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ORIGINAL ARTICLE

Efficacy and tolerability of docetaxel and cisplatin plus S-1 for advanced gastric cancer

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Summary

Purpose: The aim of this study was to evaluate the efficacy and tolerability of docetaxel and cisplatin plus S-1 (DCS) combination chemotherapy in advanced gastric cancer patients.

Methods: Chemo-naive patients with advanced gastric cancer, ECOG performance status of 0 to 1, and adequate organ function were eligible. All patients received docetaxel 75 mg/m2 and cisplatin 75 mg/m2 on day 1, plus S-1 orally 40-60 mg bid depending on body surface area on days 1-14, every 21 days. Efficacy and adverse events were evaluated every two cycles.

Results: Fifty-nine patients were enrolled from February 2009 to January 2011 and 56 of them were evaluated for efficacy and tolerability. After a median follow up of 17.6 months, the objective response rate (RR) was 75%, the disease control rate (DCR) 83.9%, the median progression free survival (PFS) and overall survival (OS) 6.5 (95% CI, 5.6-7.3) months and 15.5 (95% CI, 13.9-17.0) months, respectively. The median number of chemotherapy cycles was 5. Grade 3 or 4 adverse effects included neutropenia (60.7%), vomiting (14.3%), neurotoxicity (12.5%), thrombocytopenia (10.7%), diarrhea (10.7%), impaired liver function (3.6%), and hand-foot syndrome (1.8%).

Conclusion: Our study shows that DCS regimen is active against advanced gastric cancer with acceptable toxicities and it may be used as a new choice of first-line chemotherapy for patients with advanced gastric cancer.

Key words: advanced gastric cancer, cisplatin, docetaxel, first line chemotherapy, S1

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Introduction

Gastric cancer is the fourth most common cancer and the second cancer-related cause of death [1,2]. Advanced gastric cancer refers to unresectable, locally advanced disease, presence of distant metastasis or postoperative disease recurrence. Several clinical studies showed that the median survival time of advanced gastric cancer was only 3 to 4 months without chemotherapy, and increased to 1 year after chemotherapy [3-6]. Due to low efficacy of single-agent chemotherapy, several combination chemotherapy regimens have been tried. For example both FAM (5-FU, doxorubicin, mitomycin) [7,8] and ECF (epirubicin, cisplatin, 5-FU) [9,10] combinations have shown considerable activity and were recommended as routine treatment of advanced gastric cancer in the 1980s and 1990s, respectively. However, so far there is still no global standard regimen in the treatment of advanced gastric cancer.

In recent years, several new-generation drugs, including oxaliplatin, paclitaxel, docetaxel, capecitabine, S-1 and irinotecan have been investigated in advanced gastric cancer. Docetaxel has shown antitumor activity in gastric cancer, either as single agent or in combination with other agents [11-15]. S-1 is a new, orally administered 5-FU analog containing three components: tegafur, gimeracil and oxo potassium, and has displayed activity against gastric cancer [16,17]. Some studies have demonstrated that DCF (docetaxel, cisplatin, 5-FU) regimen was a new option of first-line chemotherapy for advanced gastric cancer with substantial toxicity [18,19].

In this study, we observed the efficacy and tolerability of docetaxel and cisplatin plus S-1 (DCS) scheme in patients with advanced gastric cancer.

Methods

This study was conducted at the Oncology Department of the First Affiliated Hospital of Jinan University and the Oncology Department of the Affiliated Hospital of Guangdong Medical College. The Institutionl Review Board of each author's Institution approved the protocol. All of the patients provided written informed consent.

Inclusion criteria

All of the patients had TNM IIV disease. Inclusion criteria included the following: cytologically or histologically confirmed advanded gastric cancer; life expectancy> 12 weeks; age between 18 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; adequate bone marrow function (leukocyte count >4.0x10^{9}L, platelet count>100x10^{9}L; adequate renal function (serum creatinine <1.25 times the upper limit of normal (ULN) and/or creatinine clearance >60 ml/min) and liver function (serum bilirubin <1.5 mg/dl, alanine aminotransferase and aspartate aminotransferase <3.0 ULN); no contraindication for chemotherapy.

Exclusion criteria

Patients with active infection, severe bone marrow suppression, severe liver or renal dysfunction were excluded from the study.

