

Docetaxel + 5-Fluorouracil + Cisplatin 3-day Combination Chemotherapy as a First-line Treatment in Patients with Unresectable Gastric Cancer

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Background: Our objective was to verify the efficacy and safety of 'docetaxel + 5-fluorouracil + cisplatin' 3-day combination chemotherapy as a first-line treatment in patients with unresectable gastric cancer.

Methods: Between January and November 2002, we enrolled 43 patients [males 31; median age 55 years (range 24–74)] with inoperable gastric cancer who had not been seen previously in Seoul National University Hospital. The regimen used was docetaxel 70 mg/m² on day 1, cisplatin 40 mg/m² on days 2 and 3, and 5-fluorouracil 1200 mg/m² over 10 h on days 1–3, every 3 weeks.

Results: A total of 168 cycles were administered. Mean cycle number per patient was 3.9. The administered dose intensity of docetaxel was 21.23 mg/m²/week, 5-FU 1092.14 mg/m²/week and cisplatin 23.82 mg/m²/week, which corresponded to 91.1, 91.0 and 89.5% of planned doses. Of the 43 patients, response evaluation was possible in 40 and, of these patients, 17 (42.5%) achieved a partial response, 13 (32.5%) stable disease, and 10 patients (25%) showed progressive disease. The median time to progression was 5.6 months [95% confidence interval (CI) 4.6–6.6 months]. Median overall survival was 9.0 months. (95% CI 4.8–13.2 months). Leukopenia occurred during 21.4% of cycles (36 of 168 cycles); 14.3% grade 1, 5.3% grade 2 and 1.8% grade 3. Anemia occurred in 16.7% (28 of 168 cycles); 11.3% grade 1, 4.8% grade 2 and 0.6% grade 3. Thrombocytopenia was not observed. Diarrhea, stomatitis and hypersensitivity occurred in 4.7% (two out of 43 patients), respectively. Neutropenic fever occurred in two patients (4.7%) and myalgia in three (7.0%).

Conclusion: 'Docetaxel + 5-fluorouracil + cisplatin' 3-day combination chemotherapy is an active and tolerable regimen as a first-line treatment in patients with unresectable gastric cancer.

Key words: cisplatin – docetaxel – 5-fluorouracil – gastric cancer – chemotherapy

INTRODUCTION

Patients with inoperable gastric cancer may benefit from palliative chemotherapy. However, to date, there is no generally accepted standard regimen.

Single chemotherapeutic agents, e.g. doxorubicin, cisplatin, 5-fluorouracil (5-FU) and mitomycin C, have long been considered as active drugs (1), and more recently drugs such as paclitaxel, docetaxel, oxaliplatin and irinotecan have been added to the list.

A number of controlled studies of two-drug combination chemotherapies, especially cisplatin-containing regimens,

have shown a significant improvement in median survival and quality of life compared with best supportive care (2,3). Of these, 5-FU and cisplatin combination (FP) has been considered as an active and safe regimen for a long time. Its use was supported by the results of a study conducted in our center in 1993 (4).

Many trials using combinations of three drugs have been conducted to improve treatment results further in advanced gastric cancer. One of the three-drug combination is adding docetaxel, a novel semi-synthetic taxoid, to '5-FU + cisplatin' (DCF). According to the interim analysis of a recent randomized phase III study by Ajani et al., the DCF regimen is superior to the FP regimen in terms of response rate, time to progression and overall survival with manageable toxicity as a first-line treatment in advanced gastric cancer (5). However, the superiority of three-drug combinations to two-drug combinations has not been accepted worldwide yet.

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In our center, because of the results of a previous study which verified a higher response rate to FP than FAM or 5-FU alone, we wished to confirm the efficacy of combining docetaxel, a novel agent, with FP.

