Original article

Docetaxel and cisplatin in patients with advanced or recurrent gastric cancer: a multicenter phase I/II study

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Abstract

Background. Because docetaxel and cisplatin are both active against gastric cancer and have different mechanisms of action, this combination may provide additive or synergistic effects against gastric cancer. This article presents a phase I study designed to determine the recommended dose of cisplatin combined with a fixed dose of docetaxel, and a subsequent phase II study that evaluated the clinical efficacy and feasibility of this combination regimen.

Methods. Patients enrolled in the study had to have histologically confirmed advanced or recurrent gastric cancer with measurable disease and adequate organ function, and to be aged 20 to 75 years, with a performance status (PS) of 0 to 2. In the phase I study, docetaxel was administered at a fixed dose of 60 mg/m² on day 1. Cisplatin was also administered on day 1, at dose levels of 60, 70, and 80 mg/m². Where dose-limiting toxicities were not observed in more than 33.3% of patients, three patients were accrued for each dose level.

Results. Recommended doses for the phase II evaluation were determined to be 60 mg/m² of docetaxel and 80 mg/m² of cisplatin. Although grade 3 or more severe leukopenia and neutropenia were observed in 71.4% and 82.1% of the patients, respectively, nonhematological toxicities were not severe. The overall response rate at the recommended dose level was 25.0% (7/28 patients), and the rate was 40% (6/15) for patients with liver metastases. The median survival time was 9.7 months and the 1-year survival rate was 39.3%.

Conclusion. Although this study failed to demonstrate a high response rate, this regimen was feasible and might be of value in further investigations in respect to the relatively high response rate in patients with liver metastasis and the favorable survival.

Key words Docetaxel · Cisplatin · Gastric cancer · Combination chemotherapy

Introduction

Gastric cancer remains a leading cause of death from malignant neoplasms in Japan, even though the methodology that enables early detection has advanced and, as a result, mortality caused by gastric cancer is gradually declining. For patients with recurrent or unresectable gastric cancer, palliative chemotherapy was the only reasonable therapeutic option, while advanced gastric cancer was considered to be poorly chemosensitive over a long period [1–3]. In recent years, however, high response rates have often been achieved in gastric cancer chemotherapy using newly developed anticancer drugs or combination regimens [4–10]. Most of these combination regimens for advanced gastric cancer consist of drugs with different mechanisms of action, such as antimetabolites (5-fluorouracil, etc.), platinum agents (cisplatin, etc.), antibiotic agents (mitomycin C, etc.), topoisomerase inhibitors (irinotecan, etc.), and taxanes (paclitaxel, docetaxel). Using drugs with different modes of action is more favorable in combination chemotherapy to obtain additive or synergistic effects against gastric cancer.

Docetaxel, a semisynthetic compound derived from a precursor extracted from the needles of the European yew tree, *Taxus baccata*, has recently been introduced into clinical practice [11]. It promotes tubulin assembly into microtubules and inhibits depolymerization to free tubulin, thus blocking cells in the M-phase of the cell cycle and leading to cell death [12]. In comparative studies, docetaxel has been found to be 1.3- to 12-fold

more active in vitro than paclitaxel. In preclinical studies, docetaxel demonstrated antitumor activity against human cancer cell lines [13]. Two phase II studies testing docetaxel as a single agent in advanced or metastatic gastric cancer yielded response rates of 21.2% and 22.2% in Japan [14,15]. Because in-vitro studies with docetaxel have not revealed any cross-resistance with cisplatin, etoposide, and 5-FU, a combination of docetaxel and these agents appears to be promising in the treatment of gastric cancer. Two recent studies have reported high response rates, of 37.2% and 56%, with the combination of docetaxel and cisplatin in advanced or metastatic gastric cancer in Europe [16,17].

Based on these backgrounds, a phase I/II study was conducted to investigate the tolerability and the efficacy of the combination of docetaxel and cisplatin in Japanese patients with gastric cancer. The phase I study was designed to determine the recommended dose of cisplatin in combination with 60 mg/m² of docetaxel, which was established as a standard dose as a single agent in a previous phase I study in Japan [18]. The phase II study was performed to evaluate the antitumor activity and the tolerability of this combination when administered at the recommended doses in patients with advanced or recurrent gastric cancer.

