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ORIGINAL ARTICLE

Multicenter phase II study of weekly paclitaxel plus cisplatin combination chemotherapy in patients with advanced gastric cancer

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Abstract
Purpose Since a weekly administration of paclitaxel has demonstrated a sustained efficacy and more favorable toxicity profile than a 3-weekly administration for various solid tumors, the present study was conducted to evaluate the efficacy and safety of a combination regimen of weekly paclitaxel plus cisplatin in patients with advanced gastric cancer.
Patients and methods Patients with previously untreated metastatic or recurrent, measurable gastric cancer received intravenous paclitaxel 100 mg/m^2 plus cisplatin 35 mg/m^2 on days 1 and 8 based on a 3-week cycle.
Results Fifty-two patients were enrolled in the current study. Two complete responses and 17 partial responses were confirmed, giving an overall response rate of 36.5%. At a median follow-up of 8.5 months, the median time to progression and median overall survival was 6.0 and 10.8 months, respectively. Grade 3 neutropenia occurred in ten patients, while no grade 4 neutropenia or febrile neutropenia was observed. The most common non-hematologic toxicity was nausea (grade 1/2, 56.9%). There were no treatment-related deaths.
Conclusion A weekly paclitaxel and cisplatin combination was found to be well-tolerated and effective in

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patients with advanced gastric cancer. Accordingly, this regimen can be regarded as an important first-line treatment option for advanced gastric cancer.

Keywords Paclitaxel · Cisplatin · Chemotherapy · Gastric cancer

Introduction

Despite a declining incidence in many developed countries, gastric cancer remains the second most common cancer-related death in the world [1]. Notwithstanding, while the prognosis for advanced gastric cancer remains poor, combination chemotherapy has improved the quality of life and overall survival compared with the best supportive care in several randomized studies [2–4]. Among the various active chemotherapeutic agents, cisplatin-based combination chemotherapy is most commonly used with a high response rate of 37–56% [5–8].

Paclitaxel, derived from the bark of the Pacific yew, *Taxus brevifolia*, is one of the most active anticancer drugs for the treatment of solid tumors, effectively blocking cancer cells in the G2/M phase through the inhibition of microtubular depolymerization [9, 10]. An administration schedule at doses of 175–225 mg/m^2 intravenous infusion every 3 weeks has been widely accepted [11]. In addition, several phase II studies have shown that paclitaxel, alone or in combination with cisplatin or 5-fluorouracil, is also active against advanced gastric cancer [12–15]. However, a relatively high incidence of grade III or IV neutropenia (14–35%) is one of the major adverse effects.

Since paclitaxel is known to be a cell-cycle-specific agent, in vitro experiments have suggested that prolonged exposure to paclitaxel, through either continuous infusion schedules or weekly administration, can lead to enhanced cytotoxicity [16–18]. Furthermore, recent clinical studies have demonstrated that weekly schedules of intravenous paclitaxel have promising antitumor activity with tolerable safety profiles for several types of solid tumors, including lung, breast, and ovarian cancer [19–21]. For example, Markman et al. [21] reported that weekly single agent paclitaxel achieved an objective response rate of 25% and only 1% of cycles were modified due to side effects in 53 patients with platinum/paclitaxel-refractory ovarian cancer. However, there is no published data on the efficacy of a combination of weekly paclitaxel and cisplatin for the treatment of advanced gastric cancer.

Accordingly, the current phase II study was conducted to evaluate the response rate, time to progression, and safety of a combination regimen of weekly paclitaxel plus cisplatin in patients with advanced gastric cancer.

Patients and methods

Eligibility

All the patients involved in the current study had histologically confirmed metastatic or recurrent gastric adenocarcinoma with at least one unidimensionally measurable lesion (i.e., a diameter ≥1 cm, as assessed by spiral computed tomography). The patients were 18–75 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale. Plus, adequate hematological (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin ≥ 9 g/dl), renal (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min), and hepatic (total bilirubin ≤ 2.0 mg/dl and serum transaminase level ≤ 3 times the upper limit of the normal range) levels were also required. Patients who had received adjuvant chemotherapy completed 4 weeks before entry were eligible. Patients were ineligible if they had previously received palliative chemotherapy or radiation therapy, or had other severe medical illnesses, CNS metastasis, another active malignancy, or history of anaphylaxis to drugs. The institutional review board of each author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Study treatment

The paclitaxel (Genexol®, CJ. Co. Seoul, Korea) 100 mg/m^2 was administered through a 1-h intravenous infusion on days 1 and 8. The cisplatin 35 mg/m^2 was also administered along with a program of forced diuresis that included at least 2,000 ml of fluids after the paclitaxel infusion over 30 min on days 1 and 8. The chemotherapy was given every 21 days and continued until disease progression, patient refusal, or an unacceptable toxicity up to nine cycles. All patients were premedicated with a dexamethasone 20 mg, ranitidine 150 mg, and diphenhydramine 50 mg intravenous injection 30 min before the paclitaxel to prevent hypersensitivity reactions. Antiemetic treatment was routinely given before each cycle of chemotherapy.

