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Original Article

A Clinical Study of Docetaxel With or Without 5′DFUR as a Second-Line Chemotherapy for Advanced Gastric Cancer

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Abstract

We conducted a clinical pilot study to evaluate the efficacy and safety of the combination of docetaxel and 5′DFUR as a second-line chemotherapy for gastric cancer. Twenty-four patients were divided into two groups by simple randomization: group A (60 mg/m^2 of docetaxel, every 3 wk) and group B (regimen A + 600 mg/body of 5′DFUR). The response rate was 17% and 42% in group A and B, respectively ($p < 0.05$). The MST from the start of the first-line was 17 mo in group B. The major adverse event was leukopenia in both groups.

Key Words: Gastric cancer; chemotherapy; taxan; docetaxcel; 5′DFUR; second-line chemotherapy.

Introduction

Gastric cancer is one of the most common neoplasms, and an estimated total of 876,341 cases/yr of gastric cancer are diagnosed worldwide *(1).* For patients whose tumors are not surgically resectable or who develop recurrence after resection, chemotherapy can provide a significant prolongation of survival in comparison to the best supportive care alone *(2,3).*

S-1–based regimens are popular as first-line chemotherapy for advanced or recurrent gastric cancer in Japan. S-1 is a new oral fluoropyrimidine that inhibits dihydropyrimidine dehydrogenase (DPD). S-1 is reported to show a response rate of 30–40% for advanced or recurrent gastric cancer *(4)* and significant prolongation of survival in patients with peritoneal metastasis from gastric cancer *(5).* However, once patients receiving S-1–based regimens develop progressive disease, no established second-line regimen can presently be offered.

In contrast to S-1, taxan shows an antitumor activity by inhibiting the microtubule/tubulin system. In addition, the combination of taxan and 5′DFUR has been reported to show a synergic antitumor efficacy, while combinations with other 5-FU, such as UFT (a mixture of tegafur and uracil), have been documented to show only an additive activity *(6).* It is thus feasible that the combination of docetaxel and 5′DFUR may be a promising second-line chemotherapy after a failure of S-1 therapy.

The purpose of this study is to evaluate the combination of docetaxel and 5′DFUR as a second-line chemotherapy for advanced gastric cancer, in comparison to a regimen of docetaxel alone. We evaluated the response rate, overall survival, and safety.

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Patients and Methods

Patient Eligibility

All patients had histologically proven metastatic or recurrent, or unresectable locally advanced, gastric cancer with measurable or evaluable lesions. They had already received first-line chemotherapy before their entry into this study and showed no response or disease progression after initial response (at least 4 wk interval between prior chemotherapy and this study). The inclusion criteria were age 20–75 yr, performance status of World Health Organization (WHO) 0–2, and an estimated life expectancy of more than 3 mo. Additional criteria included the following: a white blood cell (WBC) count between 4000 and 12,000/mm^3, absolute neutrophil count of over 2000/mm^3, platelet count of over 100,000/mm^3, hemoglobin over 9.5 g/dL, AST and ALT within twice upper limit, serum bilirubin level under 1.5 mg/dL, BUN under 25 mg/dL, serum creatinine under 1.5 mg/dL, and the measured 24-h creatinin clearance over 60 mL/min. Any patients having a history of drug hypersensitivity, serious complications, symptomatic infectious disease, bleeding tendency, symptoms attributable to brain metastasis, or active double cancer were excluded from the study. Pregnant or lactating patients were also excluded. Written informed consent was obtained from all patients and the study was approved by the ethics committees of the participating institutions. The patient enrolment was started in January 2004 and completed in December 2005. The patient progress was observed until the end of April 2006.

Study Design and Chemotherapy Regimen

This is a clinical pilot study by simple randomization. Regimen A comprised docetaxel (60 mg/m^2 1-h intravenous infusion every 3 wk) alone. Regimen B consisted of docetaxel (60 mg/m^2 1-h intravenous infusion every 3 wk) and 5′DFUR (600 mg/body orally every day). Both regimens were repeated for at least two cycles. Chemotherapy was delayed until recovery if the hematological toxicity of grade 3–4 or the nonhematological toxicity of grade 2 or more occurred. Treatment was continued until the disease progressed, an unacceptable degree of toxicity occurred, or the patients chose to discontinue the treatment.

Evaluation Criteria

Physical examinations and weekly complete blood cell counts with differential and platelet counts were obtained by serum chemistry before each cycle. Tumor reassessment was carried out by computed-tomography scans of the abdomen every two or three cycles, and serum tumor marker (CEA and/or CA19-9) and chest X-ray every cycle.