Patients and methods

Patient eligibility

All patients from the institutes shown in the Appendix had to have histologically proven gastric cancer with measurable or evaluable lesions. Additional criteria included the following: age 20 years or more but less than 75 years, performance status (PS) of the Eastern Cooperative Oncology Group (ECOG) grade 2 or less, life expectancy 3 months or more, adequate bone marrow function (white blood cell [WBC] count, $\geq 4000/\text{mm}^3$ but $\leq 12000/\text{mm}^3$; absolute neutrophil count [ANC], $\geq 2000/\text{mm}^3$; platelets, $\geq 100000/\text{mm}^3$; hemoglobin, $\geq 9.5\text{ g/dl}$), adequate liver function (total bilirubin, $\leq 1.5\text{ mg/dl}$; GOT and GPT $\leq$ twice upper limit), and adequate renal function (serum creatinine, $\leq 1.5\text{ mg/dl}$; blood urea nitrogen [BUN], $\leq 25\text{ mg/dl}$; creatinine clearance [Ccr], $\geq 60\text{ ml/min}$). Patients having a history of drug hypersensitivity, serious complications, symptoms of infection, peripheral neuropathy, edema, symptoms attributable to brain metastasis, or active secondary cancer were excluded from the study. Patients with a history of prior chemotherapy, and pregnant or lactating patients were also excluded. The institutional review board at each institute approved this study, and all patients gave their written informed consent.

Methods

Drug administration

Docetaxel was provided by Aventis Pharma Japan (Rhone-Poulenc Rorer; Japan), as a sterile solution containing 80 mg of docetaxel dissolved in polysorbate 80. Cisplatin was obtained from Nippon Kayaku (Tokyo, Japan). Docetaxel was diluted with 250 or 500 ml of 5% glucose or 0.9% saline solution and was infused over a 1-h period. After completion of the docetaxel infusion, 3-h prehydration with 750–1000 ml of an electrolyte solution was carried out before cisplatin infusion. Cisplatin was dissolved in 500–1000 ml of 0.9% saline and infused over a 2-h period. Post-hydration with 1000–2000 ml of the electrolyte solution was given as a continuous infusion over a 4-h period after completion of the cisplatin infusion. This treatment was repeated every 3 to 4 weeks, with a minimum requirement of one course in the phase I part and two courses in the phase II part until disease progression or unacceptable toxicity.

Patients could receive antiemetics for prophylactic use. However, in the first cycle of chemotherapy, no premedication to prevent hypersensitivity reactions was allowed. The administration of granulocyte-colony stimulating factor (G-CSF), at 2 $\mu\text{g/kg}$ s.c. or 5 $\mu\text{g/kg}$ i.v., was permitted when leukopenia or neutropenia of grade 3 or 4 occurred, except for the first cycle in the phase I study, and this administration was continued until the WBC or ANC recovered to grade 0.

Dose escalation schedule (Phase I)

The starting dose of cisplatin was 60 mg/m² in combination with a fixed dose of docetaxel, 60 mg/m² (level 1). Subsequent levels were determined in advance, as follows: level 2, docetaxel 60 mg/m² and cisplatin 70 mg/m²; and level 3, docetaxel 60 mg/m² and cisplatin 80 mg/m². At least three patients were enrolled at each dose level. Dose-limiting toxicities (DLTs) were assessed during the first cycle of chemotherapy. If a DLT was observed in one or two patients, an additional three patients were accrued. If a DLT was observed in all of the initial three patients or four or more of six patients, patient accrual was discontinued and this dose level was determined to be the maximum tolerated dose (MTD). In this study, the DLTs were considered to be: grade 4 leukopenia/neutropenia lasting 5 days or longer, febrile neutropenia (grade 4 neutropenia with a body temperature of 38°C or more), grade 4 thrombocytopenia, grade 2 renal dysfunction, grade 3 hepatic dysfunction, or any other nonhematologic toxicity of grade 3 or more severe, except for nausea/vomiting, anorexia, diarrhea, abdominal pain, and general fatigue.