Patients were ineligible if they had previously received docetaxel, cisplatin or S-1 therapy, or had severe comorbid conditions, CNS metastasis, or another active malignancy. Patients were also excluded if they were receiving drugs with potential interactions with S-1 (allopurinol, phenytoin, and warfarin), or were pregnant, or unable to comply with the requirements of the protocol.

Treatment methods

All patients were treated with docetaxel, cisplatin and S-1. Cisplatin (Jiangsu Haosen Pharmaceutical Co, Lianyungang, China) dose was 75 mg/m^2 on day 1, given as a 2-h intravenous infusion followed by docetaxel (Shandong Qilu Pharmaceutical Co, Jinan, China) 75 mg/m^2 given as a 2-h intravenous infusion. S-1 (Shandong New Time Pharmaceutical Co, Linyi, Shandong Province, China) was given orally twice daily for 2 weeks followed by a 1-week rest. The dose of S-1 was determined according to the patient's body surface area as follows: <1.25m^2, 40mg; 1.25-1.50m^2, 50mg; >1.50m^2, 60mg. Cycles were repeated every 3 weeks. Dexamethasone 8 mg was given orally twice daily from the day before docetaxel administration to 2 days after docetaxel treatment. Corticosteroids plus granisetron were routinely used at standard doses

when cisplatin was administered to prevent cisplatin-related nausea and vomiting. Chemotherapy was discontinued in case of disease progression or patients' refusal. Courses were repeated if the patients had leukocyte count >3.0x10^9/L, neutrophil count>1.5x10^9/L, platelets count> 50X10^9/L, serum bilirubin <1.2 mg/dl, serum creatinine <1.2mg/dl, and non-hematological toxicity <grade 1 on the day of course repetition. Granulocyte colony-stimulating factor was used only for patients with absolute neutrophil count <0.5x10^9/L, febrile neutropenia, or documented infection with neutropenia.

Efficacy and safety evaluation

Prior to participation in the study, patients underwent a number of assessments, including history, physical examination, complete blood count, serum biochemistry, urine tests, serum electrolytes, electrocardiography, chest X-rays and computed tomography (CT) scan of the abdomen and pelvis. Other investigations, such as bone scan and chest CT scan were performed if clinically indicated due to metastatic disease. Physical examinations, chest X-rays, complete blood count, urine tests and serum bio chemistry were repeated prior to each chemotherapy cycle. Tumor measurement was conducted every 2 cycles according to Response Evaluation Criteria in Solid Tumors guidelines (version 1.0). Adverse events were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Dose modifications

The doses of chemotherapeutic drugs required adjustments when the following adverse effects happened: in case of grade 2 nonhematologic toxicity, treatment was interrupted until recovery and the doses of docetaxel, cisplatin and S-1 were reduced by 25%. If patients experienced grade 3 neurotoxicity, grade 4 hypersensitivity reaction or grade 3 deteriotation in liver function tests lasting more than 3 weeks, treatment was interrupted until recovery and the doses of docetaxel, cisplatin and S-1 were reduced by 50%. The dose of S-1 was increased no more than 75 mg per cycle and reduced no less than 40 mg per cycle [20,21].

Table 1. Patient and disease characteristics (N=56)

Characteristics	*N (%)*
Gender	
Male	34 (60.7)
Female	22 (39.3)
Age, years	
Median (range)	46 (18-75)
ECOG PS	
0	26 (46.4)
1	30 (53.6)
Primary sites	
Gastroesophageal junction	11 (19.6)
Gastric body	18 (32.2)
Pylorus	27 (48.2)
Histological types*	
Papillary	13 (23.2)
Tubular	11 (19.6)
Mucinous	14 (25.0)
Mixed	9 (16.1)
Signet-ring cell	9 (16.1)
Grades of differentiation	
Well	21 (37.5)
Moderate	13 (23.2)
Poor	22 (39.3)
Sites of metastasis	
Regional lymph nodes	22 (39.2)
Peritoneum	12 (21.4)
Liver	10 (17.9)
Lung	6 (10.7)
Liver and lung	3 (5.4)
Pleura	3 (5.4)

ECOG: Eastern Cooperative Oncology Group, PS: performance status
*all adenocarcinomas

Moreover, dose reduction was required after the previous interruption. If adverse events did not improve to grade 0 or 1 after 3 interruptions (3 weeks), the patient was withdrawn from the study.