The primary endpoint was set as the tumor response and the overall survival, and the secondary endpoint was toxicity with the treatment. World Health Organization criteria were used to assess the tumor responses. A partial response (PR) was defined as a decrease of at least 50% of the sum of the diameters of measurable lesions for at least 4 wk. No change (NC) was defined as a decrease of less than 50% or an increase of less than 25% of measurable lesions, and progressive disease (PD) was defined as an increase of at least 25% measurable lesions or the appearance of new malignant lesions. Throughout the trial, adverse events were assessed based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Statistical Analysis

Overall survival was defined as the time from the start of the treatment until death or final follow-up time, using the Kaplan–Meier method, and compared with the log-rank test. Others were compared with Fisher's exact test or Mann–Whitney U test. A p value of less than 0.05 was taken to indicate a statistically significant difference.

Results

Patient Characteristics

Table 1 shows the clinical features of group A (docetaxel alone) and group B (docetaxel + 5′DFUR). The prior chemotherapy regimen (first line) was S-1 in all patients of group A, while S-1, S-1 + CDDP, and MTX + 5FU in 9, 2, and 1 patients of group B, respectively. The number of prior chemotherapy cycles were 6.1 ± 4.5 courses (range: 1–14 courses) in group A and 4.5 ± 3.2 courses (range: 1–10 courses) in group B, respectively. No statistically significant difference was seen for any of the patient factors between groups A and B.

Table 1
Patients Characteristics

	Regimen A (n = 12) Docetaxel alone	Regimen B (n = 12) Docetaxel + 5′DFUR
Age (range)	64.8±4.1 (59–71)	61.3±10.6 (38–74)
Sex		
male	9	9
female	3	3
Performance status		
0	6	5
1	5	6
2	1	1
Prior chemotherapy		
S-1	12	9
S-1 + CDDP	0	2
MTX + 5FU	0	1
Histology		
differentiated	8	6
undifferentiated	4	6
Target lesion		
primary	4	5
liver	5	3
lymph nodes	2	6
peritoneum	3	2
lung	1	0
Status		
recurrent after curative operation	6	6
remnant after palliative operation	2	0
unresectable	4	6
Cycles of second-line chemotherapy (range)	3.3±2.1 (2–9)	5.0±2.7 (2–10)
Third-line chemotherapy		
CPT11	1	2
CDDP+5FU	0	1

Response

Table 2 shows the response of group A (docetaxel alone) and group B (docetaxel + 5′DFUR). The response rate was 17% in group A and 42% in group B, respectively. The response rate of all 24 patients was 29%.Regarding the serum tumor marker level (CEA or CA19-9), six patients showed three times or more than normal limit before the start of the second-line chemotherapy in group A, and two of these six patients (33%) showed a

Table 2
Response

	Regimen A (n = 12) Docetaxel alone	Regimen B (n = 12) Docetaxel + 5′DFUR
Partial response	2	5
No change	2	2
Progressive disease	8	5

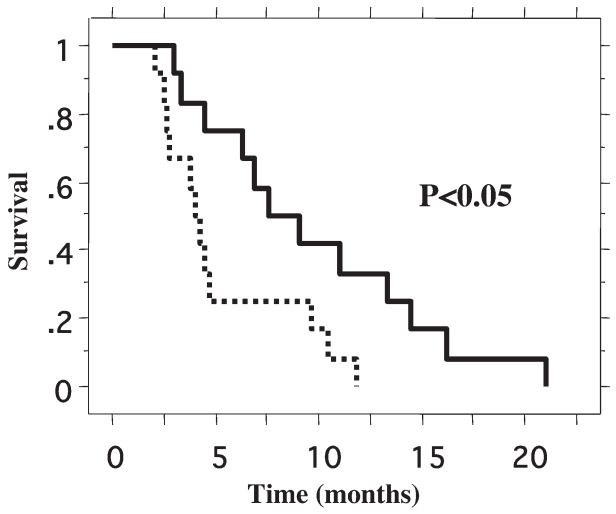

Fig. 1. Overall survival curves from the start of second-line chemotherapy (Kaplan–Meier method). Docetaxel + 5′DFUR (solid line) vs docetaxel alone (dotted line).

decrease of the marker after second-line treatment. In contrast, in group B, five patients showed three or more times the normal limit before the start of second-line chemotherapy, and four of the five patients (80%) showed a decrease in the marker after the second-line treatment.

