly increased RR and substantially reduced the incidence of Grade 3/4 neutropenia compared with bolus 5-FU [7, 8]. The biochemical modulation of leucovorin (LV) also produced superior effect over 5-FU alone [9, 10]. The simplified de Gramont regimen which adopted 2-day 5-FU infusion with LV is worthy of investigation on AGC. Docetaxel, one kind of semisynthetic taxanes, which kill cancer cells by binding to microtubules, produced high response and prolonged survival in both monotherapy and combination therapy [3, 11]. In addition, the combination of docetaxel and 5-FU analog could exert potential synergistic actions against human gastric cancer [12]. However, most available studies administered docetaxel every 3 weeks with a high dose intensity, which in turn resulted in poor tolerability. Weekly regimens of docetaxel were relatively easy to tolerate but the patients' costs and overall burden of participating increased as well [13].

Based on these rationales, we designed a phase II trial of a novel dose-dense biweekly regimen of docetaxel in combination of infusional 5-FU, to evaluate the efficacy, safety as well as impact on QoL in the first-line therapy of AGC.

Materials and methods

This was an open-labeled, single-arm, phase II trial. All the patients were treated in the Sixth Affiliated Hospital of Sun Yat-sen University. The protocol was registered at ClinicalTrials.gov (NCT01567618) and approved by the institutional review board ethics committee. All patients signed informed consent before treatment.

Patient eligibility

Eligible patients had histologically confirmed gastric adenocarcinoma and measurable unresectable or metastatic lesions. Patients were 18–80 years of age with Eastern Cooperative Oncology Group performance status (PS) of 0 (normal) to 2 (symptomatic but in bed or chair less than 50 % of waking hours) [14]. No prior chemotherapy for present lesions was allowed. Patients had adequate hematological (absolute neutrophil count $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L), hepatic (total bilirubin <34 μmol/L, transaminase levels <100 or <200 U/L in cases of hepatic metastasis) and renal (creatinine <133 μmol/L) functions, life expectancy >3 months.

Patients were excluded if there was prior surgery within 3 weeks, radiotherapy within 6 weeks, adjuvant chemotherapy within 12 months or any taxane-containing treatment before entering this trial. Patients with bone-only metastasis, symptomatic brain metastasis, other simultaneous systemic anticancer treatments, uncontrolled hypertension, unstable coronary syndrome, cardiac arrhythmia, concurrent malignancies or active infection were also ineligible.

Trial design and treatment

Patients were to receive docetaxel 60 mg/m^2 intravenously over 60 min at day 1, and 5-FU was administrated according to simplified de Gramont regimen (400 mg/m^2 iv bolus followed by 2,400 mg/m^2 46-h protracted iv infusion, every 2 weeks). Trial treatments were stopped by the development of unacceptable toxicity, patient refusal to continue or progressive disease (PD), whichever was earlier. Docetaxel dose reductions to 50 mg/m^2 and then 40 mg/m^2 were permitted in case of any Grade 4 hematological or Grade 3 drug-related non-hematological toxicities. 5-FU total dose reduction to 2,100 mg/m^2 (300 mg/m^2 iv bolus, followed by 1,800 mg/m^2 46-h infusion) was permitted for those experiencing Grade 3 drug-specific non-hematological toxicities. The relationship between toxicity and study drugs were judged by attending physicians. Any subsequent dose re-escalation was not allowed. In case of Grade >1 drug-related toxicity, chemotherapy could be delayed for a maximum of 14 days in the absence of full recovery or resolution to Grade <2.

The primary end point was RR. The secondary end points were progression-free survival (PFS), overall survival (OS), toxicity and quality of life (QoL). RR was defined as complete response (CR) plus partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15]. PFS was calculated from the first day of chemotherapy to the date of PD. OS was calculated from the first day of chemotherapy to the date of death due to any cause or last follow-up visit. All patients included received prophylactic G-CSF support (300 μg/day, on Days 5–10).

Evaluation

Target lesions were assessed every 6 weeks by independent review of contrast-enhanced thorax–abdomen–pelvis computed tomography according to RECIST. Objective responses were confirmed by a second evaluation 4–6 weeks later.

