Phase II Trial of Low-dose Paclitaxel and Cisplatin in Patients with Advanced Gastric Cancer

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Background: Paclitaxel has shown promising activity in gastric cancer and has synergism with cisplatin. This study was performed to evaluate the efficacy and toxicity of low-dose paclitaxel (145 mg/m^2) plus cisplatin chemotherapy in metastatic or relapsed gastric cancer.

Methods: Chemotherapy-naïve patients with metastatic or relapsed gastric cancer were enrolled. Paclitaxel 145 mg/m^2 was administered intravenously over 3 h, followed by cisplatin 60 mg/m^2 on Day 1 every 3 weeks in the outpatient setting.

Results: Of 39 patients enrolled, 17 (44%) had partial responses. Twelve (31%) had stable disease and eight (21%) progressive disease. Two patients (5%) were not evaluable because of early drop-out. The median time to progression was 4.7 months and the median overall survival was 12.1 months. The most common hematologic toxicity was anemia (41%). Grade 3/4 neutropenia and thrombocytopenia developed in 14 and 3%, respectively. The most common non-hematologic toxicities were peripheral neuropathy (43%) and emesis (43%). Grade 3/4 non-hematologic toxicities included emesis (11%), peripheral neuropathy (3%), diarrhea (3%) and hepatotoxicity (3%).

Conclusions: Low-dose paclitaxel and cisplatin chemotherapy was active and well-tolerated in chemotherapy-naïve gastric cancer patients. This regimen seems to have comparable efficacy to previously reported higher-dose paclitaxel plus cisplatin-containing regimens and fewer toxicities.

Key words: chemotherapy – cisplatin – gastric cancer – paclitaxel

INTRODUCTION

Despite its declining incidence in the Western world, gastric cancer is still among the most common malignancies (1) and is a major international health problem, with a particularly high incidence in South America, in many former Eastern European countries and across Asia. In Korea, according to statistics reported in 2002, gastric cancer was the most prevalent cancer (2).

Cytotoxic chemotherapy has been widely used in patients with advanced or metastatic gastric cancer and has been demonstrated to be effective in the palliative management of this disease. In randomized trials, in fact, modest improvement in overall survival (OS) and in quality-of-life was noted when compared with best supportive care alone (3–6). Vanhoefer et al. reported the results of a trial comparing three frequently used regimens [FAMTX (5-fluorouracil (5-FU), doxorubicin and methotrexate), ELF (etoposide, leucovorin and 5-FU) and FP (5-FU and cisplatin)]. The overall response rate varied from 9 to 20% and the median survival times were ∼7 months with these three regimens (7). These combination therapies remain suboptimal and a standard therapy has yet to be defined. Therefore, several new agents with complementary mechanisms of actions to existing therapy have been tried to improve the outcomes.

Many clinical evidences suggest that taxane agents have antitumor activity and these agents are used in combination with various other chemotherapeutic agents (8–20). Antitumor activity of paclitaxel has been shown in gastric cancer cell lines and in several Phase I/II trials (21–24). Recently, paclitaxel has been commonly combined with 5-FU and/or platinum

compounds in gastric cancer and various schedules and combinations of chemotherapeutic agents have been studied and showed promising results (8–10,13,16,19,20). Paclitaxel is commonly used in a three-weekly cycle with the dose of 175–225 mg/m^2/3 weeks as a single agent (21–24) or with the combination of other agents (8–10,16,20). Until now, only two Phase II studies of paclitaxel and cisplatin doublet chemotherapy have been reported; one study (19) used biweekly regimen [paclitaxel 160 mg/m^2 and cisplatin 60 mg/m^2, Day 1; with/without granulocyte colony-stimulating factor (G-CSF)] and the other study (20) performed three-weekly regimen (paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2, Day 1). These two studies showed overall response rate of 44–46% and median OS of 11.2–13.8 months (19,20).

We previously conducted a Phase II study using low-dose paclitaxel 145 mg/m^2 plus cisplatin 60 mg/m^2 on Day 1 every 3 weeks in non-small cell lung cancer (NSCLC) patients. In that study, this regimen was feasible and seemed to have reduced toxicities and maintain efficacy compared with previously reported other regimens (25). This previous experience and convenience of the scheduling in the outpatient setting prompted us to select the same regimen in gastric cancer. The aim of this study was to evaluate the efficacy and tolerance of three-weekly regimen consisting of low-dose paclitaxel and cisplatin in metastatic or relapsed gastric cancer patients as first-line treatment. We also compared the result of this low-dose paclitaxel plus cisplatin regimen with those of higher-dose paclitaxel and platinum-containing regimens of previous reports.

