Induction Chemotherapy with Docetaxel, 5-FU and CDDP (DFP) for Advanced Gastric Cancer

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Abstract. *Background: The aim of this study was to evaluate the feasibility and efficacy of modified triplet chemotherapy with docetaxel, 5-fluorouracil and cisplatin as induction chemotherapy for advanced gastric cancer (AGC). Patients and Methods: Treatment-naïve patients with AGC were eligible. The regimen consisted of 350 mg/m^2/day 5-FU by continuous infusion on days 1 to 5, 10 mg/m^2/day CDDP intravenously on days 1 to 5, and docetaxel at 60 mg/m^2/day intravenously on day 1. After 2 cycles (each cycle consisted of 4 weeks), surgical resection was attempted, 2-4 weeks after the completion of the regimen. Results: Eighteen patients were enrolled. Adverse events included grade 3 anorexia and nausea in 16.7% and 11.1% and grade 4 leukocytopenia and neutropenia in 5.6% and 27.8%, respectively. The overall response rate was 44.4%. Surgery was conducted in 15 patients. The 1- and 3-year survival rates were 75.6% and 51.1%, respectively. Conclusion: The modified triplet combination therapy is effective and well tolerated by patients with AGC.*

Although the incidence of gastric cancer is declining in Western countries, it is still the second most frequent cause of cancer-related death worldwide (1). Similar to other malignancies, the survival of patients with gastric cancer depends on the clinical stage of the disease. Surgery remains the treatment of choice for curing early-stage disease. On the other hand, the prognosis of patients with locally advanced or distant metastatic gastric cancer is still very poor even after surgery. Recent results of a randomized control trial showed that D2 lymphadenectomy plus extended para-aortic lymph node dissection provide no survival benefits compared to D2 alone (2), emphasizing the limited benefits of surgery for advanced gastric cancer (AGC). MacDonald *et al.* (3) have reported that postoperative adjuvant chemoradiotherapy significantly improved the relapse-free survival (RFS) and overall survival (OS) of patients with AGC compared with surgery alone. Furthermore, Cunningham *et al.* (4) reported in the results of the MAGIC trial that perioperative chemotherapy significantly improved both the RFS and OS of patients compared to surgery alone. These studies suggested that the selection of efficient perioperative chemotherapy for gastric cancer is important for the improvement of outcome of AGC.

Over the last decade, new active agents, including taxanes (paclitaxel (5, 6) and docetaxel (7, 8)), irinotecan (9), oxaliplatin (10), and S-1 (11, 12) have been developed and several randomized phase II/III studies have identified promising combination regimens for non-resectable cases of gastric cancer (13-18). Thus, in order to improve the rate of curative resection and to prolong the survival of patients after surgery, neoadjuvant chemotherapy (NAC) or induction chemotherapy should be investigated with chemotherapeutic regimens including novel active agents (19-22).

Docetaxel has shown promising activity when administered alone (response rate: 17-24%) (7, 8, 23, 24) or in combination with other agents (16, 25, 26). The phase III V325 study indicated that DCF (docetaxel, cisplatin and fluorouracil) was superior to CF (cisplatin and fluorouracil) in terms of response rate, time to progression, and OS (27). However, grades 3 to 4 treatment related adverse effects occurred in 82% and 57% of patients treated with DCF and CF, respectively (27). The original regimen of DCF in the V325 trial, was docetaxel at 75 mg/m^2 (1-hour intravenous infusion) plus CDDP at 75 mg/m^2 (1- to 3-hour intravenous infusion) on day 1, followed by 5-FU at 750 mg/m^2/day (continuous intravenous infusion) for 5 days every 3 weeks. To improve the feasibility of the triple-agent therapy, the dosage of docetaxel was reduced to 60 mg/m^2, which is the

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Key Words: Gastric cancer, neoadjuvant chemotherapy, docetaxel, 5-fluorouracil, cisplatin, DFP.

recommended dose in Japan (8, 23, 24). Furthermore, reduced dose 5-FU and split low-dose CDDP have been introduced to reduce the adverse events (28, 29). The aim of this study was to evaluate the toxicity and efficacy of a docetaxel, low-dose 5FU and split low-dose CDDP combination for AGC as an induction chemotherapy.