Complete blood cell count and serum chemistries were monitored weekly and biweekly, respectively. Physical examination and routine laboratory tests were performed before each cycle. Adverse events were graded according

to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

QoLs were assessed before treatment and 8 (±1) weeks after the first dose of chemotherapy with EORTC QLQ-C30 questionnaire (version 3.0) [16]. This questionnaire included global health status scales, functional scales and symptom scales. Scores were calculated according to the guidelines, yielding a range of 0–100. A higher score for a functional scale indicated better functioning, while a higher score for a symptom scale indicated a higher level of symptomatology. Incomplete forms were excluded from the QoL analysis.

Statistical analysis

In our study, assuming RR to reject treatment (p0) was 0.3, RR to accept treatment (p1) was 0.5, type I error rate α was 0.05, and power was 0.8. Simon two-stage minimax design [17] called for at most 39 subjects, of which 19 subjects would be enrolled and evaluated at the first stage; a minimum of 7 responses were needed in order to proceed to the second stage, and minimum of 17 responses were required to terminate the study and the treatment will be accepted for further development and trials. RR of 30 % (P0) or lower indicated that the regimen lacks antitumor activity; RR of 50 % (P1) or above would be considered promising. Patients would be evaluated for tolerability and efficacy if they had gone through at least one and three cycles of treatment respectively.

Survival curves were estimated with the Kaplan–Meier method. Baseline and post-treatment QoL scores were compared using paired t test. Two-sided $p < 0.05$ was considered statistical significance. Minimally clinically important difference (MCID) was defined as half the standard deviation (SD) of the baseline score. 0.5–0.8 SD of the baseline score was defined as slight change, 0.8–1.5 SD as moderate change and >1.5 SD as significant change [18].

Results

Patients

From July 2012 to September 2013, 39 patients were enrolled in the phase II study. Twenty-five (64.1 %) were males and 14 (35.9 %) were females, with the median age of 55 (28–80). Most of the patients (79.5 %) had poorly differentiated adenocarcinoma and nearly half of them originated from the antrum. Twenty-nine (74.3 %) had multiple metastasis involving two or more organ systems. Metastatic sites included peritoneum (27, 69.2 %), abdominal lymph nodes (20, 51.3 %), liver (7, 18.0 %) and others (4, 10.3 %). Totally, 23 (59 %) were chemo-naïve patients. Patient characteristics are summarized in Table 1.

Table 1 Patient characteristics

Characteristic	($n = 39$)
Age, median (min–max)	55 (28–80)
Gender	
Male	25 (64.1 %)
Female	14 (35.9 %)
*ECOG PS**	
0	6 (15.4 %)
1	18 (46.2 %)
2	15 (38.4 %)
Histology	
Well differentiated	2 (5.1 %)
Moderately differentiated	6 (15.4 %)
Poorly differentiated	31 (79.5 %)
Primary tumor site	
Esophagogastric junction	8 (21.5 %)
Fundus	1 (2.6 %)
Body	11 (28.2 %)
Antrum	19 (48.7 %)
Disease status	
Locally advanced	2 (5.1 %)
Recurrent	9 (23.1 %)
Metastatic	28 (71.8 %)
Site of metastasis	
Peritoneum	27 (69.2 %)
Liver	7 (18.0 %)
Lymph node	20(51.3 %)
Other	4 (10.3 %)
Number of organ involved	
1	10 (25.7 %)
2	16 (41.0 %)
≥3	13 (33.3 %)
Prior treatment	
Untreated	23 (59.0 %)
Surgery only	11 (28.2 %)
Surgery + adjuvant chemotherapy	5 (12.8 %)

**ECOG PS* Eastern Cooperative Oncology Group performance status

Response and survival

In total, 38 out of 39 patients were assessable for response, whereas one patient withdrew consent after the first cycle. The overall RR was 51.3 % (95 % CI 34.8–67.6 %), with one patient (2.6 %) of CR and 19 patients (48.7 %) of PR. Fifteen patients (38.4 %) had stable disease and three (7.7 %) had PD (seen in Table 2). The median PFS was 6.7 (95 % CI 5.1–8.2) months, and the median OS was 14.0

Table 2 Tumor response according to RECIST 1.1

Response	Number (%)
Response	20 (51.28)
Complete response	1 (2.60)
Partial response	19 (48.70)
Stable disease	15 (38.46)
Progressive disease	3 (7.69)
Not evaluable	1 (2.56)