PATIENTS AND METHODS

ELIGIBILITY

Patients with histologically confirmed adenocarcinoma of the stomach (except carcinomas of the esophagogastric junction) were enrolled onto this study. The eligible patients included those with unresectable advanced disease, metastatic disease and relapsed disease after resection. All patients had to have at least one measurable disease (defined as a mass with demarcated dimensions on computed tomography, routine chest X-ray or physical examination). Patients who were previously treated with palliative chemotherapy were excluded. However, patients who had received adjuvant chemotherapy after curative resection were eligible if they had a treatment-free period for at least 12 months from the end of adjuvant chemotherapy to the first relapse.

Other eligibility criteria included age of 18–75 years old; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate hematologic baseline function [absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l], hepatic function [serum bilirubin $\leq 1.25 \times$ upper normal limit (UNL), serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ UNL, serum alkaline phosphatase $\leq 5.0 \times$ UNL (unless bone metastasis was present in the absence of any liver disease)] and renal function (serum creatinine

≤ 1.5 mg/dl); life expectancy >3 months; at least 3 weeks from surgery and 4 weeks from previous radiotherapy. Patients were ineligible if they had brain metastasis or a history of previous or concomitant malignancy, except for curatively treated non-melanoma skin cancer or *in situ* cervical cancer. Neither pre-existing motor or sensory neurologic symptoms $\geq$Grade 2 on the basis of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) were allowed nor active infections or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment were allowed. All patients gave written informed consent according to institutional regulations.

TREATMENT

Hydrocortisone 100 mg, pheniramine maleate 45.5 mg, and famotidine 20 mg were administered intravenously (i.v.) 30 min before paclitaxel (Taxol®; Bristol-Myers-Squibb Company, Princeton, NJ, USA) for hypersensitivity prophylaxis. Then the patients received paclitaxel 145 mg/m^2 as 3 h i.v. infusion, followed by cisplatin 60 mg/m^2 as 15 min i.v. infusion with a standard hydration method on Day 1. All patients received adequate antiemetic therapy before chemotherapy. The treatment was administered on outpatient basis and repeated every 3 weeks, provided patients recovered from all toxic effects. This combination chemotherapy continued up to six cycles if the disease progression or substantial toxicity did not develop. After six cycles, additional three cycles of chemotherapy could be administered if the patients wished or the investigator judged the additional administration to be beneficial for the patients. G-CSF was not routinely used in the present study.

RESPONSE TO TREATMENT AND ADVERSE EFFECTS

Response was assessed using WHO criteria. A complete response (CR) was defined as the disappearance of all clinical evidence of tumor for a period of at least 4 weeks. A partial response (PR) was defined as $\geq 50\%$ decrease in the bidimensional tumor measurements for at least 4 weeks, without the appearance of any new lesions or progression of any existing lesions. Progressive disease (PD) was defined as the development of any new lesions or a >25% increase in the sum of the products of all measurable lesions. Stable disease (SD) was defined as tumor response that did not meet the criteria for CR, PR or PD.

Toxicities were evaluated based on the NCI-CTC before each treatment. Dose modifications and treatment delays were performed as necessary according to the extent of hematological and organ toxicity. Treatment could be delayed for up to 3 weeks if the ANC was $<1.0 \times 10^9$/l and/or platelet count was $<75 \times 10^9$/l. Drug doses were reduced by 25% in case of severe neutropenia (ANC $<0.5 \times 10^9$/l), thrombocytopenia (platelet count $<25 \times 10^9$/l), febrile neutropenic fever, or severe peripheral neuropathy or other severe non-hematologic toxicities of NCI-CTC $\geq$Grade 3. If serum creatinine was >2.0 mg/dl or creatinine clearance was

≤10 ml/min before the next cycle or if patents had Grade 4 neurotoxicity or Grade 3 neurotoxicity that was not reversible within 2 weeks after dose reduction, administration of drugs was discontinued.

STATISTICAL ANALYSIS

The primary end point of this trial was the response rate of the combination chemotherapy using low-dose paclitaxel and cisplatin for unresectable locally advanced or metastatic gastric cancer. This study followed the optimal Simon two-step design (26). It was believed that a response rate of >20% would justify continuing the trial (H0). The expected response rate was 40% (H1). The probability of accepting the treatment with the response probability H0 (20%) was $\alpha = 0.10$. The probability of rejection of the treatment with the response probability H1 (40%) was $\beta = 0.10$. If at least 3 of the first 17 patients would show an objective response in the first stage, it was planned to recruit a total of 37 patients.