Patients and Methods

Patients. Patients with locally advanced and/or distant metastatic gastric cancer who were treated at Osaka University Hospital (Osaka, Japan) between October 2001 and January 2008 were enrolled in this study. Staging laparoscopy was performed for patients with serosa-invading gastric cancer to detect peritoneal dissemination. The inclusion criteria were as follow: age, 20-75 years; no prior chemotherapy; ECOG performance status, 1 -2 (30); existence of measurable target lesions by RECIST criteria (31); adequate function of major organs; no other active malignancy; estimated life expectancy of more than 3 months and provision of written informed consent. Patients were excluded if they were found to have severe co-morbid conditions, infectious diseases, brain metastasis, massive pleural effusion, massive pericardial effusion, peripheral neuropathy or a past history of drug allergy. Furthermore, pregnant and breast-feeding women were also excluded. The patients were classified according to the Japanese Classification of Gastric Cancer (32). The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine.

Treatment regimen. The regimen used for the treatment of the enrolled patients is illustrated in Figure 1. This regimen was repeated every 4 weeks for a total of 2 cycles. All the patients underwent hematological tests and physical examination before the start of each course. If the following toxicities occurred, the next administration was delayed until full recovery from the toxicity and the doses of all the drugs (docetaxel, 5-FU, and CDDP) were reduced by 25% in the following course: leukocyte count <3000/μl; platelet count $<10.0\times10^4$/μl or non-hematological toxicity of ≥grade 3. If complete resection was expected or the non-curative resection factor was liver metastasis only, surgery was attempted 2-4 weeks after the chemotherapeutic regimen. The primary end point was the overall response rate for chemotherapy, while the secondary end points were OS, the toxicity profile and the rate of complete resection.

Evaluation of toxicity, response and survival. Blood cell counts and blood chemistry (including liver and renal function tests) were performed at least once a week. The toxicity of the chemotherapy was monitored and graded according to the Common Toxicity Criteria of the National Cancer Institute version 2.0 (http://www.cancer.gov). The tumor response was assessed by computed tomography at every cycle of treatment and evaluated by the Response Evaluation Criteria in Solid Tumor (RECIST) (31). The RECIST criteria are defined as follows: complete response (CR), the disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the longest diameters of the target lesions, taking as reference the baseline sum of the longest diameters; progressive disease (PD), at least a 20% increase in the sum of the longest diameters of the target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD), neither sufficient shrinkage to quality for PR nor sufficient increase to quality for PD, taking as reference the smallest sum of the longest diameter since the treatment started.

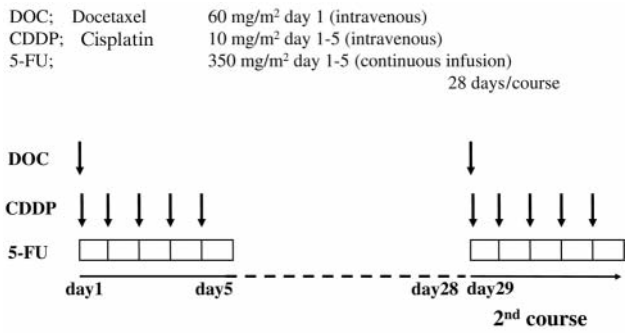


Figure 1. *Treatment regimen. The regimen was repeated every 4 weeks for a total of 2 cycles.*

Statistical analysis. Numerical values are expressed as the median (range). Survival was defined from the first day of chemotherapy to death from any cause and calculated by the Kaplan-Meier method. All the calculations were performed with the software package Statview Version 5.0 (SAS Institute, Inc, Cary, NC, USA).

Results

Patient characteristics. A total of 18 patients with AGC (adenocarcinoma) were enrolled in this trial. The Eastern Cooperative Oncology Group performance status was 0 or 1 in 16 (89%) patients. The reasons for induction chemotherapy were bulky N2 lymph node (LN) metastasis in 3 patients, N3 metastasis in 5 patients, tumor invasion of adjacent organs (T4) in 3 patients, liver metastasis in 3 patients, lung metastasis in 2 patients, distant LN metastasis in 1 patient and peritoneal dissemination in 1 patient. The patient characteristics are listed in Table I.