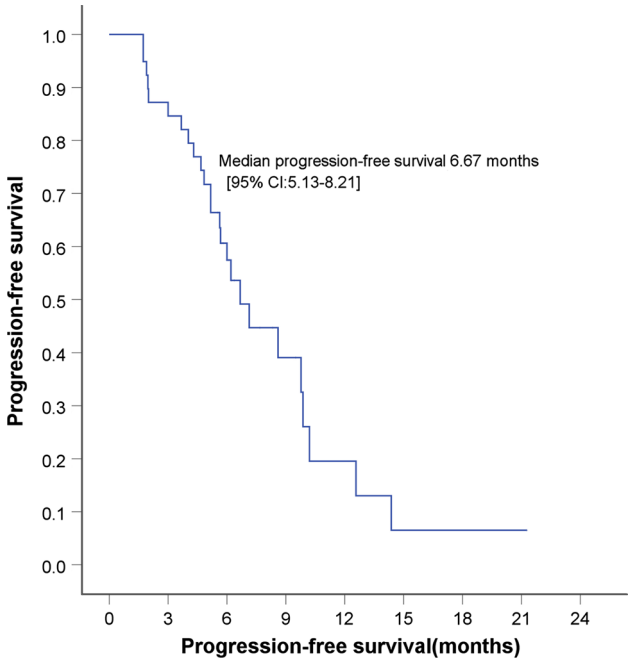

Fig. 1 Progression-free survival

(95 % CI 6.5–21.4) months. Survival curves of PFS and OS were illustrated in Figs. 1 and 2.

Safety

All patients received at least one cycle of treatment and were therefore evaluable for toxicity. A total of 313 cycles were administered, with a median of 7 per patient (1–15). Treatment was delayed for a median of 5 days (3–10) in 14 cycles (4.6 %). Twenty-seven patients discontinued treatment after PD, and one patient withdrew consent after Grade 3 neurotoxicity. There was no toxicity-related death. Detailed toxicity profile is listed in Table 3.

The most common hematological toxicities were anemia (34, 87.2 %) and neutropenia (26, 66.7 %). Grade 3/4 anemia was seen in 11 (28.2 %) patients, and Grade 3/4 neutropenia was seen in 2 (5.2 %) patients. No patient

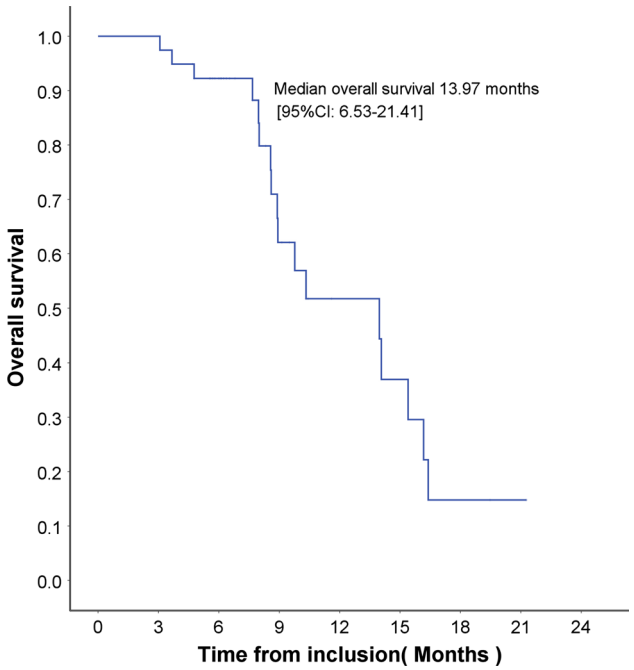

Fig. 2 Overall survival

experienced Grade 3/4 thrombocytopenia. Non-hematological toxicities were generally mild-to-moderate and manageable. Grade 3 non-hematological toxicities were liver dysfunction (3, 7.7 %), fatigue (3, 7.7 %) and neurotoxicity (1, 2.6 %). No patient had Grade 4 non-hematological toxicity. Dose reductions of docetaxel were performed in seven cases from 60 to 50 mg/m^2.

Quality of life

Sixty out of 78 expected questionnaires were completed (76.9 %), 30 (76.9 %) patients finished the baseline assessment, and 30 (76.9 %) patients finished the second assessment. Nine subjects were excluded from the analysis because of insufficient data leaving 30 patients for evaluation.