Time to progression (TTP) and OS were secondary end points. OS was calculated from the start of the study treatment until death. TTP was calculated from the first day of the chemotherapy until the date of progression. OS and TTP curves were obtained using the Kaplan–Meier method.

RESULTS

PATIENT CHARACTERISTICS

From December 2002 to June 2004, 39 patients with a median age of 57 years (31–75 years) were enrolled from three institutions. Patient characteristics are given in Table 1. The majority of the study population was male (79%, 31 out of 39). Six patients (15%) had an ECOG performance status of 2. Thirty patients (77%) had primary metastatic disease and nine (23%) had recurrent disease. All patients had measurable tumor lesions. Lymph nodes, peritoneum as well as liver were the most common metastatic sites. The metastasis involved two organs in 17 patients (44%) and three or more organs in 9 patients (23%). Among nine patients who had previously received surgery for gastric cancer with curative intent, five patients received adjuvant chemotherapy after surgery with 5-FU and cisplatin.

DRUG DELIVERY

Of 39 patients who received chemotherapy, two patients were non-evaluable for response owing to early drop-out after the first cycle of chemotherapy; these two patients withdrew their consent. A total of 174 treatment cycles were delivered, with patients receiving a median of five (range 1–9) cycles. Sixteen of the patients received the planned six cycles of chemotherapy. Among these 16 patients, 4 patients received additional three cycles. Treatment was discontinued prematurely in two patients because of chemotherapy-associated toxicities; one patient rejected further treatment owing to severe emesis

Table 1. Patient characteristics

Patient characteristics ($n = 39$)	
No. of patients enrolled	
Assessable for response and toxicity	37 (95%)
Drop-out (withdrawal of consent during chemotherapy)	2 (5%)
Median age (range)	57 years (31–75)
Gender (male : female)	31 (79%) : 8 (21%)
ECOG performance status (0–1 : 2)	33 (85%) : 6 (15%)
Disease status	
Metastatic	30 (77%)
Recurrent	9 (23%)
Site of metastasis	
Lymph nodes	32 (82%)
Peritoneum	20 (51%)
Liver	10 (26%)
Abdominopelvic mass	5 (13%)
Ovary	2 (5%)
Bone	2 (5%)
Lung	1 (3%)
No. of organs involved	
1	13 (33%)
2	17 (44%)
≥3	9 (23%)
Previous treatment	
Surgery	
Curative surgery	9 (23%)
Palliative surgery	6 (15%)
Adjuvant chemotherapy	5 (13%)

ECOG, Eastern Cooperative Oncology Group.

and the other could not receive further chemotherapy owing to Grade 4 hepatotoxicity.

Relative dose intensity was calculated for each patient and for each drug according to the method of Hryniuk (27). The calculated mean relative dose intensity of paclitaxel and cisplatin was 95 and 95%, respectively.

OBJECTIVE TUMOR RESPONSES

Among the 39 patients who received the combination chemotherapy, two patients (5%) were not evaluable for response (early withdrawal of consent). According to an intent-to-treat analysis, overall response rate was 44% (17 out of 39 patients achieved PR). Twelve patients (31%) had SD and eight patients (21%) had tumor progression.

ADVERSE EVENTS

Toxicities associated with treatment are listed in Table 2. Thirty-seven patients were assessable for toxicity. The

Table 2. Adverse events

Adverse events	All patients (*n* = 37), number (%)		
	All events	Grade 3 events	Grade 4 events
Hematologic toxicities			
Neutropenia	13 (35%)	5 (14%)	0 (0%)
Anemia	15 (41%)	0 (0%)	0 (0%)
Thrombocytopenia	1 (3%)	1 (3%)	0 (0%)
Neutropenic fever	0 (0%)	–	–
Non-hematologic toxicities			
Emesis	16 (43%)	4 (11%)	0 (0%)
Diarrhea	4 (11%)	1 (3%)	0 (0%)
Hepatotoxicity	8 (22%)	0 (0%)	1 (3%)
Nephrotoxicity	3 (8%)	0 (0%)	0 (0%)
Peripheral neuropathy	16 (43%)	1 (3%)	0 (0%)

hematologic toxicity was mild and the most common hemato-logic toxicity was anemia (41%). However, there was no Grade 3/4 anemia. Among Grade 3/4 hematologic toxicities, neut-ropenia was most common (14%) and all were Grade 3 tox-icities. Grade 3 thrombocytopenia was observed in one case (3%). No patient experienced febrile neutropenia.