Statistics

PFS was defined as the time from treatment initiation to the first sign of disease progression. OS was defined as the time from treatment initiation to the date of death or last follow-up. Follow-up time was defined as the time interval between chemotherapy initiation and the last visit or last telephone contact.

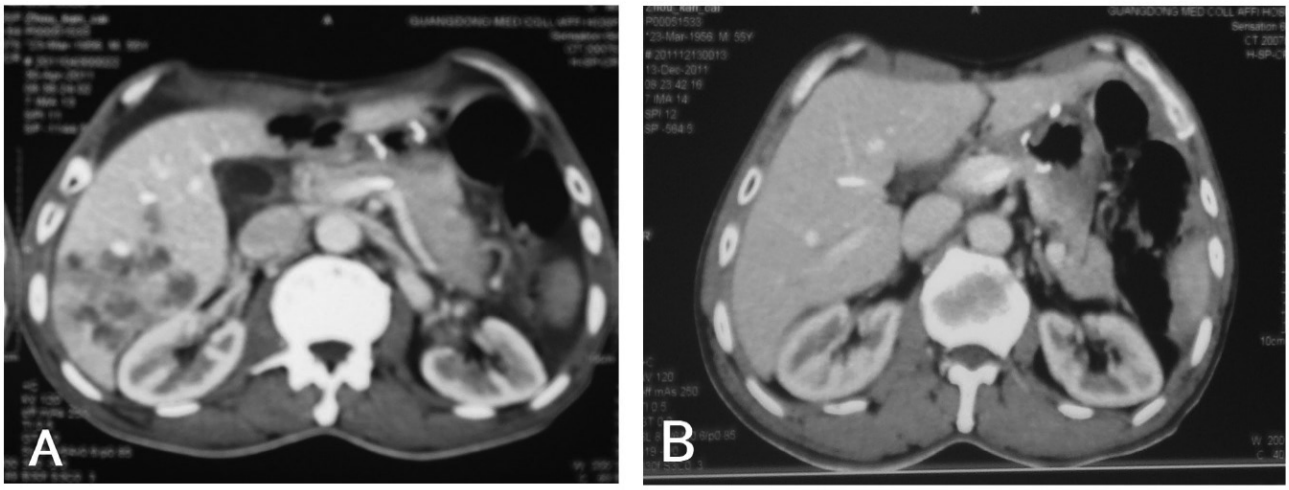

Figure 1. CT showing a male patient aged 55 years with histologically confirmed liver metastasis and complete response after 6 cycles of chemotherapy. A: before chemotherapy; B: after 6 cycles of chemotherapy.

All statistical analyses were conducted by SPSS 13.0. PFS and OS were calculated using the Kaplan-Meier method, with the median event time and a two-sided 95% confidence interval (95% CI) for the median provided for each of these endpoints.

Results

Patient characteristics

From February 2009, a total of 59 patients were enrolled onto the study. One patient discontinued chemotherapy due to intestinal obstruction in the first cycle. In addition, 2 patients refused continuation of chemotherapy and dropped out because of massive hemorrhage of the digestive tract after the first and third cycle, respectively. Finally, 56 of them were eligible for efficacy and tolerability evaluation. Patient characteristics are displayed in Table 1. There were 34 males and 22 females with median age 46 years (range 29-71). Twenty-six patients had ECOG PS 0 and 30 PS 1. The primary sites were as follows: gastroesophageal junction (N=11), gastric body (N=18), and pylorus (N=27). Histological types included papillary adenocarcinoma (N=13), tubular adenocarcinoma (N=11), mucinous adenocarcinoma (N=14), mixed adenocarcinoma (N=9), and signet-ring cell adenocarcinoma (N=9). Grades of differentiation included well differentiated (N=21), moderately well (N=13) and poorly differentiated (N=22) tumors. Metastatic sites are described in Table 1. Regional nodal metastases predominated, followed by peritoneal metastases.