After 8 weeks of chemotherapy, significant improvements were seen in global health status and emotional functioning scales; moderate improvements were seen in physical functioning, nausea and vomiting, pain and appetite loss scales; slight improvement was seen in constipation scale. Deteriorations were seen in three scales: Financial difficulty scale deteriorated moderately, and social functioning and fatigue scales deteriorated slightly. The other scales remained stable (Table 4).

Discussion

Although in recent years, usage of molecular-targeted therapeutic drugs on patients with advanced gastric cancer

Table 3 Toxicity profile

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	11 (28.2 %)	12 (30.8 %)	10 (25.6 %)	1 (2.6 %)
Neutropenia	22 (56.4 %)	2 (5.1 %)	2 (5.1 %)	0 (0 %)
Febrile neutropenia	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Thrombocytopenia	2 (5.1 %)	1 (2.6 %)	0 (0 %)	0 (0 %)
Non-hematological				
Stomatitis	5 (12.8 %)	4 (10.3 %)	0 (0 %)	0 (0 %)
Nausea and vomiting	8 (20.5 %)	2 (5.1 %)	0 (0 %)	0 (0 %)
Diarrhea	5 (12.8 %)	2 (5.1 %)	1 (2.6 %)	0 (0 %)
Constipation	4 (10.3 %)	0 (0 %)	0 (0 %)	0 (0 %)
Fatigue	21 (53.8 %)	5 (12.8 %)	3 (7.7 %)	0 (0 %)
Alopecia	24 (61.5 %)	13 (33.3 %)	NA	NA
Edema	10 (25.6 %)	0 (0 %)	0 (0 %)	0 (0 %)
Nail change	8 (20.5 %)	11 (28.2 %)	0 (0 %)	NA
Hand–foot syndrome	4 (10.3 %)	3 (7.7 %)	0 (0 %)	NA
Liver dysfunction	11 (28.2 %)	1 (2.6 %)	3 (7.7 %)	0 (0 %)
Neurotoxicity	0 (0 %)	0 (0 %)	1 (2.6 %)	0 (0 %)

NA not applicable

have brought forth some promising results, chemotherapy remains to be the backbone of systemic therapy for AGC; hence, the efficacy of new drug combination or dosage regimen is still worth exploring. In most regimen for AGC including the DCF and ECF, drugs were administrated every 3 week, but according to the Gompertzian tumor kinetics model [19], tumor cells growth follow a pattern which is characterized by an initial rapid growth of cells followed by a decrease in the doubling rate as tumor size increases. Thus, a shorter chemotherapy interval allows us to interrupt the rapid growth phase and harvest a higher efficacy. Trial C9741 has proven that dose-dense chemotherapy improves clinical outcome of breast cancer [20]. Similar trials had been conducted for AGC patients showing non-inferiority compared with the conventional regimen. Thus, we designed a dose-dense regimen combining biweekly docetaxel and 5-Fu, hoping to gain a higher response rate, due to the possibly higher myelosuppression rate, prophylactic use of G-CSF was adopted.

The results of this Phase II trial confirmed the feasibility and efficacy of combining biweekly docetaxel and simplified de Gramont regimen in previously untreated AGC patients. This treatment combination led to a RR of 51.3 % (20/39). Median PFS and OS were 6.7 and 14.0 months, respectively. QoL was improved in seven scales in the EORTC-C30 questionnaire.

When compared with previous published studies on first-line treatment of AGC, our regimen appears to have a more favorable disease control rate. Similar trial such as the V325 trial reported RR ranging from 25 to 37 % [21] and PFS ranging from 4.2 to 7.3 months. This might be partly attributed to the biweekly design of our regimen which shortened the treatment interval and maintained a high dose density. The satisfactory toxicity profile is another important reason considering it led to less treatment discontinuation and withdraw. We also achieved a satisfactory survival outcome, for most previous trials reported a median survival less than a year. It should also be noticed that most of our patient received second-line or support care after treatment failure, and we assume that patients with successful first-line treatment tend to be more acceptable to second-line treatment, thus prolonging the survival.