Non-hematologic toxicities consisted mainly of emesis and peripheral neuropathy. Nausea and vomiting occurred in 16 patients (43%) and were generally mild or moderate Grade 3/4 emesis was noted in 4 patients (11%). Sixteen patients (43%) developed peripheral neuropathy. However, neuropathy was generally mild and only one patient (3%) experienced severe (Grade 3) peripheral neuropathy after fifth cycle. Neurological cumulative toxicities had developed as follows: four Grade 1/2 peripheral neuropathy (11%) after first cycle; 11 Grade 1/2 neuropathy (30%) after second cycle; 13 Grade 1/2 neuropathy (35%) after third and fourth cycles; 15 Grade 1/2 neuropathy (41%) and one Grade 3 neuropathy (3%) after fifth and sixth cycles. Transiently impaired liver function was observed in eight patients (22%) and one patient (3%) developed Grade 4 hepatic toxicity. Diarrhea was noted in four patients (11%) and one patient (3%) developed Grade 3 diarrhea. Two patients (5%) experienced infusion-related hypersensitivity during first course of chemotherapy. All hypersensitive reactions resolved with the discontinuation of paclitaxel and did not reappear during a re-challenge with additional i.v. dosage of corticosteroid and antihistamine. Two patients were dropped out from this study because of adverse events after chemotherapy: one patient rejected further treatment owing to severe emesis and the other could not receive further chemotherapy owing to Grade 4 hepatotoxicity. There was no treatment-related death.

SURVIVAL

With the median follow-up of 19.2 months, the median TTP was 4.7 months [95% confidence interval (CI) = 3.5–5.9 months] (Fig. 1). The median TTP of responders (*n* = 17)
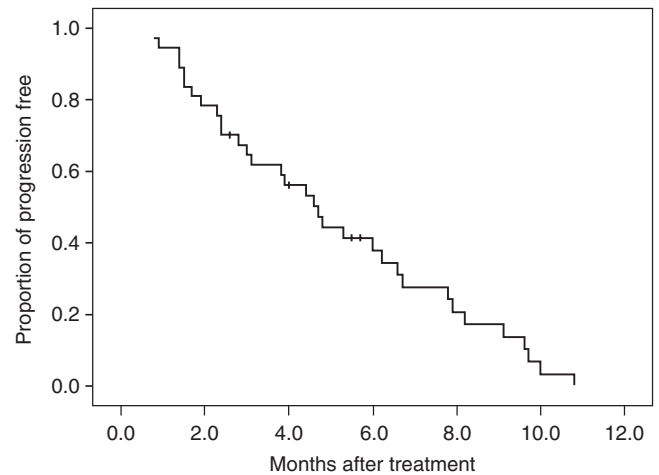
Figure 1. Time to progression curve.
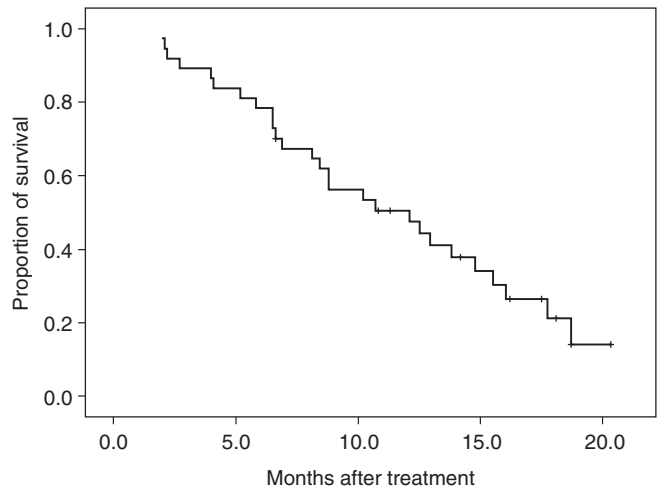
Figure 2. Overall survival curve.

was 6.0 months (95% CI = 3.5–8.5 months). The median OS was 12.1 months (95% CI = 7.0–17.1 months) (Fig. 2). After failure of first-line paclitaxel and cisplatin chemother-apy, 29 patients received second-line chemotherapy; 14 patients received oxaliplatin/leucovorin/5-FU (FOLFOX), 4 patients irinotecan/leucovorin/5-FU (FOLFIRI), 6 patients capecitabine (±cisplatin), 4 patients S-1 and one patient FP. Until now, 27 patients died of their disease.

