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Phase II Study of Docetaxel and Cisplatin as First-line Chemotherapy in Patients with Recurrent or Metastatic Gastric Cancer

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Purpose: **Palliative chemotherapy for patients with recurrent or metastatic gastric cancer has been shown to have a survival benefit. Docetaxel monotherapy has achieved appreciable results for treating gastric cancer. We investigated the clinical efficacy and feasibility of a docetaxel and cisplatin combination regimen for patients suffering with recurrent or metastatic gastric cancer.**

Materials and Methods: **Patients with histologically proven, bidimensionally measurable lesions of recurrent or metastatic gastric cancer, and they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and no prior palliative chemotherapy were eligible for this study. The combination chemotherapy regimen consisted of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 on day 1, and this was repeated every 3 weeks until disease progression.**

Results: **32 patients were enrolled from 2002 to 2005. The objective response rate was 31.3% (95% confidence interval (CI): 14.2～48.2%) with no CR. The disease control rate was 59.4%. At a median follow up of 38.9 months, the median overall survival was 7.4 months (95% CI: 6.3～8.5). The median time to progression was 4.7 months (95% CI: 3.1～6.3). During a total of 106 cycles, grade 3 or 4 hematological toxicities were observed as follows: neutropenia (39 of 106 cycles) and anemia (3 of 106 cycles). The grade 3 or 4 non-hematological toxicities included anorexia (18.9%) and nausea/vomiting (21.7%).**

Conclusion: **Docetaxel and cisplatin combination chemotherapy showed promising anti-tumor activity and this was well tolerated as a first-line treatment for patients with recurrent or metastatic gastric cancer. Further large, randomized phase III studies are warranted.** ***(Cancer Res Treat. 2007;39:49-53)***

Key Words: **Docetaxel, Cisplatin, Stomach neoplasms**

INTRODUCTION

Gastric cancer is the most prevalent malignancy in Korea, and it is 20.2% of all solid tumors (1). Advanced gastric cancer with distant metastasis or recurrence remains incurable, and these patients have a median survival of only 6～9 months. Cisplatin based combination chemotherapies such as FP (5-FU, cisplatin), FAP (5-FU, adriamycin, cisplatin) and EAP (etoposide, adriamycin, cisplatin) have been used since the 1980's (2,3). However, the results of cisplatin-based regimens have not been satisfactory, and they have shown a response rate of less than 50%. Therefore, the need for new chemotherapeutic agents such as paclitaxel, docetaxel, irinotecan and gemcitabine has been recognized and many trials with newer regimens are now ongoing. This study aimed to evaluate the efficacy and safety of docetaxel and cisplatin combination chemotherapy for patients with recurrent or metastatic gastric cancer.

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MATERIALS AND METHODS

This was non-randomized, prospective, open labeled, single institutional phase II trial. The study protocol was in accordance of the Declaration of Helsinki, and it was approved by the relevant ethical committees of our institution. Written informed consent was obtained from all the patients.

1) Patient eligibility

Eligibility criteria included the following: a patient age of 18 years or more but less than 75 years, histologically proven gastric adenocarcinoma, no prior palliative chemotherapy, a performance status (PS) of the Eastern Cooperative Oncology Group (ECOG) grade 2 or less, bidimensionally measurable disease, an adequate bone marrow function (white blood cells

4,000～12,000/μl, an absolute neutrophil count (ANC)≥1,500/μl, platelet count≥100,000/μl, hemoglobin≥10 g/dl), an adequate hepatic function (total bilirubin≤twice the upper normal limit, AST and ALT≤three times the upper normal limit), an adequate renal function (serum creatinine≤1.5 mg/dl) and an adequate cardiac function (normal electrocardiography or a left ventricular ejection fraction >50%).

The patients excluded from this trial were those with a history of other malignancies, uncontrolled concurrent medical illness, active angina, myocardial infarction or congestive heart failure within the previous 6 months, symptoms attributable to brain metastasis and symptoms of severe infection. Pregnant or lactating patients were also excluded.

