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Original Article

Clinical efficacy and safety of standard versus modified DCF regimens in treatment of advanced gastric cancer

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Abstract: Docetaxel and cisplatin plus fluorouracil (DCF) is one standard regimen in the treatment of advanced gastric cancer (AGC). Due to substantial toxicity of DCF, modified DCF regimens have been developed to improve efficacy and safety. This study aimed to compare the clinical efficacy and safety between the standard DCF regimen and three common modified DCF regimens. A total of 97 consecutive AGC patients were admitted. Patients are divided into the standard DCF group (n=53) and three modified DCF groups with regimen of docetaxel, oxaliplatin and capecitabine (DOX, n=14), regimen of docetaxel, oxaliplatin and 5-fluorouracil (DOF, n=13), and regimen of paclitaxel, docetaxel and 5-fluorouracil (PDF, n=17), respectively. The efficacy and associated adverse reactions were compared between groups with different DCF regimens. The overall response rates were 37.2% (DCF), 42.9% (DOX), 33.3% (DOF) and 35.3% (PDF), respectively, and DOX group showed relatively higher efficacy than those in the other three groups. The median progression-free survival (PFS) was 4.8, 6.0, 4.7 and 4.0 month, and median overall survival (OS) was 9.3, 11.8, 9.0 and 8.0 month in DCF, DOX, DOF and PDF groups, respectively. There were no statistical differences among groups in PFS and OS (P>0.05). The incidence of hematological toxic reactions was relatively lower in the modified DCF groups than in the standard DCF group. The hand-foot syndrome was most common in the DOX group and neurotoxic reactions in the DOX and DOF groups. All adverse reactions were mild (Degree I-II), and there were no statistically significant differences in incidence of adverse reactions among groups (P>0.05). In conclusion, three modified DCF regimens are not inferior options for AGC treatment compared with the standard DCF. DOX regimen can be considered as is a superior alternative regimen for first-line treatment of AGC, which demonstrates moderately increased efficacy and significantly reduced adverse reactions.

Keywords: Advanced gastric cancer (AGC), first-line chemotherapy, clinical efficacy, clinical safety

Introduction

Gastric cancer (GC) is one of the major gastrointestinal malignancies worldwide. Despite progressive decline in incidence recently, gastric cancer still remains the common malignancy (6.8%) and the third cause of death from malignancies (8.8%) in the world [1]. About half gastric cancer cases are in Eastern Asia (mainly in China). Age-standardized incidence of gastric cancer in Eastern Asia was twice that of the global average incidence. Eastern Asia also has the highest mortality of gastric cancer [2].

Prognosis of gastric cancer is poor because the majority of patients present with inoperable advanced gastric cancer (AGC). Clinical application of molecular targeted drugs is limited due to high cost and poor efficacy [3]. Conventional chemotherapy is the current primary approach for treatment of AGC. Standard DCF regimen, which is composed of docetaxel (DOC, 75 mg/m^2, d1), cisplatinum (DDP, 75 mg/m^2, d1) and 5-fluorouracil (5-Fu, 750 mg/m^2/d, d1-5, q21d), is the current first-line treatment of AGC [4]. DCF regimen has been widely used in intraperitoneal and intravenous chemotherapy for AGC [5]. Despite its excellent efficacy was confirmed in AGC [6], the standard DCF regimen has serious adverse effects, especially high incidence of grade III-IV neutropenia (82%) and neutrope-

nia-related fever and infection (29%). These adverse effects have restrained the clinical application of standard DCF regimen in AGC patients, particularly in elderly and infirm people [7].

Chemotherapy plays an important role in the treatment of AGC owing to its effects of alleviating relevant symptoms and prolonging patient's life span of AGC. The combined chemotherapy of DDP and 5-Fu has previously been considered as an ideal regimen for the treatment of AGC [8]. In recent years, a novel drug DOC has been added to this combined thermotherapy regimen and brought more benefit, thus producing the so-called DCF regime. The standard DCF regimen has markedly improved the survival of AGC patients in the V325 trial [6] and became the first-line regimen proposed by several national tumor authorities. However, this regimen is accompanied with serious side effects, with up to 82% incidence of grade III-IV bone marrow suppression [7]. Additionally, DCF cannot be tolerated by elderly patients, particularly in Asia. To increase the clinical efficacy and decrease the toxic effects, attempts are made to modify the standard DCF regimen for benefiting more AGC patients.