Dose modifications

Based on the hematologic and nonhematologic toxicities, dose reduction was carried out in the subsequent cycle of chemotherapy. Both drugs were reduced by 25% if the following toxicities had occurred in the previous course: grade 4 leukopenia/neutropenia lasting 5 days or longer, grade 4 thrombocytopenia, reversible grade 2 neurotoxicity (if neurotoxicity of grade 3 or more occurred, treatment was discontinued), grade 3 hepatic dysfunction, or grade 3 stomatitis. Cisplatin was reduced by 25% if grade 2 renal dysfunction was observed in the previous course.

Monitoring program

Pretreatment evaluation included a complete medical history and physical examination, a complete blood cell count (CBC) with differential and platelet counts, and a standard biochemical profile, as well as measurement of the serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9. During treatment, CBC with differential and platelet counts and standard biochemical profile were monitored on a weekly basis. A detailed medical history was taken and a physical examination was performed before each course of treatment to document the disease symptoms and toxicities of the chemotherapy. A clinical neurological evaluation was performed in each cycle. Lesions were evaluated in each cycle if they were assessable by endoscopic examination, X-ray, or computed tomography (CT) scan.

Treatment evaluation

The antitumor effects and adverse reactions were evaluated in accordance with the criteria of the Japan Society for Cancer Therapy [19], which were established based on the WHO criteria. Briefly, a complete response (CR) was defined as the complete disappearance of all measurable and evaluable lesions for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or more reduction in the sum of the products of the longest diameters of measurable lesions for a minimum of 4 weeks. No change (NC) was defined as the failure to observe a partial or complete response or progressive disease for at least 4 weeks. Progressive disease (PD) was defined as that with a 25% or more increase in the sum of the products of the longest perpendicular diameters of measurable lesions, or the appearance of new lesions. For primary lesions, the responses were evaluated according to the criteria proposed by the Japanese Research Society for Gastric Cancer [20].

Statistical considerations

The survival rate was estimated by statistical analysis, using the Kaplan-Meier method, and calculated from the initial date of treatment to the date of death from any causes or to the last follow-up. Optimal two-stage

designs, according to Simon [21], were adopted for the phase II study. Fifteen patients were enrolled in the first stage and recorded a sufficient number of responses. In the second stage, an additional 10 patients were recruited, making a total of 25. The number of patients to be enrolled in this study was calculated to be 25, the number that was required for dismissing the assumption that the 95% confidence interval (CI) would be 10% under the conditions of $\alpha = 0.05$ and $\beta = 0.20$, assuming an expected response rate of 30%.

Results

Between August 1998 and January 2001, a total of 37 patients with advanced or recurrent gastric cancer were enrolled in this phase I/II study.

Phase I study

Of the ten patients enrolled in the phase I part, nine patients were eligible for the phase I study. One patient had never received the treatment agents because of missing the order of administration and was excluded from the analysis. The characteristics of the nine eligible patients are shown in Table 1. There were seven men and two women, with a median age of 63 years (range, 36–71 years). No DLTs were observed during the dose escalation study, even at the highest dose level, and this level, docetaxel 60 mg/m² and cisplatin 80 mg/m², was recommended for the phase II study. In this phase I study, one patient achieved a PR at dose level 2 (docetaxel 60 mg/m², cisplatin 70 mg/m²).