Adverse events. Eighteen patients received a total of 32 treatment cycles. The average number of cycles administered per patient was 1.8. Four patients received only one cycle of chemotherapy, two were due to tumor progression and two due to toxicity and deterioration of performance status. The most common adverse events were gastrointestinal toxicity, leukocytopenia and neutropenia. Grade 3 anorexia and nausea occurred in 16.7% and 11.1% of the patients, respectively. Grade 4 leukocytopenia and neutropenia occurred in 5.6% and 27.8% , respectively. The adverse events are summarized in Table II.

Response to induction chemotherapy. None of the 18 enrolled patients showed a CR, while 8 showed PR, 8 showed SD, and 2 showed PD by the RECIST criteria. The overall response rate was 44.4% . The response rate in the intestinal type primary tumors was 33.3% and in the diffuse type was

Table I. *Patient characteristics*.

n		18	
Median age (range)		57 (35-75)	
Male/Female		15/3	
ECOG-PS 0/1/2		4/12/2	
Borrman type 1/2/3/4		1/6/8/3	
Histopathological type			
Intestinal/diffuse	6/12		
Localization U/M/L		6/5/7	
cStage IIIB/IV		3/15	
Non-curative resectable factor			
Bulky N2	3	N3	5
T4	3	H1	3
Lung	2	P1	1
Distant LN	1		
Mean no. of treatments (range)		1.8 (1-2)	

ECOG: Eastern Cooperative Oncology Group, PS: performance status, LN/N: lymph node, U: upper third portion of the stomach, M: middle third portion of the stomach, L: lower third portion of the stomach, T4: tumor invasion of adjacent structures, H1: liver metastasis, P1: peritoneal dissemination.

Table II. *Adverse events (n=18)*.

	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Non hematological toxicity				
Alopecia	3 (16.7)	3 (16.7)	0 (0)	0 (0)
Fatigue	5 (27.8)	3 (16.7)	0 (0)	0 (0)
Anorexia	2 (11.1)	1 (5.6)	3 (16.7)	0 (0)
Nausea	7 (38.9)	2 (11.1)	2 (11.1)	0 (0)
Stomatitis	3 (16.7)	0 (0)	0 (0)	0 (0)
Hematological toxicity				
Leukocytopenia	0 (0)	8 (44.4)	6 (33.3)	1 (5.6)
Neutropenia	1 (5.6)	4 (22.2)	6 (33.3)	5 (27.8)
Anemia	1 (5.6)	5 (27.8)	2 (11.1)	0 (0)
ALT	2 (11.1)	0 (0)	0 (0)	0 (0)

National Cancer Institute Common Toxicity Criteria Version 2.0; ALT: alanine aminotransferase.

Table III. *Tumor response to chemotherapy (n=18)*.

	No (%)				
	CR	PR	SD	PD	RR
Overall	0 (0)	8 (44.4)	8 (44.4)	2 (11.1)	44.4%
Metastases					
LN (17)	0 (0)	8 (47.1)	9 (52.9)	0 (0)	47.1%
Liver (3)	0 (0)	2 (66.7)	0 (0)	1 (33.3)	66.7%
Lung (2)	0 (0)	0 (0)	2 (100)	0 (0)	0%
Peritoneal (1)	0 (0)	0 (0)	1 (100)	0 (0)	0%
Histological type					
Intestinal (6)	0 (0)	2 (33.3)	3 (50.0)	1 (16.7)	33.3%
Diffuse (12)	0 (0)	6 (50.0)	5 (41.7)	1 (8.3)	50.0%

Evaluated by RECIST, CR: complete response, PR: partial responses, SD: stable disease, PD: progressive disease, RR: response rate, LN: lymph node metastasis.

50.0% . The response rate for each target organ is listed in Table III. Histopathological examination showed no residual tumors (grade 3) in resected specimens of one patient.