2) Treatment schedule and dose modification

Docetaxel (75 mg/m^2) was administered as a 1-hour intravenous infusion on day 1. After completion of the docetaxel infusion, cisplatin (75 mg/m^2) was infused for 1 hour with administering adequate hydration, diuretics and mannitol on day 1. The cycle was repeated every 21 days. Antiemetic prophylaxis with 5-HT$_3$-receptor antagonist was routinely prescribed. Also, prophylaxis consisting of dexamethasone was used for the anaphylaxis caused by docetaxel.

Toxicities were graded according to the National Cancer Institute of Clinical Trials group expanded Common Toxicity Criteria (NCI-CTC) scale version 2.0. When patients experienced neutropenia (ANC<1,500/μl), thrombocytopenia (platelet count <100,000/μl), or any other nonhematologic toxicity greater than grade 2, then both the cancer drugs were reduced by 25%. The administration of granulocyte-colony stimulating factor was permitted when grade 3 or 4 neutropenia occurred. The cisplatin dose was reduced by 20% for the cases of grade 2 peripheral neuropathy and it was reduced by 50% if the creatinine clearance rate was less than 50 ml/min.

3) Evaluations of treatment and determination of response

The pretreatment evaluation included a complete medical history and physical examination, a complete blood count (CBC) with the differential counts, and blood chemistries for the liver and renal functions. During the first cycle, CBCs were performed weekly and thereafter CBCs were performed before the beginning of each cycle.

A detailed medical history and physical examination were performed before each course of treatment to document the disease symptoms and the toxicities of the chemotherapy. The patients' blood chemistries were examined every 3 weeks. Image studies such as CT scan or ultrasonography were examined every 6 weeks to evaluate the response to chemotherapy.

The tumor response was evaluated according to the WHO criteria (4). A complete response (CR) was defined as the complete disappearance of all known disease without the appearance of new lesions, as confirmed by two examinations performed at least 4 weeks apart. A partial response (PR) was defined as a decrease of 50% or more in the sum of the products of the perpendicular diameters of each measurable lesion, as confirmed by two examinations performed at least 4 weeks apart, along with no progression or appearance of other new lesions. Disease that failed to fulfill the above criteria, but did not show a 25% or greater increase in the total tumor load was classified as a stable disease (SD) in the absence of any new lesions. Progressive disease (PD) was defined as an increase of 25% or more in the size of at least one measurable lesion.

4) Statistical analysis

The primary end point of this study was to determine the objective response rate of the docetaxel and cisplatin combination regimen for patients with recurrent or metastatic gastric cancer as first line chemotherapy. The secondary end points were to measure the toxicity, time to progression (TTP), and the overall survival (OS). Descriptive statistics are reported as proportions and medians. Kaplan-Meier estimates were used in the analysis of all the time-to-event variables, and the 95% confidence interval (CI) for the median time to events was computed. TTP was defined as the time from the initiation of treatment to the date of documented disease progression. The OS was measured from the time of registration to the date of death resulting from any cause. The OS and TTP were assessed by the Kaplan-Meier method. The dose intensity was calculated as the ratio of the total dose divided by the total treatment duration. The relative dose intensity was calculated as the ratio of the dose intensity actually delivered to the dose intensity planned by the protocol.

RESULTS

1) Patient characteristics

32 patients were prospectively enrolled from 2002 to 2005. The median age was 57 years (range: 27～74) and the male and female ratio was 23 : 9. The ECOG PS was 0 in 12 patients, 1 in 15 patients and 2 in 5 patients. Most of them (21 patients) had a histologic grade of poorly differentiated tumor. By clinical stage, 27 patients had stage IV disease and 5 patients had disease relapse after curative gastrectomy. The major metastatic sites were the liver (11 patients), peritoneum (10 patients) and lymph nodes (6 patients) (Table 1).

2) Exposure to study medication

A total of 106 cycles were administered with a median of 3 cycles per patient (range: 1～6 cycles), and 27 patients were evaluable for treatment response. The relative dose intensity of docetaxel and cisplatin was 82.4% and 80.4% respectively. Seventeen of 32 patients (53.1%) received second-line chemotherapy, and most of which contained irinotecan and/or 5-FU.