In the modified DCF regimens, one or two drugs are replaced by similar drugs at different dosages and administration intervals. For example, the anti-microtubular docetaxel (DOC) in the standard regimen is often replaced by paclitaxel (PTX) with similar mechanism, both of which have potent anti-cancer activity. Oxaliplatin (L-OHP) is the third generation of platinum drugs, which has similar mechanism and efficacy as DDP but less emetogenic potential and renal toxicity. Gu et al. [9] proved that L-OHP has synergistic action with PTX, thus is considered as the best choice to replace DDP in the first-line treatment for AGC. CAPE is a novel oral fluorouracil which can be transformed to 5-Fu through thymidine phosphorylase (TP) *in vivo*. Because tumor cells has higher concentration and enzymatic activity of TP than normal cells, CAPE shows more preference to tumor cells than to normal cells, and has better efficacy and lower toxicity than 5-Fu, as has been validated by a meta-analysis based on REAL-2 and ML 17032 [10]. Moreover, CAPE can be orally taken, thus is more convenient and safer than 5-Fu. Therefore, CAPE is considered an ideal candidate to replace 5-Fu in modified DCF regimes. To date, several modified DCF regimens such as DOX (Docetaxel, L-OHP and CAPE), DOF (Docetaxel, oxaliplatin and 5-fluorouracil) and PDF (Paclitaxel, docetaxel and 5-fluorouracil) [11, 12] have been developed and demonstrated certain efficacy in the treatment of AGC. Recently, comparative analysis was conducted between the standard DCF and modified DOX, DOF, and PDF regimens, to identify a high-efficacy and safe DCF regimen for first-line treatment of AGC. However, the modified regimens are reported in small-size phase II clinical studies only [13, 14], but not in high-level, multi-centre, phase-III randomized controlled trials (RCTs).

In the present study, we conducted an eight-year comparative analysis on the short- and long-term efficacy and associated adverse reactions of the standard and three modified DCF regimens as the first-line treatment for AGC patients. The results were analyzed to identify a superior alternative of chemotherapy regimen for AGC.

Materials and methods

Patient selection

This clinical trial included 97 consecutive patients with AGC who were admitted into the Affiliated Tumor Hospital of Guangxi Medical University (Nanning, China) during January 1, 2005 to December 31, 2012. The inclusion criteria were as follows: (1) Subjects were diagnosed as stage IV or unresectable local AGC, or adenocarcinoma in the esophagogastric junction by pathological or cytological examinations according to cancer staging manual of the American Joint Committee on Cancer (7^{th} Edition, 2010) [15]; (2) Subjects received standard or modified DCF regimen as the first-line treatment; (3) The age of subjects was ranged from 18 to 75 years old, and their physical condition was scored as 0~2 points according to standards of the Eastern Collaborative Oncology Group; (4) There was no central nervous system (CNS) metastasis or significant major organ dysfunction; (5) No other malignant history. The exclusion criteria were as follows: (1) Subjects had developed into incontrollable CNS metastasis; (2) Female subjects with pregnancy and lactation; (3) Subjects had secondary primary tumors; (4) Subjects had other serious diseases or with significant organ damage ineligible for chemotherapy.

Table 1. Characteristics of patients in the four treatment arms (n)

Features	Standard DCF	DOX	DOF	PDF
Gender				
Male	36	10	9	11
Female	17	4	4	6
Median age (years)	51	52	53	52
ECOG score				
0-1	45	12	11	14
2	8	2	2	3
Pathological type				
Medium-well differentiated adenocarcinoma	18	6	5	5
Ring cell carcinoma	13	3	2	4
Poorly differentiated adenocarcinoma	22	5	6	8
Metastasis site				
Retroperitoneal lymph nodes	18	4	3	5
Liver	15	6	5	7
Lung	12	3	2	3
Clavicle lymph node	6	2	1	2
Ovary	24	4	5	6
Peritoneum	32	7	6	8
Others	8	0	0	1
Previous operation				
Radical gastrectomy	27	5	6	11
Palliative resection	12	4	3	4
Previous radiochemotherapy				
Yes	27	5	6	11
No	26	9	7	6