There had been several combination methods regarding these three drugs. These combinations had been studied actively in head and neck cancer (6–10). In various combinations, docetaxel could usually be used up to 70–80 mg/m², cisplatin up to 75–100 mg/m² and 5-FU up to 4000 mg/m² per cycle with manageable toxicity. We wanted to shorten the treatment duration and avoid the overnight continuous infusion so that the regimen can be used on a day care system basis without the need for an infusion pump. Among these methods, Janinis et al. used docetaxel 80 mg/m² on day 1, cisplatin 40 mg/m² on days 2 and 3, and 5-FU 1000 mg/m² by 24 h continuous infusion on days 1–3 every 4 weeks in head and neck cancer (6). Based on this regimen of Janinis et al., we previously conducted a phase I/II study in head and neck cancer using docetaxel 70 mg/m² on day 1, cisplatin 40 mg/m² on days 2 and 3, and 5-FU 1200 mg/m²/day over 10 h on days 1–3 every 3 weeks in our center (data not yet published) which was initiated in March 2001. In that study, this regimen was considered feasible. This experience prompted us to select the same scheduling for gastric cancer at the time when we were considering this three-drug combination in that cancer. This regimen is different from that used by Ajani et al., which included docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1 and 5-FU 750 mg/m²/day administered by continuous infusion on days 1–5 every 3 weeks.

Furthermore, since drug toxicity profiles usually differ somewhat in ethnic groups, we wanted to determine the safety of the DCF regimen for use in Korean patients with gastric cancer.

Thus, we conducted a phase II study to determine the efficacy and safety of 'docetaxel + 5-FU + cisplatin' 3-day combination chemotherapy consisting of docetaxel 70 mg/m² on day 1, cisplatin 40 mg/m² on days 2 and 3 and 5-FU 1200 mg/m²/day over 10 h on days 1–3 as a first-line treatment in patients with inoperable gastric cancer.

PATIENTS AND METHODS

ELIGIBILITY CRITERIA

Patients entered into this study were required to fulfill the following eligibility criteria: (i) histologically proven gastric cancer with measurable metastatic lesions; (ii) age between 18 and 75 years old; (iii) Eastern Clinical Oncology Group (ECOG) scale performance status of 0, 1 or 2; (iv) no prior palliative chemotherapy; (v) adequate functions of bone marrow (white blood cell count >4000/μl and platelet count >100 000/μl), liver (serum bilirubin level <2.0 mg/dl and serum transaminase level less than three times the upper limits of normal range) and kidney (serum creatinine level <1.5 mg/dl, blood urea nitrogen level <25 mg/dl and creatinine clearance >50 ml/min); (vi) no other severe medical

conditions; (vii) no secondary malignancy; and (viii) no clinical evidence of metastasis to the central nervous system.

Informed consent was provided by all patients. This study was approved by our institutional review board.

TREATMENT SCHEDULE

The chemotherapy regimen consisted of: docetaxel 70 mg/m² intravenous infusion over 1 h on day 1, 5-FU 1200 mg/m²/day intravenous infusion over 10 h on days 1–3, and cisplatin 40 mg/m² intravenous infusion over 15 min on days 2 and 3. We used a dexamethasone 10 mg intravenous push 15 min before docetaxel infusion and dexamethasone 8 mg per os twice a day for 2 days. Also, pre- and post-cisplatin hydration with dextrose was performed on days 2 and 3. A serotonin antagonist was used as an antiemetic.

Treatment was repeated every 3 weeks until disease progression, patient refusal or unacceptable adverse reactions.

DOSE MODIFICATIONS

Chemotherapy was delayed until neutrophils were recovered (>1500/μl) or platelets reached >100 000/μl, or until resolution of any significant non-hematological toxicity. Doses of all drugs were reduced by 25% in subsequent cycles in the case of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 4 neutropenia or grade 3–4 thrombocytopenia lasting for >3 days, or in the case of febrile neutropenia, which was treated with granulocyte colony-stimulating factor (G-CSF) and antibiotics. The dose of all drugs was reduced by 25% in subsequent cycles in the case of NCI-CTC grade 3–4 mucositis and in the case of poor performance status (over ECOG 2). Cisplatin was reduced by 25% when the glomerular filtration rate was between 60 and 40 ml/min.

EVALUATION

For evaluation of tumor response, the best objective imaging technique for the particular patient was selected from the pre-treatment evaluation. The same technique was then performed every two cycles by the same investigator. Objective response to chemotherapy in measurable lesions was evaluated by the standard World Health Organization criteria. Toxicity was graded according to NCI-CTC Version 2.0.

All patients who received more than two cycles of chemotherapy were evaluable for response and time to progression. Patients who developed rapid tumor progression after any amount of therapy were also evaluated. Patients who received at least one cycle of chemotherapy were evaluable for toxicity, and all patients were included in the intent-to-treat survival analysis.

END-POINTS

The primary end-point was response rate and time to progression, and the secondary end-point was overall survival.