Table 1. Phase I study: patient characteristics ($n = 9$)

No. of patients entered	10
No. of patients evaluated	9
Sex	
Male	7
Female	2
Median age, years (range)	63 (36–71)
Performance status (ECOG)	
0	9
1	0
2	0
Histological subtype	
Intestinal	3
Diffuse	6
Stage III/IV/relapse	0/5/4
Site of disease	
Primary	5
Liver	1
Lung	1
Lymph node	6
Peritoneum	5

ECOG, Eastern Cooperative Oncology Group

Table 2. Phase I study: hematologic toxicities (in the first cycle)

Docetaxel/cisplatin (mg/m ²)	Level 1 (60/60) (n = 3) Grade		Level 2 (60/70) (n = 3) Grade		Level 3 (60/80) (n = 3) Grade	
	3	4	3	4	3	4
Leukopenia	1	0	0	1	0	0
Neutropenia	1	1	0	1	1	0
Hemoglobin	0	0	0	0	1	0

Table 3. Phase I study: adverse reactions (in the first cycle)

Toxicity	Grade				Incidence	Incidence of grade 3–4
	1	2	3	4		
Leucopenia	1	6	1	1	100.0	22.2
Neutropenia	1	3	2	2	88.9	44.4
Hemoglobin	2	2	1	0	55.6	11.1
GOT	3	1	0	0	44.4	0.0
GPT	3	1	0	0	44.4	0.0
Nausea/vomiting	5	2	0	0	77.8	0.0
Anorexia	3	4	0	0	77.8	0.0
Alopecia	6	1	–	–	77.8	–
General fatigue	3	1	0	0	44.4	0.0
Diarrhea	1	0	0	2	33.3	22.2

In the first cycle, the incidence of hematologic toxicities at each dose level is shown in Table 2 and the incidence of all adverse reactions is shown in Table 3. The incidences of hematologic toxicities were 100% for leukopenia, 88.9% for neutropenia, and 55.6% for anemia, and the incidences of grade 3–4 toxicities were 22.2%, 44.4%, and 11.1%, respectively. Neutropenia was the predominant toxicity associated with this combination regimen. Elevations of GOT and GPT were each seen in 44.4% of the patients. The incidences of major nonhematologic toxicities were 77.8% for nausea/vomiting, anorexia, and alopecia; 44.4% for general fatigue; and 33.3% for diarrhea. However, the grade 3 or higher nonhematological toxicity seen in the phase I part was diarrhea, with an incidence of 22.2%. There were no apparent correlations between the doses of the agents and the frequency or severity of these toxicities.

Recommended dose level

Patient characteristics

In the phase II study, a total of 27 patients were enrolled. However, 2 patients were excluded from the analysis: 1 patient had never received the treatment due to missing the order of administration, and the other patient did not provide sufficient examinations for the response assessment. Three patients at the recom-

mended dose level in the phase I part were included, giving a total of 28 patients as the subjects of this analysis. The characteristics of the 28 patients are shown in Table 4. There were 26 men and 2 women, with a median age of 59 years (range, 47–71 years). The ECOG PS was 0 in 24 patients, 1 in 3 patients, and 2 in 1 patient. Histological examination revealed that 11 had the intestinal subtype and 17 patients had the diffuse subtype. By clinical stage, 1 patient had stage III disease, 17 patients had stage IV disease, and 10 patients had a disease relapse after gastrectomy. Major metastatic sites were the liver (15 patients), the lung (5 patients), the lymph nodes (22 patients), and the peritoneum (4 patients).

A total of 61 cycles of therapy were delivered in the 28 patients, with a median of 2 cycles/patient (range, 1–6 cycles/patient).

Response rate and survival

Of the 34 patients registered and treated with this regimen, 8 patients achieved objective responses, with a response rate of 23.5% (95% confidence interval CI, 10.7%–41.2%). In the 28 patients treated at the recommended dose level, there were no complete responses, but there were 7 partial responses, giving an overall response rate of 25% (95% CI, 10.7%–44.9%). In addition, 12 patients had no change, while 7 patients had progressive disease. Table 5 shows the data on the response rates according to the metastatic sites and histo-

logical types. The response rates by each target site were as follows: 18.8% (3/16) for the primary lesion, 40.0% (6/15) for liver metastases, 20.0% (1/5) for lung metastases, and 22.2% (4/18) for abdominal lymph node metastases.