Chemotherapy regimens

The AGC patients were divided into four groups according to the received regimens: the standard DCF group (n=53), the DOX group (n=14), the DOF group (n=13), and the PDF group (n=17, **Table 1**). Medical treatment cycles of the DCF, DOX, DOF, and PDF regimens were 4, 5, 3, and 3, respectively. The detailed chemotherapy doses and intervals in each regimen were shown in **Table 2**.

Data collection

Medical records of eligible patients were reviewed in terms of age, tumor-node-metastasis (TNM) stage, pathological type, differentiated degree, treatment regimen, clinical efficacy, and adverse reactions. A telephone follow-up was conducted from 2012 to 2015.

Efficacy and side effect evaluation

Efficacy of the standard and modified DCF regimens was evaluated and classified into four grades (complete response, CR; partial remission, PR; stable disease, SD; and progression disease, PD) according to the Response Evaluation Criteria in Solid Tumors (version 1.1) RECIST 1.1 [16]. Short-term efficacy was evaluated with the response rate (RR) and calculated as (CR+PR)/total cases; long-term efficacy was evaluated with the progression-free-survival (PFS), overall survival (OS), 6-month PFS rate, and 1-year OS rate. PFS was defined as the duration from the first day of treatment to tumor progression or death, and OS as the duration from the first day of treatment to the last follow-up visit or death. The 6-month PFS rate was the percentage of the number of cases with PFS≥6 months to the total cases, and the 1-year OS rate was the percentage of the number of cases with OS≥6 months to the total cases. Chemotherapy-related adverse effects were evaluated according to Common Toxicity Criteria of the Common Terminology Criteria for Adverse Events (version 3.0).

Statistical analysis

Clinical data were processed and analyzed using SPSS17.0 (SPSS Inc., Chicago, IL, USA) software. Group comparison of rates was conducted by using chi-square test or Fisher's exact probabilities. Survival analysis and curves were established using Kaplan-Meier or log-rank test. $P<0.05$ was considered statistically significant.

Results

Short- and long-term efficacy

A total of 94 patients were evaluated for short-term efficacy of four chemotherapy regimens for three patients refused to do CT or other imaging examinations, including 51 of the DCF group, 14 of the DOX group, 12 of the DOF

Table 2. The administration of standard DCF regimen and modified DCF regimens

	Specific usage and dosage
Standard DCF	DOC 75 mg/m^2, d1; DDP 75 mg/m^2, d1; 5-Fu 750 mg/m^2/d, d1-5; q21d
DOX	DOC 75 mg/m^2, d1; L-OHP 100 mg/m^2, d1; CAPE 1000 mg/m^2/d, bid, d1-7; q21d
DOF	DOC 75 mg/m^2, d1; L-OHP 135 mg/m^2, d1; 5-Fu 750 mg/m^2/d, d1-5; q21d
PDF	PTX 175 mg/m^2, d1; DDP 75 mg/m^2, d1; 5-Fu 750 mg/m^2/d, d1-5; q21d

Table 3. Overall response of the four treatment arms [n (%)]

	Cases	CR	PR	SD	PD	CR+PR	*P* value
DCF	51	1 (2.0%)	18 (35.2%)	16 (31.4%)	16 (31.4%)	19 (37.2%)	0.961
DOX	14	0 (0%)	6 (42.9%)	5 (35.7%)	3 (21.4%)	6 (42.9%)	
DOF	12	0 (0%)	4 (33.3%)	5 (41.7%)	3 (25.0%)	4 (33.3%)	
PDF	17	0 (0%)	6 (35.3%)	4 (23.5%)	7 (41.2%)	6 (35.3%)	