Dose modification

The next course of treatment was only begun when the neutrophil count was $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, and any other treatment-related toxicities were less than or equal to grade 1; otherwise, treatment was withheld for up to 2 weeks. If adverse events did not improve to grade 0 or 1 after 2 weeks, the patients were excluded from the study.

Treatment was continued at the same dose if patients experienced grade 1 toxicities or other toxicities considered by the investigator unlikely to become serious or life threatening (e.g., alopecia). For all other treatment-related adverse events with a grade 2 intensity or higher, the dose modification scheme described below was implemented. The paclitaxel and cisplatin treatment on day 8 was omitted in the presence of a grade $\geq$3 hematological or non-hematological toxicity, and the patient then reevaluated weekly until regressing to less than or equal to grade 1. Missed doses of paclitaxel and cisplatin were not made up. The subsequent cycle of treatment was reduced by 20% in the case of a repeated grade 2 or any grade 3 toxicity, and reduced by 40% in the case of a repeated grade 3 or any grade 4 toxicity during the preceding cycle. If a dose reduction of more than 40% was required, the patients were excluded from the study.

Study assessments

A screening assessment, including a medical history, physical examination, ECG, chest X-ray, and tumor assessment, was conducted within 2 weeks before starting treatment. Further assessments conducted within 7 days before starting treatment included vital signs, ECOG performance status, and laboratory tests. Complete blood counts were performed weekly during the first cycle and every cycle thereafter, and biochemical tests performed before each cycle. Tumors were measured every two cycles until the tumor progressed. The tumor responses were classified according to the response evaluation criteria in solid tumors (RECIST) guidelines [22]. Patients with a complete response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical analysis

The current trial used a two-stage optimal design, as proposed by Simon, with an 80% power to accept the hypothesis and 5% significance to reject the hypothesis [23]. Plus, the current trial was designed to detect a response rate of 40% as compared to a minimal, clinically meaningful response rate of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with a measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, time to progression (TTP), and survival analyses were all estimated using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of a CR or PR until evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, while overall survival was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

Results

Patient characteristics

From June 2005 to December 2005, a total of 52 patients were enrolled in the current study from 9 centers. The characteristics of the patients are summarized in Table 1. The median age was 54 (range, 23–74) years, with 33 males and 19 females. Most of the patients (98.1%) had a good performance status (ECOG 0 or 1). Thirty-five (67.3%) patients had a metastatic disease, while 17 patients had a recurrent disease after surgical resection (total or subtotal gastrectomy) of the primary tumor. Distal lymph nodes and the liver were the most common sites of the metastases. No patients had received prior chemotherapy or radiotherapy.

Efficacy

Forty-six (88.5%) of the 52 patients were assessable for response, with the remaining 6 being lost to follow-up or patient refusal. All efficacy data are reported using the intent-to-treat patient population. Two cases of CR and 17 cases of PR were confirmed, giving an overall response rate of 36.5% (95% CI, 23.0–50.1%). The response characteristics are shown in Table 2. The median duration of response in the 19 responding patients was 6.8 (95% CI, 4.0–9.6) months, and the median TTP for all patients was 6.0 (95% CI, 3.2–8.9) months at a median follow-up duration of 8.5 (range, 2.4–13.8) months (Fig. 1). Twenty-five patients (48.1%) received a second-line therapy, such as irinotecan,

Table 1 Patient characteristics

Characteristic	Number of patients, $n = 52$ (%)
Age (years)	
Median (range)	54 (23–74)
Male/female	33 (63.5)/19 (36.5)
ECOG performance status	
0	9 (17.3)
1	42 (80.8)
2	1 (1.9)
Disease status	
Metastatic	35 (67.3)
Recurrent	17 (32.7)
Location of primary tumor	
Upper	8 (15.4)
Middle and lower	44 (84.6)
Histology	
Adenocarcinoma	47 (90.4)
Signet ring cell carcinoma	5 (9.6)
Metastatic sites	
Lymph node	34 (65.4)
Liver	14 (26.9)
Peritoneum	14 (26.9)
Ovary	5 (9.6)
Others (bone, kidney, pancreas)	4 (7.7)
Number of metastases	
1	19 (36.5)
2	14 (26.9)
≥3	19 (36.5)