Our study also showed an acceptable toxicity profile. Grade 3/4 neutropenia was apparently less frequent (5.1 %, 2/39) in our study, which could be considered remarkable when compared with previous published data (23.5–66.7 %) [22–27]. This could be explained by our prophylactic use of G-CSF (300 μg/day for five consecutive days) which was not allowed in the other studies. Relatively lower dose intensity of docetaxel in our study than in 3-week regimens might be another important reason for the low incidence of neutropenia. Anemia (28.2 %) was the most common Grade 3/4 toxicity. It was significantly higher than those reported by previous study (2–22 %). Among our study, more than one-third of patients were PS 2. Poor PS was usually closely related with a low hemoglobin concentration. High incidence of anemia in our study could also be the result of higher dose density of docetaxel, and no dose reduction or delay was required according to the protocol. Liver dysfunction was the most common Grade 3/4 non-hematological toxicity, seen in three patients (7.8 %). This could possibly caused by the

Table 4 Change of QoL according to EORTC C30

Scale	Average score (before treatment)	Average score (after treatment)	SD of baseline score	Mean difference/SD	Outcome	Paired *t* test (*p* value)
Global health status/QoL						
Global health status/QoL	21.05	74.78	21.62	2.49	Significantly improved	<0.01
Functional scales						
Physical functioning	53.16	87.72	25.77	1.34	Moderately improved	<0.01
Role functioning	36.84	30.63	31.75	−0.20	Stable	<0.01
Emotional functioning	54.61	87.90	19.92	1.67	Significantly improved	<0.01
Cognitive functioning	66.23	58.67	21.4	−0.35	Stable	<0.01
Social functioning	34.21	23.11	18.96	−0.59	Slightly deteriorated	<0.01
Symptom scales/items						
Fatigue	27.78	41.19	20.97	0.64	Slightly deteriorated	<0.01
Nausea and vomiting	41.23	3.95	36.91	−1.01	Moderately improved	<0.01
Pain	46.49	17.86	30.3	−0.94	Moderately improved	<0.01
Dyspnoea	8.44	19.65	27.33	0.41	Stable	<0.01
Insomnia	20.35	23.42	25.89	0.12	Stable	<0.01
Appetite loss	47.37	16.67	21.41	−1.43	Moderately improved	<0.01
Constipation	27.19	5.63	29.87	−0.72	Slightly improved	<0.01
Diarrhea	15.84	20.77	34.48	0.14	Stable	<0.01
Financial difficulties	26.31	55.89	32.1	0.92	Moderately deteriorated	0.02

SD standard deviation

parenteral nutrition needed in patients with poor gastrointestinal function. There was also one patient who experienced Grade 3 neurotoxicity. Similar cases with neurotoxicity caused by 5-FU had already been reported in the literature [28]; it is generally considered to be related to dihydropyrimidine dehydrogenase deficiency, but due to the patient's rejection, relevant tests were not performed.

For the QoL analysis, our results were quite impressive when compared to previous studies. In a series of trials that compared QoL after chemotherapy with baseline, most of them demonstrated a lack of improvement. In the phase III trial of Webb et al. [29], after receiving 12 weeks of ECF or FAMTX therapy, no difference was found versus the baseline score according to the EORTC C30 questionnaire. Similarly, in the trial conducted by Ross et al. [30], 3 months of ECF or MCF therapy brought about no improvement or even significantly decline of QoL. Although in the results reported by Sadighi et al. [31], after 3 cycles of TCF regimen, the fatigue and pain scale showed improvement with scores change of 4.6 and 5.7, respectively. The other scales remained stable or deteriorated in this trial. However, the clinical significance of such minor changes of score was doubtable. It is also notable that, in the trials mentioned above, only 35–85 % of the patients assessed at baseline completed the second assessment during therapy. It is very likely that most of these missing cases had already experienced disease progress making them unable to finish the assessment. Considering this selection bias, the result might be even worse. In our study, QoL had improved significantly after 8 weeks of treatment according to the EORTC-C30 when compared to the baseline score. The patients enrolled in our study were in relatively poorer PS, and thus, the high anti-tumor efficacy of our regimen might provide relief from the tumor related symptoms. Also, due to the prophylactic use of G-CSF adopted by our regimen, lower incidence of severe toxicity may be another important reason for the QoL improvement.

In conclusion, this modified dose-sense biweekly regimen of docetaxel and 5-FU was efficient and well tolerated even for AGC patient. QoL was also improved during the treatment. However, due to the limited small sample size, its superiority is yet to be tested in large-scale trial. But according to the results achieved so far, it is promising and viable for AGC.

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Conflict of interest All the authors declare they have no conflict of interest.

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