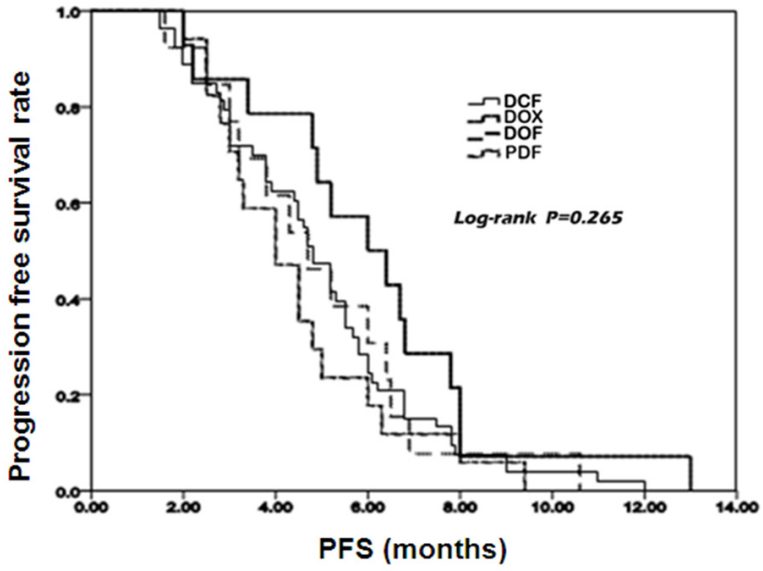

Figure 1. The progression free survival of the four treatment arms.

Table 4. The 6-month PFS rate and 1-year OS rate of the four treatment arms [n (%)]

	Cases	6-month PFS	1-year OS rate
DCF	53	12 (22.6%)	12 (22.6%)
DOX	14	7 (50%)	4 (28.6%)
DOF	13	4 (30.8%)	3 (23.1%)
PDF	17	3 (17.6%)	3 (17.6%)
P		0.203	0.947

Note: PFS: progression-free survival; OS: overall survival.

group, and 17 of the PDF group. Among all 94 patients, only one in the DCF group achieved CR. The RR rates of different chemotherapy regimens were 37.2% in the DCF group (n=18), 42.9% in the DOX group (n=6), 33.3% in the DOF group (n=4) and 35.3% in the PDF group (n=6), showing no statistically significant differences among groups (*P*> 0.05) (**Table 3**).

Till June 30, 2013, the median total follow-up period was 9.8 months and no case was lost. Median PFS values were 4.8, 6.0, 4.7 and 4.0 months and the 6-PFS rates was 22.6%, 50.0%, 30.8% and 17.6% in the DCF, DOX, DOF and PDF groups, respectively. Neither of the two indices There were no statistically significant differences among groups in PFS and 6-PFS rate (*P*>0.05) (**Figure 1** and **Table 4**). Median OS values were 9.3, 11.8, 9.0 and 8.0 months and the 1-OS rate was 22.6%, 28.6%, 23.1%, and 17.6% in the DCF, DOX, DOF, and PDF groups, respectively. There were no significant differences among groups in PFS and 6-PFS rate (*P*>0.05) (**Figure 2** and **Table 4**).

Hematological and non-hematological adverse effects

The most common hematological effect of four chemotherapy regimens was bone marrow suppression. Compared with the standard DCF group (81.1%), the incidence of leucopenia and neutropenia was significantly lower in the DOX (46.1%), DOF (69.2%) and PDF (64.7%) groups (*P*<0.05). The modified DCF groups showed lower incidences in Grade III-IV leukopenia,