Survival

The overall survival curves from the start of the second-line chemotherapy are shown in Fig. 1. The median survival time (MST) was 4.0 and 7.6 mo in group A and B, respectively ($p < 0.05$). In contrast, the MST from the start of the first-line chemotherapy was 10 and 17 mo in group A and B, respectively (p=0.21). In all 24 patients, the MST from the start of the first-line and second-line was 16 and 4.7 mo, respectively. The MST from the start of the second line of 7 responders was significantly longer than that of 17 non-responders (11.8 vs 4.5 mo, respectively. $p < 0.01$). Similarly, the MST of six patients who showed the decrease in the tumor marker after second-line treatment was longer than that of the five patients who showed an increase (9.6 vs 3.0 mo, respectively; $p < 0.01$).

Toxicity

Table 3 summarizes the toxicity observed during all the treatment courses. Adverse events occurred in 92% of the patients in both groups A and B, and Grade 3 or 4 adverse events occurred in 58% and 50% of the patients in groups A and B, respectively. No treatment-related deaths occurred.

Discussion

In this study, docetaxel plus 5′DFUR combination therapy showed a significant prolongation of survival (7.6 mo) in comparison to docetaxel alone (4.0 mo). The response rate of combination therapy (42%) was better than that of docetaxel single therapy (17%), even though the difference did not reach statistical significance. Another study of docetaxel combination (with cisplatin) as second-line chemotherapy for gastric cancer reported the median survival to be 6 mo and the response rate to be 26.7% *(4).* In contrast, docetaxel single therapy showed a 3.5 mo of median survival and a 4.8% response rate *(7).* These reports and our results suggest that the combination of docetaxel and other agents is thus more effective than docetaxel alone as a second-line chemotherapy for gastric cancer.

In a review of second-line chemotherapy for advanced gastric cancer, the mean response rate for all 12 trials was reported to be 20.8% and the mean of median survival was 5.6 mo *(8).* In comparison to those results, our study (using the combination of docetaxel and 5′DFUR) showed a better efficacy (response rate: 42%) and survival (median: 7.6 mo). Our findings also showed a good survival from the start of the first-line chemotherapy using the combination regimen (median 17 mo). The combination of docetaxel and 5′DFUR thus seems one of the promising regimens as a second-line chemotherapy for gastric cancer.

Regarding toxicity, no difference was observed between the combination therapy (docetaxel + 5′DFUR) and docetaxel alone. Hematological toxicity appeared most frequently, and severe leukopenia of grades 3 or 4 occurred in 33% of the patients in both groups. A study of docetaxel + cisplatin as a second-line chemotherapy reported grades 3 or 4 hematological toxicity to appear in 26.7% of the patients *(4),* and those results were similar to ours. The administration of G-CSF to patients with neutropenia supported their recovery and resulted in no infectious complications, and no treatment-related deaths occurred.

Table 3
Toxicity

	Regimen A (n = 12) Docetaxel alone [all (Grade 3 or 4)]	Regimen B (n = 12) Docetaxel + 5′DFUR [all (Grade 3 or 4)]
Leukopenia	6 (4)	8 (4)
Neutropenia	5 (4)	6 (4)
Thrombocytopenia	1 (1)	
Anemia	1 (1)	
Anorexia	4 (1)	3 (1)
Nausea	4 (1)	1 (0)
Stomatitis	2 (1)	3 (0)
Diarrhea	1 (0)	
Fatigue	3 (1)	4 (0)
Alopecia	5 (-)	7 (-)

Wilson et al. reported factors associated with a greater likelihood of response to second-line chemotherapy for gastric cancer: including, PS 0–1, re-treatment after failure of non-platinum-based regimens, previous response or stable disease with first-line chemotherapy, and treatment of locally advanced rather than metastatic disease *(8)*. In our study, no significant differences were observed regarding those factors between the combination regimen and single therapy, and no differences between the responders and non-responders were observed, either. However, it is quite important to clarify the predictive factors for the response to second-line chemotherapy, because responders showed a good survival in our study and other reports *(8);* however, not all patients are indicated to receive second-line chemotherapy.

In conclusion, we revealed the advantages of docetaxel-combination therapy (docetaxel + 5′DFUR) in comparison to docetaxel single therapy as a second line for gastric cancer. A large-scale phase III study is therefore necessary to confirm the utility of this regimen and identify any predictive factors for determining the patient response to this therapeutic regimen.

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