DISCUSSION

Although randomized trials had demonstrated that chemother-apy provides survival and symptomatic benefits in patients with advanced gastric cancer over supportive care alone (3–6), these benefits were fairly modest. Until recently, 5-FU and/or cisplatin-based combination chemotherapy has been commonly used, but the continuing lack of substantial progress in advanced gastric cancer with such chemothera-peutic regimens has prompted investigators to evaluate new agents and/or drug combinations including docetaxel, paclit-axel, irinotecan, capecitabine, S-1, etc.

Table 3. Phase II trials of paclitaxel plus platinum combination chemotherapy in chemotherapy-naïve patients with gastric cancer

Study	Treatment	No. of patients	Grade 3/4 neutropenia (%)	Grade 3/4 peripheral neuropathy (%)	RR (%)	TTP (months)	OS (months)
Kim et al. (9)	P: 175 mg/m^2 (3 h infusion, Day 1)	41	34	0	51	3.9*	6.0
	F: 750 mg/m^2 (24 h infusion, Days 1–5)						
	C: 20 mg/m^2 (2 h infusion, Days 1–5)						
	(Every 4 weeks)						
Kollmannsberger et al. (10)	P: 175 mg/m^2 (3 h infusion, Days 1 and 22)	45	15	2	51	9.0	14.0
	L: 500 mg/m^2 (2 h infusion, weekly)						
	F: 2 g/m^2 (24 h infusion, weekly)						
	C: 50 mg/m^2 (1 h infusion, Days 8 and 29)						
	(Six weeks of therapy followed by 2 weeks of rest were considered one cycle)						
Honecker et al. (13)	P: 80 mg/m^2 (1 h infusion, weekly)	29	3**	10	48	8.0	11.0
	L: 500 mg/m^2 (2 h infusion, weekly)						
	F: 2 g/m^2 (24 h infusion, weekly)						
	C: 50 mg/m^2 (1 h infusion, Days 8 and 29)						
	(Six weeks of therapy followed by 1 week of rest were considered one cycle)						
Kornek et al. (19)	P: 160 mg/m^2 (3 h infusion, Day 1)	45	33	13	44	7.0	11.2
	C: 60 mg/m^2 (1 h infusion, Day 1)						
	(Every 2 weeks, with or without G-CSF)						
Gadgeel et al. (16)	P: 200 mg/m^2 (3 h infusion, Day 1)	27	33	8	33	4.9*	7.5
	Cb: AUC of 5.0 (Day 1)						
	(Every 3 weeks)						
Park et al. (20)	P: 175 mg/m^2 (3 h infusion, Day 1)	36	29	9	46	4.9	13.8
	C: 75 mg/m^2 (Day 1)						
	(Every 3 weeks)						
This study	P: 145 mg/m^2 (3 h infusion, Day 1)	39	14	3	44	4.7	12.1
	C: 60 mg/m^2 (15 min infusion, Day 1)						
	(Every 3 weeks)						

RR, response rate; TTP, median time to progression; OS, median overall survival; P, paclitaxel; F, 5-fluorouracil; C, cisplatin; L, folinic acid (leucovorin); Cb, carboplatin; AUC, area under the concentration–time curve.
*Median response duration was presented.
**Grade 3/4 leucopenia was presented.

Paclitaxel has shown encouraging activity as a single agent (200–225 mg/m^2, every 3 weeks) in gastric cancer, with a response rate of 17–28% (21–24). Various schedules and combinations of chemotherapeutic agents including paclitaxel have been developed. Paclitaxel appears to have a schedule-dependent synergy with platinum compounds, as documented in established human gastric cancer cell lines (28). This synergy has led to the development of paclitaxel–platinum combination regimens in a number of solid tumors, including gastric cancer (8–10,13,16,19,20).

The present study evaluates the efficacy and toxicities of low-dose paclitaxel (145 mg/m^2) plus cisplatin combination chemotherapy in patients with advanced gastric cancer. This regimen achieved an overall response rate of 44% and median OS of 12.1 months (95% CI = 7.0–17.1 months), and thus it

compared favorably with the reported efficacy of common two- or three-drug combinations including FAMTX (7), ELF (7,29,30), FAP (5-FU, doxorubicin and cisplatin) (31) and FP (7,32). Also, the outcome of the present study seems to be similar to the results of other previous studies using paclitaxel and platinum-containing regimens for advanced gastric cancer. Although this study is a Phase II trial, as shown in Table 3, this low-dose paclitaxel plus cisplatin regimen seems to have similar treatment outcomes to those of higher-dose paclitaxel and cisplatin regimen with/ without 5-FU.