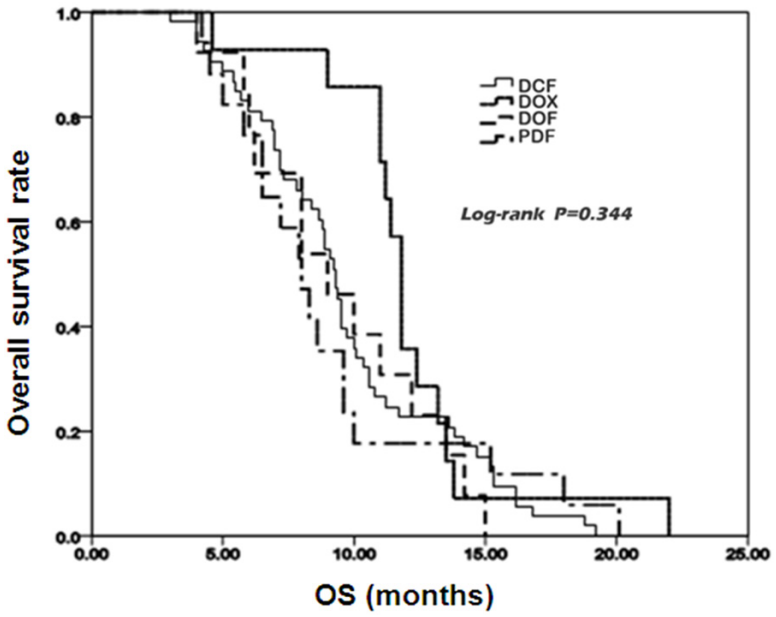

Figure 2. The overall survival of the four treatment arms.

neutropenia, and related fever than the standard DCF group, but the differences were not statistically significant among groups ($P>0.05$). Compared with the standard DCF group, three modified DCF groups showed statistically significantly lower incidence of hemoglobin drop ($P<0.05$), but showed no statistically significantly difference in platelets ($P>0.05$, **Table 5**).

The most common side reactions in AGC patients were nausea, vomiting, and diarrhea, whose incidences were not statistically significantly different among groups ($P>0.05$). Hand-foot syndrome occurred most frequently in the DOX group with mild symptoms (grade I-II, 21.4% *vs.* 0-3.8%, $P=0.05$), whereas neurotoxic reactions were relatively common in the DOX and DOF groups with mild symptoms (grade I-II) but rare in the other groups (28.6-30.7% *vs.* 3.8-5.9%, $P<0.05$). Other side reactions such as hepatic and renal dysfunctions were uncommon and their incidences had no statistically significant differences among groups (**Table 6**).

Discussions

In this study we showed that in AGC patients receiving DCF, DOX, DOF and PDF regimens, the therapeutic efficacy was relatively higher in the DOX group than in the other three groups in response rate (42.9% *vs.* 33.3-37.2%), median progression-free-survival (6.0 *vs.* 4.0-4.8 months), 6-month progression-free-survival rate (28.6% *vs.* 17.6-22.6%), median overall survival (11.8 *vs.* 8.0-9.3 months), and 1-year overall survival rate (50.0% *vs.* 17.5-30.8%), with no statistical differences among groups ($P>0.05$). Our evaluation results of the DCF group were similar to those in the V325 trial (RR 37.2% *vs.* 37.0%, median PFS 4.8 *vs.* 5.6, median OS 9.3 *vs.* 9.2) [6], proving the reliability of the present study.

The efficacy of three modified DCF regimens was not inferior to that of the standard DCF regimen. In addition, DOX group achieved relatively higher RR, median PFS and OS than the other regimens possibly through the synergistic effect of L-OHP, DOC and CAPE [17]. The DOX regimen shortened the administration time (from 14 to 7 days) without decreasing the efficacy, suggesting that the anti-tumor activity of CAPE is independent of the administration time [18]. The current preclinical studies indicate that anticancer activity could be reached by continual 7-day administration of CAPE, but longer administration failed to increase the efficacy further [19]. Therefore, the 7-day DOX regimen has potential advantage and feasibility for AGC treatment, which is worthy of further investigation.

In the treatment of AGC, a major adverse effect of the standard and modified DCF regimens was hematologic toxicity. DCF group had higher incidences of adverse effects than the DOX, DOF and PDF groups in rates of leukopenia (81.1% vs. 46.1%-69.2%), neutropenia (69.8% vs. 29.4%-35.7%) and hemoglobin drop (77.3% vs. 35.7%-69.2%). The three modified DCF regimens exhibited a generally descending trend in hematologic adverse reactions. The DOX regimen showed lowest incidences of leukopenia and haemoglobin drop, and PDF regimen had fewest neutropenia rate despite a lack of statistically significant difference ($P>0.05$). These findings illustrate that the modified DCF regimens can be better tolerated in AGC patients than standard DCF regiem.