STATISTICAL CONSIDERATIONS

The study followed the optimal Simon two-step design. It was believed that a response rate of >25% would justify continuing the trial (H0). The response rate was expected to be 45% (H1). The probability of accepting the treatment combination with response probability H0 (25%) is $\alpha = 0.10$. The probability of rejection of the combination with response probability of H1 = 40% is $\beta = 0.10$. If at least three of the first 14 patients showed an objective response, the study could be continued to a total of 43 patients. If a response of at least 14 patients could be documented, the hypothesis H0 could be rejected. Time to progression was determined as the interval between the initiation of treatment and the date when disease progression was first documented or the date of death from any cause. Overall survival was measured from the date of treatment initiation to the date of death. Follow-up time was measured from the day of first treatment administration to the study's cut-off date (for living patients). Time to progression and overall survival were estimated by the Kaplan–Meier method, and the confidence intervals (CIs) were calculated based on Greenwood's formula.

RESULTS

PATIENT CHARACTERISTICS

From January to November 2002, 43 patients (31 men, 12 women) were enrolled in the study. The patient characteristics are listed in Table 1. The median age of the patients was 55 years (range 24–74). Thirty-nine patients (90.7%) had performance status 0 or 1. All patients had measurable metastatic lesions, and metastatic sites were located in the liver in 11 patients (25.6%), intra-abdomen lymph node in 22 patients (51.2%), peritoneum in 19 patients (44.2%), lung in three patients (7.0%), supraclavicular lymph node in four patients (9.3%), and ovary, kidney and adrenal gland in one patient each.

DRUG EXPOSURE

A total of 168 chemotherapy cycles were administered (mean 3.90 cycles per patient, range 1–8). Treatment was extended to eight cycles in a patient with a partial response who expressed a wish for further therapy. The dose was reduced in 24 cycles (14.3%). The duration of delay was a total of 30 weeks. The actual administered dose of docetaxel was 21.23 mg/m²/week, that of 5-FU was 1092.14 mg/m²/week, and that of cisplatin was 23.82 mg/m²/week, which corresponded to 91.1, 91.0 and 89.5% of planned doses.

The most common reason for dose reduction was cytopenia. Other causes were decreased renal function and poor performance status.

EFFICACY

The response to treatment could not be evaluated in three patients. Two patients were lost to follow-up before response

Table 1. Patient characteristics

Characteristic	No. of patients
Patients enrolled	43
Age (years)	
Median	55
Range	24–74
Sex	
Male	31
Female	12
Performance status	
0, 1	39
2	4
Metastatic site	
Liver	11
Lymph nodes (intraabdomen)	22
Peritoneum	19
Lung	3
Supraclavicular lymph node	4
Ovary	1
Kidney	1
Adrenal	1

Table 2. Response

Response	No. of patients (%)
Complete response (CR)	0 (0)
Partial response (PR)	17 (42.5)
Stable disease (SD)	13 (32.5)
Progressive disease (PD)	10 (25.0)

evaluation and one patient refused further chemotherapy after one cycle. The systemic toxicities of these three patients were evaluated.

Efficacy data are shown in Table 2. Of the 40 evaluable patients, no patient showed complete remission and 17 patients achieved partial response. The overall response rate was 42.5%. Thirteen patients (32.5%) showed stable disease and 10 patients (25.0%) progressive disease. The response to chemotherapy did not differ significantly according to the sex, age (younger than 65 years versus older), performance status (ECOG 0 and 1 versus 2) and metastatic sites.

The median time to progression was 5.63 months (95% CI 4.67–6.60). The median overall survival was 9.03 months (95% CI 4.80–13.26). These are shown in Figs 1 and 2.

Among the patients who responded to chemotherapy, no one underwent surgery.

Sixteen patients received second-line chemotherapy after failure of this regimen. [irinotecan-based chemotherapy in five patients, oxaliplatin-based chemotherapy in six patients, paclitaxel-based chemotherapy in three patients and CKD-602 (a new camptothecin agent)-based chemotherapy in two patients].