Table 2 Tumor response (intention-to-treat analysis)

Response	Number ($n = 52$, %)[a]
Confirmed response	19 (36.5)[a]
Complete response	2 (3.9)
Partial response	17 (32.7)
Stable disease	19 (36.5)
Progressive disease	8 (15.4)
Not assessable	6 (11.5)

[a] 95% Confidential interval = 23.0–50.1%

capecitabine, S-1, or oxaliplatin after disease progression. Twenty-five patients had died at the time of the present evaluation. The estimated median overall survival was 10.8 months (95% CI, 6.6–15.0 months) with a estimated 1-year survival rate of 44.4 ± 8.7% (Fig. 1).

Toxicity

The hematologic and non-hematologic toxicities that occurred during the current study are summarized in Table 3. A total of 170 cycles (median 3, range 1–9 cycles) were administrated in 51 patients assessable for toxicity. The most severe hematologic adverse event was neutropenia, which occurred with a grade 3 intensity in 13 patients (25.5%) and in 20 cycles (11.8%). However, no grade 4 neutropenia or febrile neutropenia was observed. Nausea and fatigue were

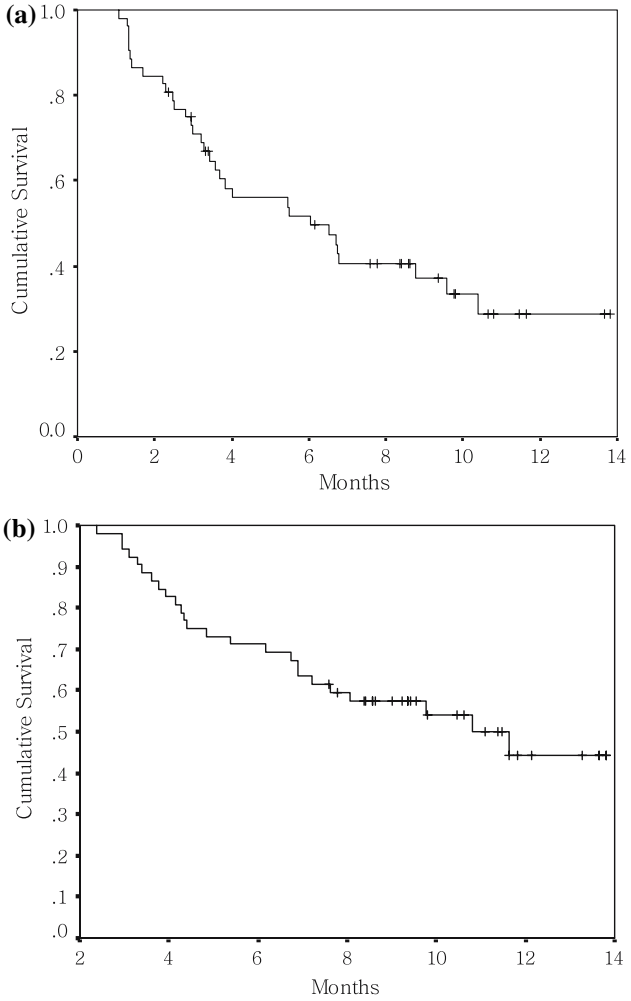

Fig. 1 Kaplan–Meier curves for time to disease progression (**a**) and overall survival (**b**) for intention-to-treat population ($n = 52$). The median time to progression and median overall survival was 6.03 and 10.8 months, respectively

the most common non-hematological toxicities. Grade 1/2 nausea and fatigue was observed in 66.7 and 29.4% of patients, respectively. Yet, no grade 4 non-hematologic toxicity was observed. Five patients (7.7%) were hospitalized due to treatment toxicities (four due to infections and one due to general weakness); however, there were no treatment-related deaths during this study. Overall, 6 (11.5%) patients and 15 (8.8%) cycles required a dose reduction of paclitaxel on day 1, while dose omissions of paclitaxel on day 8 were needed in 12 (7.1%) cycles. Also, a total of 24 (14.1%) cycles were delayed. The most common reasons for the dose modification of paclitaxel were neutropenia (5 patients, 12 cycles) and nausea (3 patients, 3 cycles). The mean dose intensity for the paclitaxel and cisplatin over all treatment cycles was 59.66 and 21.07 mg/m^2/week, corresponding to 89.5 and 90.3% of the planned dose intensities, respectively.