Clinical response

Fifty-six patients completed more than 2 cycles of chemotherapy and were assessed for clinical response. One patient discontinued chemotherapy due to intestinal obstruction in the first cycle. In addition, 2 patients refused continuation of chemotherapy and dropped out because of massive hemorrhage of the digestive tract after the first and third cycle, respectively. At the time of analysis (December 2011), 33 (58.9%) patients had died, 16 (28.6%) were alive and 7 (12.5%) were lost to follow-up. All 56 patients received a total of 315 cycles of chemotherapy (median 5, range 3-7). The total follow-up and the median follow-up time were 21.4 and 17.6 months, respectively. Three cases (5.36%) achieved CR (one case of CR is shown in Figure 1), 39 cases (69.6%) PR, 5 cases (8.9%) SD, and in 10 cases (17.8%) there was disease progression (PD). The RR was 75%, and DCR 83.9%. The median PFS was 6.5 months (95% CI 5.6-7.3), the median OS 15.5 months (95% CI 13.9-17.0) (Figure 2), and the one-year survival rate was 82.5%.

Adverse effects

The adverse effets are summarized in Table 2. The main treatment-related grade 3/4 adverse effects

Table 2. Adverse events (N=56)

Adverse events	*Grade N (%)*					
	1	*2*	*3*	*4*	*1/2*	*3/4*
Haematological						
Neutropenia	6 (10.7)	5 (8.9)	19 (33.9)	15 (26.8)	11 (19.6)	34 (60.7)
Anemia	22 (39.3)	8 (14.3)	4 (7.1)	0 (0)	30 (53.6)	4 (7.14)
Thrombocytopenia	3 (5.4)	2 (3.6)	4 (7.1)	2 (3.6)	5 (9.0)	6 (10.7)
Non-haematological						
AST/ ALT	5 (8.9)	3 (5.4)	2 (3.6)	0	8 (14.3)	2 (3.6)
Creatinine	4 (7.1)	0	0	0	4 (7.1)	0
Nausea	12 (21.4)	9 (16.1)	8 (14.3)	0	21 (37.5)	8 (14.3)
Vomiting	10 (17.8)	9 (16.1)	8 (14.3)	0	19 (33.9)	8 (14.3)
Diarrhea	6 (10.7)	4 (7.1)	6 (10.7)	0	10 (17.8)	6 (10.7)
Bleeding	3 (5.4)	0	0	0	3 (5.4)	0
Rash	3 (5.4)	2 (3.6)	0	0	5 (9.0)	0
Pigmentation	5 (9.0)	2 (3.6)	0	0	7 (12.6)	0
Hand-foot syndrome	1 (1.8)	1 (1.8)	1 (1.8)	0	2 (3.6)	1 (1.8)
Alopecia	4 (7.1)	2 (3.6)	0	0	6 (10.7)	0
Neurotoxicity	7 (12.6)	10 (17.8)	5 (8.9)	2 (3.6)	17 (30.4)	7 (12.5)

included neutropenia (60.7%), thrombocytopenia (10.7%), impaired liver function (3.6%), vomiting (14.3%), diarrhea (10.7%), hand-foot syndrome (1.8%), and neurotoxicity (12.5%). There was no treatment-related death.

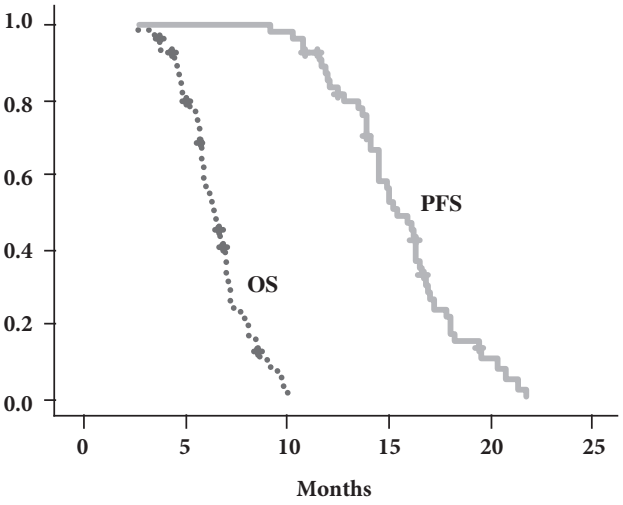

Figure 2. Kaplan-Meier overall survival (OS) and progression-free survival (PFS) of 56 patients. Median OS=15.5 months, median PFS=6.5 months.