The median survival time of the 28 patients was 9.7 months, and the 1-year survival rate was 39.3% (95% CI, 21.2%–57.4%). Figure 1 shows the survival curve of the 28 patients at the recommended dose level.

Adverse reactions

All 28 patients were evaluated for toxicities. Adverse reactions occurred in all patients. The incidences of the main adverse reactions, scored as the highest grade seen per patient, are listed in Table 6. Grade 3 or 4 leukopenia was observed in 71.4% (20/28) of the patients.

Table 4. Patient characteristics at the recommended dose level ($n = 28$)

No. of patients entered	31
No. of patients evaluated	28
Median age, years (range)	59 (47–71)
Sex	
Male	26
Female	2
Performance status (ECOG)	
0	24
1	3
2	1
Histological subtype	
Intestinal	11
Diffuse	17
Stage III/IV/relapse	1/17/10
Site of disease	
Primary	18
Liver	15
Lung	5
Lymph node	22
Peritoneum	4

The 28 patients consisted of 3 patients at dose level 3 in the phase I study and 25 patients in the phase II study

Grade 3 or 4 neutropenia was the most frequent severe adverse reaction, and occurred in 82.1% (23/28) of the patients. G-CSF was administered in 59.0% of the 61 treatment cycles because of neutropenia (first cycle, 53.6%; second cycle, 77.8%; third cycle, 66.7%; fourth cycle, 33.3%; fifth cycle and sixth cycle, 0%). The incidences of GOT, GPT, and creatinine increases were 42.9%, 32.1%, and 35.7%, respectively. The incidences of grade 3 or 4 nontematologic adverse reactions were 17.9% for anorexia, 17.9% for diarrhea, 10.7% for general fatigue, 3.6% for nausea/vomiting and 7.1% for rash. No treatment-related deaths occurred during this study.

Discussion

Gastric cancer is known to be moderately chemosensitive, although chemotherapy by itself mostly has only palliative effects for advanced or recurrent gastric

Fig. 1. Survival curve at the recommended dose level ($n = 28$). Medium survival time, 9.7 months (95% confidence interval [CI], 238-not detected); 1-year survival rate, 39.3% (95% CI, 21.2%–57.4%)

Table 5. Response rates at the recommended dose level

	No. of patients	CR	PR	NC	PD	NE	Response rate (%)
All patients	28	0	7	12	7	2	25.0
Primary	16	0	3	10	0	3	18.8
Site of metastatic disease							
Liver	15	0	6	5	2	2	40.0
Lung	5	0	1	2	0	2	20.0
Abdominal lymph node	18	0	4	8	3	3	22.2
Peritoneum	1	0	0	1	0	0	0
Histological subtype							
Intestinal	11	0	2	6	2	1	18.2
Diffuse	17	0	5	6	5	1	29.4

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable

Table 6. Adverse reactions at the recommended dose level ($n = 28$)

Toxicity	Grade				Incidence	Incidence of grade 3–4
	1	2	3	4		
Leukopenia	1	7	17	3	100.0	71.4
Neutropenia	1	2	7	16	92.9	82.1
Thrombocytopenia	5	1	0	0	21.4	0.0
Hemoglobin	3	13	5	0	75.0	17.9
GOT	9	3	0	0	42.9	0.0
GPT	5	4	0	0	32.1	0.0
Creatinine	8	2	0	0	35.7	0.0
Anorexia	5	14	4	1	85.7	17.9
Diarrhea	5	5	3	2	53.6	17.9
Nausea/vomiting	14	12	1	0	96.4	3.6
General fatigue	13	6	2	1	78.6	10.7
Alopecia	16	8	–	–	85.7	–
Fever	7	11	0	0	64.3	0.0
Rash	3	1	2	0	21.4	7.1

The 28 patients consisted of 3 patients at dose level 3 in the phase I study and 25 patients in the phase II study

cancer. However, when compared with best supportive care, chemotherapy has been reported to have marginal survival benefits. The efficacy of chemotherapy has been evaluated using the response rate as a surrogate endpoint [22–24]. Recently, with the development of new drugs, such as S-1, CPT-11, and taxanes, multidrug combination therapies have yielded high response rates, ranging from approximately 30% to 50%. However, the response rate does not always correlate with survival, and a novel chemotherapy regimen with higher safety and favorable survival is required to provide survival prolongation.