Table 3 Adverse reactions

	Grade (% of patients, $n = 51$)[a]				Grade (% of cycles, $n = 170$)[a]			
	1	2	3	4	1	2	3	4
Hematologic								
Anemia	19.6	49.0	13.7	3.9	35.9	32.4	4.7	1.2
Leukopenia	25.5	9.8			14.1	4.7		
Neutropenia	33.3	17.6	25.5		15.9	11.8	11.8	
Thrombocytopenia		2.0				1.8		
Non-hematologic								
Anorexia	3.9	7.8			2.4	4.1		
Nausea	49.0	17.6	5.9		31.2	7.6	1.8	
Vomiting	5.9	11.8	3.9		4.7	5.3	1.2	
Fatigue	21.6	7.8	2.0		21.8	2.9	0.6	
Stomatitis	11.8	2.0			4.1	0.6		
Alopecia	29.4	27.5	2.0		23.5	22.9	0.6	
Diarrhea	9.8	2.0			4.7	0.6		
Constipation	9.8				3.5			
Abdominal pain	9.8	2.0			4.7	1.2		
Myalgia	17.6				7.6			
Neuropathy	23.5	5.9			22.9	1.8		
Allergic reaction	9.8	2.0			3.5	0.6		
Febrile neutropenia								

[a] NCI-CTCAE v3.0

Discussion

In the current study, the combination chemotherapy of weekly paclitaxel and cisplatin, which can be administered on an outpatient basis, produced active antitumor activity and a safe toxicity profile in patients with advanced gastric cancer. The overall response rate (36.5%), median TTP (6.0 months), and median overall survival (10.8 months) following treatment with the present regimen were comparable with previous results reported for cisplatin-based combinations [5–8, 14, 15], where a continuous infusion of a 5-flourouracil (5-FU) and cisplatin regimen achieved a response rate of 51% and median TTP of 5.45 months [5], while docetaxel plus cisplatin regimens achieved a response rate and median TTP of 48% and 6.6 months, respectively [7].

Paclitaxel has been shown to be active and safe in the treatment of previously untreated advanced gastric cancer and it appears to have a schedule-dependent synergy with platinum compounds [12–15]. For example, Ajani et al. [12] reported that paclitaxel as a single agent based on a 3 or 24-h infusion produced a response rate of 17 and 20%, respectively, with a median response duration of 6.5 months in the treatment of advanced gastric cancer. In combination with cisplatin and/or 5-flourouracil, several phase II studies have reported encouraging response rates ranging from 32 to 51% for the first and second line settings [13, 14, 24, 25]. Given these results, the present authors already performed a phase II study using a combination of paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 based on 3-week intervals and demonstrated a comparable activity with a response rate of 33% [14]. However, the median TTP of 4.8 months and median overall survival of 6.7 months were relatively short compared to the results of previous studies due to five early deaths as a result of disease progression or treatment-related death.

Recently, the weekly administration of paclitaxel has demonstrated a sustained efficacy together with a more favorable toxicity profile (e.g., less myelotoxicity) than a 3-weekly administration for various solid tumors [19–21]. Accordingly, the current study employed paclitaxel at a weekly dose of 100 mg/m^2 to increase the dose intensity, while at the same time reducing the hematologic toxicity. Consequently, the dose intensity of paclitaxel in the present study was 59.7 mg/m^2/week, which was higher than that in previous studies at 175 mg/m^2 of paclitaxel based on a 3-week cycle [13–15, 24, 25].

One of the major toxicities related to paclitaxel is myelosuppression. Chemotherapy-induced severe neutropenia can also result in treatment-related hospitalization or mortality, thereby compromising the quality of life and increasing medical expenditure. In a previous study by the current authors (175 mg/m^2 and cisplatin 75 mg/m^2 based on 3-week intervals), grade 3/4 neutropenia was observed in 33% of patients and febrile neutropenia in 1 patient (2.6%) [15]. However, in the present study, only grade 3 neutropenia occurred in 13 patients (25.5%) and in 20 cycles (11.8%). Plus, no grade 4 neutropenia or febrile neutropenia was observed. Furthermore, in a phase II study by

Honecker et al. [26] that also adopted weekly paclitaxel (80 mg/m^2), 5-fluorouracil (2 g/m^2), and cisplatin (50 mg/m^2 on days 8 and 29) for the treatment of advanced gastric cancer, only one patient (3%) experienced grade 3/4 neutropenia. As such, the weekly administration of paclitaxel instead of 3-weekly paclitaxel may reduce the additive myelosuppression in combination chemotherapy.

In conclusion, weekly paclitaxel plus cisplatin combination chemotherapy was found to be well tolerated and effective in patients with advanced gastric cancer. Accordingly, this regimen can be regarded as an important first-line treatment option for advanced gastric cancer.

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