Discussion

Gastric cancer is the second leading cause of cancer-related deaths on a global scale [1,2]. Palliative chemotherapy improves survival outcomes of advanced gastric cancer patients compared with best supportive care alone. RR is only 50% or less, and the median duration of survival is approximately 9-10 months. To improve clinical results, combination chemotherapy using established or novel cytotoxic agents had been the focus of several clinical trials [3-9].

According to the V325 study, docetaxel combination with cisplatin and 5-FU (DCF) was an effective regimen for advanced gastric cancer, which manifested better efficacy than CF on 2-year survival rate, PFS and OS in first-line treatment [22,23]. In 2006, the United States FDA approved DCF scheme as first-line treatment of advanced gastric cancer. However, DCF displayed severe hematological toxicity, even with dose reduction [18,19]. The need of new chemotherapy regimens is urgent for patients with advanced

gastric cancer. At present, some studies have demonstrated that S-1 displays considerable activity against solid tumors, with less leukocytopenia and mucositis than 5-FU [24-27], and this was the reason to use S-1 instead of 5-FU to observe the efficacy and safety of DCS in this study. Our results showed CR, PR and SD in 5.36, 69.6 and 8.9% of the patients respectively. The RR was 75% and the DCR 83.9%. The median PFS and OS were 6.5 and 15.5 months, respectively, which were longer than those achieved by DCF [22, 23]. In relation to effectiveness, our results seemed to be better compared to DCF regimen. Although there were 10 cases of mucinous adenocarcinoma and 7 cases with signet-ring cell adenocarcinoma in the present study, which are known to be non sensitive to chemotherapy, the 1-year survival rate was 82.5%. Our results displayed better RR, PFS and OS than the V325 study.

We also observed less toxicity of the docetaxel combination plus cisplatin and S-1 compared to DCF. Severe grade 3/4 toxicities included haematotoxicity (neutropenia 60.7% and thrombocytopenia 10.7%), impaired liver function (3.6%), vomiting (14.3%), diarrhea (10.7%), hand-foot syndrome (1.8%) and neurotoxicity (12.5%), while grade 3/4 neutropenia, diarrhea, and neurotoxicity in DCF were 82.0, 19.0, and 17.1%, respectively [22,23], proving that DCS is well tolerated. On the other hand, as an orally administered agent, S-1 dosage can be adjusted according to grade of adverse events, making it possible to continue chemotherapy more easily.

A phase study of DCS in advanced gastric cancer has been reported in 2010 by Sato et al. [20]. The regimen consisted of docetaxel (60 mg/m^2), cisplatin (60 mg/m^2) on day 8, and S-1 (40 mg/m^2 bid), day 1 to day 14, every 3 weeks. The RR was 87.1%, CR was 3.2% and PR 83.8%. The following grade 3/4 adverse reactions were recorded: neutropenia (64.5%), thrombocytopenia (22.6%), impaired liver function (6.5%) and diarrhea (16.1%). Our regimen was similar to that study in terms of RR although our study included some cases with poorly differentiated pathology and multiple metastases. The fact that the haematological and non-haematological toxicities of our study were lower than in the study of Sato et al. could possibly be explained with the different drug doses and administration schedule.

Targeted therapies combined with chemotherapy are currently the focus of novel treatments in advanced gastric cancer. Trastuzumab and chemotherapy had been demonstrated to improve survival and RR with HER2-positive breast cancer. Many studies found overexperession of HER2 in 7-34% of cases with gastric cancer [28,29]. Histologically, HER2 overexpression is more frequently associated with differentiated tumors and intestinal-type tumors [30,31], both of which would imply a more favorable outcome. In 2012 a clinical study reported that combinations of trastuzumab plus docetaxel-based regimens were effective and well tolerated in previously treated metastatic gastric cancer Chinese patients with HER2 overexpression [32]. In that study, PR was 59.1% and SD 31.8%, while no unexpected toxicities were observed. In our study, HER2 expression was not estimated, so the patients received chemotherapy without co-administration of targeted agents. Further studies are needed to define the efficacy of trastuzumab plus DCS chemotherapy in advanced gastric cancer.

In conclusion, our study suggests that the DCS combination chemotherapy is effective and well tolerated as first line treatment for patients with advanced gastric cancer. However, this study is limited by its small sample size. Future randomized, double-blind, placebo-controlled clinical trials are warranted to clarify the role of this regimen in advanced gastric cancer.

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