3) Response rate and survival

By the intention-to-treat analysis of the full population, the objective response rate (RR) was 31.3% (95% CI: 14.2～48.2) with 10 partial responses, 9 cases of stable diseases (28.1%), and 8 cases of progressive diseases (25%), for a disease controlled rate of 59.4% (Table 2). At a median follow up of 38.6 months, the median OS was 7.4 months (95% CI: 6.3～8.5) and the median TTP was 4.7 months (95% CI: 3～16.3) (Fig. 1, 2).

Table 1. Patients and their disease characteristics

	No. (%)
No. of enrolled patients	32
No. of evaluable patients	27
Gender	
Male	23 (71.9)
Female	9 (28.1)
Median age (range)	57 (27～74)
ECOG PS	
0	12 (37.5)
1	15 (46.9)
2	5 (15.6)
Disease status	
Recurrent	5 (15.6)
Metastatic	27 (84.4)
Histologic grade	
Well differentiated	2 (6.3)
Moderately differentiated	9 (28.1)
Poorly differentiated	21 (65.6)
Metastatic site	
Liver	11 (34.3)
Peritoneum	10 (31.2)
Lymph node	6 (18.8)
Colon	3 (9.4)
Bone	3 (9.4)
Ovary	2 (6.3)
Anastomosis site	2 (6.3)
Others	4 (12.5)

Table 2. Response to treatment

Response	No. (%)
Progressive disease	8 (25)
Stable disease	9 (28.1)
Partial response	10 (31.3)
Complete response	0 (0)
Not assessable	5 (15.6)
Objective response rate	31.3%
Disease control rate	59.4%

4) Toxicity

For a total of 106 administered cycles, the most common hematological toxicity was neutropenia. Grade 3 or 4 neutropenia was observed in 39 cycles (36.8%). Febrile neutropenia occurred in 6 cycles (5.7%). The frequent grade 3 to 4 non-hematological toxicities included nausea/vomiting in 23 cycles (21.7%), anorexia in 20 cycles (18.9%), and lethargy in 17 cycles (16%). Only one patient discontinued treatment because of toxicity (grade 4 vomiting). Still, the toxicities were generally manageable (Table 3).

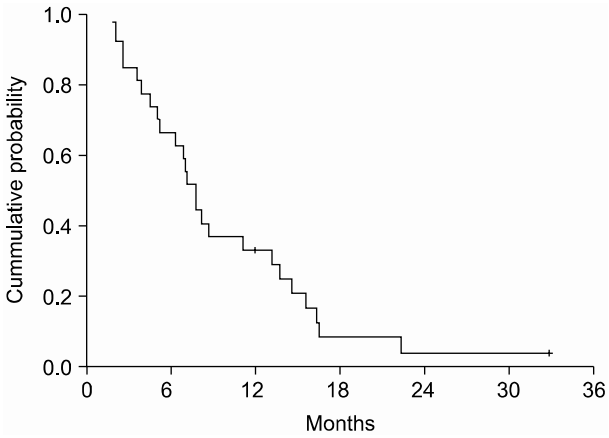

Fig. 1. Overall survival curve by the Kaplan-Meier method. The median OS was 7.4 months (95% CI: 6.3～8.5).

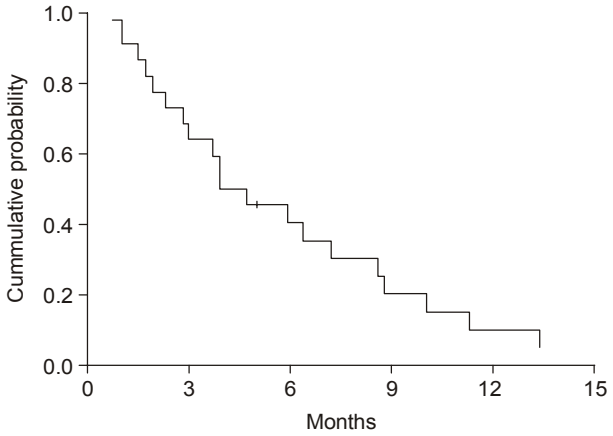

Fig. 2. Time to progression curve by the Kaplen-Meier method. The median TTP was 4.7 months (95% CI: 3.1～6.3).