Table 5. Hematologic toxicity of the four treatment arms [n (%)]

Regimens	Cases	Leucopenia		Neutropenia		Neutropenia with fever	Hemoglobin		Platelet	
		I-IV	III-IV	I-IV	III-IV		I-IV	III-IV	I-IV	III-IV
DCF	53	43 (81.1)	17 (32.1)	37 (69.8)	13 (24.5)	8 (15.1)	41 (77.3)	32 (60.4)	7 (13.2)	2 (3.8)
DOX	14	6 (46.1)	2 (14.2)	5 (35.7)	2 (14.2)	1 (7.1)	5 (35.7)	2 (14.2)	0 (0%)	0 (0%)
DOF	13	9 (69.2)	2 (13.5)	4 (30.7)	2 (13.5)	0 (0%)	9 (69.2)	3 (23.1)	2 (13.5)	0 (0%)
PDF	17	11 (64.7)	4 (23.5)	5 (29.4)	1 (5.9)	1 (5.9)	10 (58.8)	5 (29.4)	0 (0%)	0 (0%)
P		0.02	0.391	0.003	0.288	0.205	0.028	0.002	0.06	>0.05

Table 6. Nonhematologic toxicity of the four treatment arms [n (%)]

Regimens	Cases	Nausea and vomiting		Diarrhea		Hepatic dysfunction	Kidney dysfunction	Hand foot syndrome	Neurotoxicity
		I-IV	III-IV	I-IV	III-IV	I-IV	I-IV	I-IV	I-I V
DCF	53	19 (35.8)	4 (7.5)	13 (24.5)	3 (5.7)	3 (5.7)	5 (9.4)	2 (3.8)	2 (3.8)
DOX	14	3 (21.4)	1 (7.1)	4 (28.6)	0 (0)	1 (7.1)	1 (7.1)	3 (21.4)	4 (28.6)
DOF	13	2 (13.5)	0 (0%)	2 (13.5)	0 (0)	1 (7.7)	01 (7.7)	0 (0)	4 (30.7)
PDF	17	4 (23.5)	0 (0%)	2 (11.8)	1 (5.9)	0 (0%)	0 (0%)	0 (0)	1 (5.9)4
P		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	0.050	0.01

Among non-hematological reactions, hand-foot syndrome was common in the DOX group only (21.4%) while the neurotoxic reactions occurred frequently in the DOX (28.6%) and DOF groups (30.7%). All these reactions were mild (grade I-II), which could be tolerated in AGC patients and gradually disappeared after the therapy was discontinued. Other adverse reactions such as nausea, vomiting and hepatic, and renal dysfunction were mild, with no statistically significant differences in their incidences among groups. In AGC patients receiving modified DCF regimens, the incidences of adverse reactions of this study were significantly lower as compared with other reports such as the clinical trail REAL-2 [20] (Hand-foot syndrome: 45.9%; neurotoxic reactions: 83.7%).

There are some disadvantages in our present study. This is a retrospective study with small sample size, and the confounding factors could not be eliminated by randomized method. However, our work represents the first study to compare the standard and three common modified DCF regimens in clinical efficacy and safety of AGC patients. Our results provide reference data for clinical application of proper modification of DCF, especially the 7-day DOX regimen, for treatment of AGC. Higher-level, multi-center and large-scale RCTs will be carried out to further prove the clinical significance of the DOX regimen in treatment of AGC.

In conclusion, our results showed that the modified DCF regimens were comparable to the standard DCF regimen regarding the efficacy, and allowed avoiding common adverse effects and achieved excellent safety and tolerance profiles. The 7-day DOX regimen increased RR, median PFS and OS, thus providing a superior alternative for AGC treatment.

Disclosure of conflict of interest

None.

Authors' contribution

Rong Liang and Xin-Yu Chen analyzed the data and wrote the manuscript; Yan Lin, Xiao-Qiong Lu, Chun-Ling Yuan, Qian Li, Si-Na Liao, Xiao-Li Liao, Yu-Mei Zhang, Chao-Yong Liang and Yong-Qiang Li collected and analyzed the data; Xiao-Hua Hu designed the study and revised the manuscript.

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