The maximum tolerated dose could not be determined even at the highest dose of cisplatin (80 mg/m²) in the present phase I study. In the light of this, 80 mg/m² of cisplatin combined with 60 mg/m² of docetaxel was determined to be the recommended dose for the phase II study, without further dose escalation of these drugs. This recommendation was made for the following reasons: (1) dose-dependency in the incidence of adverse events was not found, (2) tumor response was seen in three patients at the level 2 dosage, and (3) each dose of these drugs is at the maximum of the approved range to use as a single agent in Japan.

At this recommended dose level, the overall response rate was 25.0% (7/28), the median survival time was 9.7 months, and the 1-year survival rate was 39.3%. The period of progression-free survival was not analyzed as data, because it was not an endpoint. Of particular note, the response rate was highest; 40% (6/15) in the patients with liver metastasis. As for adverse reactions, neutropenia was the predominant type of toxicity associated with this chemotherapy. Grade 3 or 4 neutropenia was the most frequent severe adverse reaction and occurred

in 23 (82.1%) patients, although the application of G-CSF rendered the condition manageable.

In the two Japanese pivotal phase II studies, as a single agent, docetaxel demonstrated response rates of 21.7% (10/46) and 21.9% (7/32) for patients who had previously received chemotherapy (mainly 5-fluorouracil, cisplatin), while the response rates were 20% and 22.6% for chemotherapy-naïve patients. These results suggest that docetaxel is effective in patients who have undergone previous treatment [14,15]. In addition, using chemotherapy with docetaxel and cisplatin for the treatment of advanced or recurrent gastric cancer, Roth et al. [16] reported a response rate of 56% (2 CRs and 25 PRs) among 48 evaluable patients with 85–100 mg/m² of docetaxel and 75 mg/m² of cisplatin. Ridwelski et al. [17] reported a response rate of 37.2% (4 CRs and 12 PRs) among 43 evaluable patients with 75 mg/m² of docetaxel and 75 mg/m² of cisplatin. The overall response rate in the present study (docetaxel/cisplatin 60/80 mg/m²) was 25% (7 PRs), and the response rates of the primary lesion, liver metastases, lung metastases, and abdominal lymph node metastases were 18.8%, 40%, 20%, and 22.2%, respectively. When compared with the response rates reported in the clinical studies conducted in Europe, the response rate of this trial was low. Although it is difficult to specify the cause of the difference in response rates between the Japanese and the European studies, there might be differences in patient backgrounds, dosage, dose intensity, and sample size, as well as differences in the evaluation methods, including differences in evaluation of the response in the gastric primary lesion. In this trial, combination therapy using docetaxel and cisplatin showed a high response rate (40%) for liver metastases,

suggesting that it is a clinically applicable regimen for the treatment of liver metastases. In addition, the survival results in our study, with a median survival time of 9.7 months and a 1-year survival rate of 39.3%, were comparable to those in the European trials: a median survival time of 9 months in Roth's study and a median survival of 10.4 months, with a 1-year survival rate of 42.0%, in Ridwelski's study. Furthermore, because the period of progression-free survival was not designated as an endpoint in our study, we cannot make a comparison with the European data. These results suggested that the differences in overall response rates between our study and the European studies might be caused by differences in the evaluation methods for the response, while the second-line and the following treatment might have contributed to the favorable survival despite the low response rate in our study. Although the overall response rate of this combination therapy was not significantly higher than those of each monotherapy, this regimen is feasible, and it might be of value to undertake further investigations in respect to the relatively high response rate in liver metastasis and the favorable survival.

Acknowledgments We are grateful to Drs. T. Taguchi, M. Yoshida, K. Nagao, and S. Yoshida for their helpful advice and N. Hirabayashi, W. Koizumi, and K. Shirao for their extramural review during the study.

Appendix

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