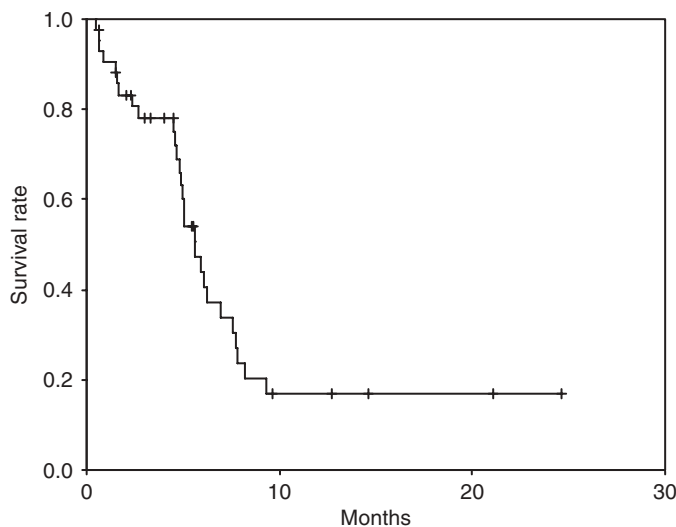


Figure 1. Progression-free survival. The median time to progression was 5.6 months (95% CI 4.7–6.6 months).

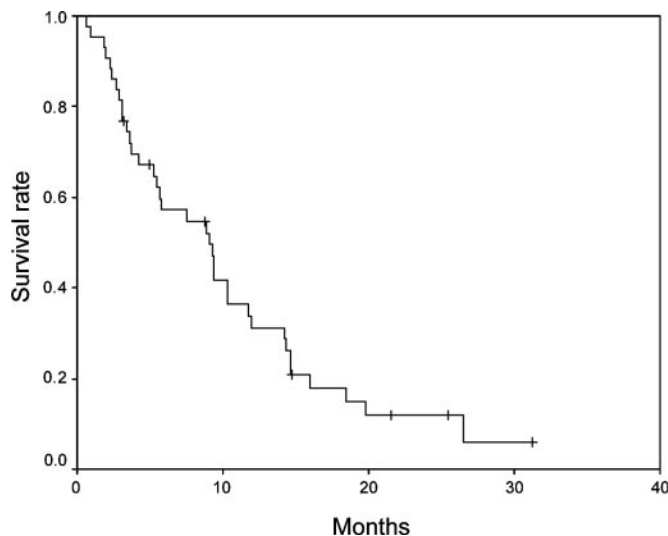


Fig. 2. Overall survival. The median overall survival was 9.03 months (95% CI 4.8–13.2 months).

ADVERSE REACTIONS

The toxicity profile is summarized in Table 3. The most frequent hematological toxicity was leukopenia. Fever was observed in only two patients and the episodes were easily managed with antibiotics without G-CSF support. No patients received prophylactic G-CSF.

Grade 1 or 2 asthenia was observed in 19.9% of patients. Other non-hematological toxicities included nausea, vomiting, oral mucositis, diarrhea and myalgia. A hypersensitivity reaction occurred in two patients. One patient experienced chest tightness and dyspnea just 15 min after initiation of docetaxel infusion. Another patient was febrile and showed facial flushing and dyspnea during docetaxel infusion. These events were promptly reversed with another dose of 10 mg dexamethasone.

Table 3. Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicity (per cycle)				
Leukopenia	14.3%	5.3%	1.8%	0%
Anemia	11.3%	4.8%	0.6%	0%
Thrombocytopenia	0%	0%	0%	0%
Non-hematological toxicity (per patient)				
Asthenia	6 (13.9%)	3 (7.0%)	0	0
Oral mucositis	1 (2.3%)	1 (2.3%)	0	0
Diarrhea	1 (2.3%)	1 (2.3%)	0	0
Hypersensitivity	2 (4.6%)	0	0	0
Myalgia	1 (2.3%)	2 (4.6%)	0	0

There were no toxic deaths due to chemotherapy. Two patients required hospitalization due to fever.

One patient expired within 30 days after completing the treatment.

DISCUSSION

Patients with inoperable gastric cancer may benefit from palliative chemotherapy. There are many regimens consisting of a single drug, two-drug combination, three-drug combination and even more. However, at present, there is no 'standard' chemotherapy regimen generally accepted.

Traditionally, the combination of 5-FU and cisplatin (FP) has been considered active and safe (overall response rate up to 50%, time to progression 5.4 months, overall survival <1 year).