In previous reports about a dose–response effect of paclitaxel, no obvious benefit was observed for high-dose paclitaxel in various solid tumors including head and neck (33), lung (34,35), breast (36,37) and ovary cancer (38,39). An ECOG

randomized trial in NSCLC compared paclitaxel (24 h infusion schedule) in doses of 250 mg/m^2 plus G-CSF and 175 mg/m^2 combined with the same dose of cisplatin. Response rate, failure-free survival and OS were virtually identical for the two arms (34). Another randomized trial from the Hellenic Cooperative group compared paclitaxel (3 h schedule) in doses of 225 and 175 mg/m^2 combined with the same dose of carboplatin in NSCLC. Although higher-dose paclitaxel prolongs the median TTP, the differences in response rate and OS were not statistically significant (35). Two trials involving patients with metastatic breast cancer have addressed the dosing question for 3 h infusion of paclitaxel (36,37). One trial compared doses of 135 and 175 mg/m^2 (Bristol-Myers-Squibb 048) (36) and the other compared doses of 175, 210 and 250 mg/m^2 (Cancer and Leukemia Group B 9342) (37). In spite of the prolongation of median TTP in higher-dose paclitaxel group, no differences were observed in response rates and OS in both studies. Also, in head and neck cancer (33) and ovarian cancer (38,39), no survival benefit was observed. Therefore, although there is some variation regarding other end points, the literature is consistent in reporting no survival benefit for higher-dose paclitaxel in various solid tumors. These results may be explained by the plateauing of cytotoxicity observed *in vitro* as paclitaxel concentration increases. This is probably a result of saturation of paclitaxel binding sites on β-tubulin at the paclitaxel plasma steady-state concentrations achieved with doses of 135 mg/m^2 or greater (24 h infusion) (40). Our data also suggest a similar efficacy result between low- and higher-dose paclitaxel-containing regimens in advanced gastric cancer patients.

Furthermore, toxicities were mild in low-dose paclitaxel plus cisplatin regimen of the present study. Only two patients discontinued therapy because of toxicities from chemotherapy. Major toxicities were emesis, peripheral neuropathy, anemia and neutropenia, which were similar results to higher-dose paclitaxel plus platinum-containing regimen. However, Grade 3/4 neutropenia and peripheral neuropathy developed only in 14 and 3% of patients. These frequencies were less than those of higher-dose paclitaxel plus platinum-containing regimens (Table 3). As shown in Table 3, dose intensity of paclitaxel may be related with severe neurotoxicities, especially when combined with cisplatin. By using low-dose paclitaxel and cisplatin we could reduce the frequency of severe neuropathy, which is the most troublesome toxicity of paclitaxel-containing regimen. In addition, the combination of low-dose paclitaxel and cisplatin has the advantage of convenient delivery of drugs in the outpatient setting and 1 day treatment duration, compared with other regimens containing paclitaxel and cisplatin that developed similar rates of severe neurotoxicities (9,10). This regimen is easier to prescribe than previous 5-FU-containing infusional regimen such as FP, which is one of the most widely used regimen for gastric cancer and requires admission or continuous infusion device for the administration of drugs. Compared with docetaxel-containing regimens, this combination of low-dose paclitaxel and cisplatin seems to have the favorable toxicity profiles; especially, less severe myelosuppression (11,12,14,15,17,18).

In conclusion, first-line low-dose paclitaxel (145 mg/m^2) plus cisplatin chemotherapy in the outpatient setting was an active and well-tolerable regimen in the treatment of advanced gastric cancer. Also, compared with higher-dose paclitaxel and platinum regimen, this regimen showed similar efficacy and fewer myelosuppression and peripheral neuropathy. This study suggests that paclitaxel doses of >145 mg/m^2/3 weeks seem to have more toxicities and no further clinical benefits when combined with cisplatin. Further randomized Phase II clinical trial for determining the optimal dose and schedule of a combination of paclitaxel and cisplatin in gastric cancer is necessary. In addition, this combination could be further evaluated as a salvage treatment in previously 5-FU-based chemotherapy-failed gastric cancer patients.

Acknowledgments

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