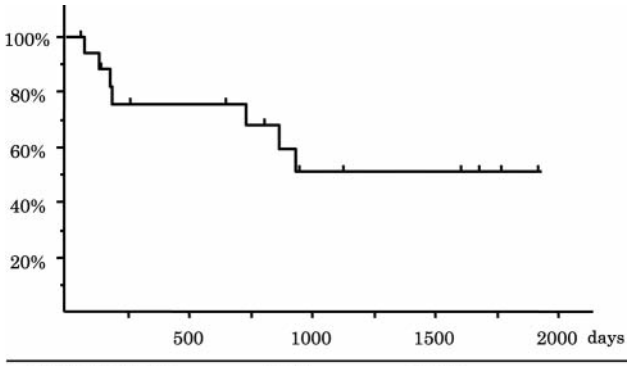
Surgery. Gastrectomy was conducted in 15 out of the 18 patients. Surgery was considered curative in 11 patients and non-curative in 4 patients. The two patients with lung metastasis and one patient with distant lymph node metastasis were excluded. Total gastrectomy was performed in 8 patients, distal gastrectomy in 6 patients, and pancreato-duodenectomy in one patient due to tumor spread to the pancreatic head. Extended surgery was conducted in 10 patients: para-aortic lymphadenectomy in 6 patients, partial hepatectomy in 2 patients, left pancreatectomy and splenectomy in 1 patient and transverse colectomy in 1 patient. The Roux-en Y reconstruction technique was performed after gastrectomy in all the patients who underwent gastrectomy. The median operative time was 295 min and the median blood loss during surgery was 970 ml. The median duration of hospital stay after surgery was 21 days. Postoperative complications developed in 6 patients and the overall morbidity rate was 40% . Pancreatic fistula developed in 2 patients, liver infarction in 1 patient, liver dysfunction in 1 patient, abdominal abscess in 1 patient, bowel obstruction in 1 patient and peritoneal paralysis in 1 patient.

A repeat operation was performed in 1 patient with suspected liver infarction, and cholecystectomy and reconstruction of the hepatic artery were performed for the patient. One patient (6.7%) died of liver failure three months after surgery due to progressive disease of hepatitis C liver cirrhosis. Out of the 11 patients who underwent curative-surgery, 8 received adjuvant chemotherapy (oral S-1 after surgery).

Survival. The median survival had not been reached after a median follow-up of 40 months. The 1- and 3-year survival rates were 75.6% and 51.1% , respectively. Figure 2 depicts the survival curve of all 18 patients calculated by the Kaplan-Meier method.

Discussion

The phase III V325 trial showed that DCF therapy had significant benefits for OS, time to progression and response rate compared to the CF therapy but as mentioned, grade 3 to 4 toxicity occurred in many of the patients (82%). In a Swiss randomized phase II trial, the trio therapy was modified as docetaxel 75 mg/m^2, CDDP 75 mg/m^2 on day 1 plus 5-FU divided into 1-14 days



Median observation period	1-year survival rate	3-year survival rate	MST
1,256 days (72-2,342)	75.6%	51.1%	1,932 days

Figure 2. *Overall survival curve calculated by the Kaplan-Meier method for all 18 patients enrolled in this study.*

infusion of 300 mg/m^2 (33). Grade 3 or 4 neutropenia occurred in 80% and febrile neutropenia in 41% of the patients compared to 29% in the V325 trial. According to these results, we considered that the triumvirate therapy should be modified to a reduced dosage form especially for induction chemotherapy before surgery. Two late phase II trials performed in Japan recommended that docetaxel should be administered intravenously at a dose of 60 mg/m^2 every 3-4 weeks (23, 24). Therefore, the dose of docetaxel was reduced to 60 mg/m^2 and low-dose continuous 5-FU and CDDP was selected. With these modifications, the incidence of grade 3/4 neutropenia and non-hematological toxicity decreased to 61.1% and 27.8% , respectively. Furthermore, febrile neutropenia was only noted in 5.6% of the patients. The adverse events in the present study were acceptable and no treatment-related death was observed. However, one patient with hepatitis C-related liver cirrhosis died three months after surgery. The patient initially recovered after surgery, but the disease status of liver failure progressed after that, suggesting a possible association with the induction chemotherapy. The less toxic regimen showed an overall response rate (PR and CR) by RECIST of 44.4% in the 18 patients. The lymph node and liver metastases showed higher responses 47.1% and 66.7% of the affected patients respectively, but the lung metastases in the two affected patients showed no response. The response rate was in concordance with the reported rate of 36.6% in the Swiss trial (33) and 37% in the V325 study (27).

In conclusion, along with excellent efficacy and moderate toxicity, the reduced dose combination chemotherapy of docetaxel, 5-FU and CDDP is feasible as an induction chemotherapy for patients with AGC.

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Received April 24, 2009
Revised July 6, 2009
Accepted July 17, 2009