Docetaxel is a novel semi-synthetic taxoid, which has demonstrated activity against human gastric carcinoma cell lines *in vitro* and *in vivo* (11). The use of this agent for the treatment of patients with advanced or metastatic gastric cancer resulted in a response rate of 15–24% when it was given as first-line therapy (12–14) and 18–24% when given as a second-line therapy (15,16).

The two-drug combination of docetaxel and cisplatin resulted in a response rate of 37–53% (17–19). Trials using the three-drug combination of docetaxel, 5-FU and cisplatin were also conducted (20–22).

Various drug combination schedules were used in these trials. As mentioned earlier, the DCF regimen used by Ajani et al. was a 5-day regimen, which included docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, and 5-FU 750 mg/m²/day administered by continuous infusion on days 1–5 every 3 weeks. In the study of Roth et al., the DCF dosing schedule was docetaxel 85 mg/m² on day 1, cisplatin 75 mg/m² on day 1 and 5-FU 300 mg/m²/day administered by continuous infusion on days 1–14, every 3 weeks (23).

In this study, we selected a 3-day regimen composed of docetaxel 70 mg/m² on day 1, cisplatin 40 mg/m² on days 2 and 3, and 5-FU 1200 mg/m² over 10 h on days 1–3 every 3 weeks, which shortens the treatment duration to 3 days, and the infusion time of 5-FU to 10 h, and thus it can be used on a

day care system basis. Also, a continuous infusion pump is not necessary. As mentioned earlier, the choice of this regimen was influenced by our center's experience in head and neck cancer, where the regime was considered active and feasible in interim analysis. Among an initial 14 patients in the first stage of this present study, six patients showed partial response and the toxicity was tolerable, so the study continued to a total of 43 patients.

Our study showed 42.5% overall response rate, 5.6 months of median time to progression and 9.03 months of median overall survival. The response rate was superior to the one expected (40%). As compared with the results of Ajani et al.'s phase III study showing a 38.7% overall response rate, 5.2 months of time to progression and 10.2 months of overall survival, the efficacy of our 3-day regimen is not inferior to their 5-day regimen.

In terms of administered dose intensity, that of docetaxel was 21.23 mg/m²/week, 5-FU 1092.14 mg/m²/week and cisplatin 23.82 mg/m²/week, which corresponded to 91.1, 91.0 and 89.5% of planned doses in our study. In the study of Ajani et al., the dose of docetaxel was 23 mg/m²/week, 5-FU 1110 mg/m²/week and cisplatin 23 mg/m²/week. The cycles with dose reduction were 12% in Ajani et al.'s study, and 14.3% in our study, which are similar.

Considering the toxicity profile, in Ajani et al.'s study, grade 3/4 neutropenia was 84% and febrile neutropenia was 16%, and in cycles with G-CSF it was 66%. However, in our study, grade 3/4 neutropenia was only 1.8%. We think the main reason why the hematological toxicity profile in our study was mild is that we did not check the CBC (complete blood count) weekly. The data shown here are those taken 2 days before the next cycle when the nadir already had been passed. However, the most important fact was that neutropenic fever occurred in only two patients and the episodes were easily managed with antibiotics without G-CSF support. No patients received prophylactic G-CSF.

Non-hematological toxicity was mild to moderate in the majority of patients and consisted mainly of oral mucositis, diarrhea or myalgia in 4.7–7.0% of patients in our study. According to Ajani et al.'s data, stomatitis occurred in 23% and diarrhea in 20%.

Two patients showed a hypersensitivity reaction, which was not severe. This may have been due to the corticosteroid prophylaxis given routinely with each dose of docetaxel. Despite its reported toxicities, the triple combination was well tolerated with a median 3.9 cycles of treatment given per patient.

It is intriguing that the toxicity profile is mild in Korean gastric cancer patients; the reason for this is unclear at present and thus should be the subject of further study.

In conclusion, the 3-day combination of 'docetaxel, 5-FU and cisplatin' is active as a first-line treatment in patients with unresectable gastric cancer and its toxicity is manageable. However, we would like to note that it is still not conclusive whether a three-drug combination should be used as a first-line treatment in gastric cancer. The superiority of three-drug combinations to two-drug combinations has not been accepted

worldwide yet. As compared with the result of an FP regimen in our center, the response rate, median time to progression and median overall survival of DCF are similar, even though a head-to-head comparison is impossible. Therefore, a further randomized phase III trial should be conducted to resolve this issue. We are planning to carry one out in the near future.

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