Table 3. Frequency of common toxicities

Toxicity (total 106 cycles)	Grade 3	Grade 4	Overall (%)
Neutropenia	16	23	39 (36.8)
Febrile neutropenia	6	0	6 (5.7)
Anemia	3	0	3 (2.8)
Thrombocytopenia	0	1	1 (0.9)
Nausea/vomiting	22	1	23 (21.7)
Anorexia	20	0	20 (18.9)
Lethargy	17	0	17 (16)
Stomatitis	6	0	6 (5.7)
Diarrhea	5	0	5 (4.7)
Neuropathy	1	0	1 (0.9)

Table 4. Comparison with the other phase II trials

	No. of patients	Docetaxel (mg/m^2)/ Cisplatin (mg/m^2)	RR (%)	OS (months)	TTP (months)	Grade 3 & 4 neutropenia (%)
Present study	32	75/75	31.3	7.4	4.7	36.8
Roth	46	85/75	56	9	6.6	57
Ridwelski	43	75/75	37.2	10.4	6.1	18.6 (leukopenia)
Ajani	76	85/75	26	10.5	5.0	87
Yashushi	27	60/80	25	9.7	-	82.1
Park	86	75/75	43.5	11.5	7.0	17.4

DISCUSSION

According to the annual report of the cancer registry program in the Republic of Korea, gastric cancer is the most prevalent solid tumor in Korea, and it is estimated to be 20.2% of all solid tumors (1). When compared with the best supportive care, chemotherapy for advanced or recurrent gastric cancer has been reported to have survival benefits (5,6). This study evaluated the efficacy and safety of docetaxel and cisplatin for treating recurrent or metastatic gastric cancer. Docetaxel and cisplatin combination treatment achieved an objective response rate of 31.3% (95% CI: 14.2～48.2%). In Table 4, this study's results are compared with those of the previous phase II studies. Overall, the RRs range from 26% to 43.5%. The TTPs ranged from 5.0 to 7.0 months, and the median OS ranged from 9.0 to 11.5 months (7～11). The objective response of this study was generally consistent with those from the previous studies. The median OS was 7.4 months (95% CI: 6.3～8.5) and the 2-year survival rate was 6.9%. The median TTP was 4.7 months (95% CI: 3.1～6.3) and 1-year progression free survival was 9%. There were no independent factors that had an influence on survival such as age, the nodal status, the histologic grade and the performance status. A poor performance status and histologic grade had independent adverse effects on the TTP on univariate analysis, but not on multivariate analysis.

In this study, the relative dose intensities were 82.4% and 80.4% for docetaxel and cisplatin, respectively. Although it didn't show a very high value, grade 3 or 4 neutropenia developed in only 36.8% of the patients, which is a lower percentage compared with the above mentioned studies. Additionally, only one patient discontinued treatment because of toxicity (grade 4 vomiting). Therefore, this suggests that the toxicity of docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) combination treatment may be manageable. In Table 4, the incidence of grade 3 or 4 neutropenia was less than that of most other studies with the exception of only one study by Park et al (11). The application of a lower dose of docetaxel compared to other studies may have contributed to this result (7～11).

The limitations of this study are the small number of enrolled patients and that it is a non-randomized trial. Further clinical trials are warranted with using different dose schedules and dosages of docetaxel for the palliative treatment of gastric cancer.

CONCLUSIONS

The combination of docetaxel and cisplatin as first-line chemotherapy was revealed to have a modest anti-tumor effect and manageable toxicity for the palliative treatment of recurrent or metastatic gastric cancer. However, more optimal systemic chemotherapy is still needed and conducting clinical trials with using novel anti-tumor agents is warranted.

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