Phase II study of weekly paclitaxel, cisplatin, and 5-fluorouracil for advanced gastric cancer

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Abstract

Background Our previous phase I study provided evidence that weekly paclitaxel, cisplatin, and bolus 5-fluorouracil (weekly PCF) was effective and well tolerated in patients with advanced gastric cancer. This study was conducted to confirm the efficacy and toxicity of weekly PCF.

Methods Eligibility criteria were as follows: pathological confirmation; measurable lesion(s); and no history of treatment with taxanes, platinum-based compounds, or intravenous 5-fluorouracil (1 regimen of pre-treatment with oral 5-fluorouracil agents was allowed). Paclitaxel (80 mg/m², 1 h), cisplatin (25 mg/m², 2 h), and 5-fluorouracil

(600 mg/m², bolus) were administered on days 1, 8, and 15, every 4 weeks.

Results Between March 2006 and May 2009, 46 patients were enrolled and 45 were assessed. Eighteen had a history of pre-treatment with oral 5-fluorouracil agents. The response rate was 56% [95% confidence interval (CI) 41–70%]. Median progression-free survival was 160 days (95% CI 145–214 days). Median overall survival was 552 days (95% CI 350–843 days). Grade 3–4 major adverse reactions observed were neutropenia (76%), leucopenia (38%), anaemia (27%), febrile neutropenia (22%), exacerbation of performance status (16%), and anorexia (13%).

Conclusion A weekly PCF regimen is promising for advanced gastric cancer, although it is associated with moderate hematological and minimal non-hematological toxicities.

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Introduction

Gastric cancer is a disease that can be treated by surgery; however, the prognosis remains poor for cancers that cannot be treated by surgery or in cases of recurrence. Nearly 700,000 people die each year from gastric cancer; thus, it is the second most deadly cancer [1]. The frequency of gastric cancer is particularly high in Asia, Eastern Europe, and South America, and 50,000 people die annually from gastric cancer in Japan [2]. In clinical trials, groups treated with chemotherapy for advanced gastric cancer (AGC) were shown to live longer than untreated groups [3–5].

In recent years, the efficacy of paclitaxel (PTX) administered every 3 weeks for AGC has been observed in

phase II clinical trials, but high rates of adverse events such as neutropenia and peripheral neuropathy have also been recognized [6, 7]. In this context, weekly PTX has been reported to be superior in terms of safety and equivalent in efficacy [8, 9]. Because adverse events with weekly PTX are minimal, weekly PTX has often been used as second- or third-line chemotherapy; several phase I and II clinical trials have also been conducted using PTX in combination with other drugs in front-line treatment [9–12]. Ninomiya et al. reported a 39% response rate (RR) in a phase II clinical trial that combined weekly PTX with continuous intravenous infusion (c.i.v.) of 5-fluorouracil (5-FU) in AGC treatment [13]. Nagata et al. reported a 41% RR in a phase II clinical trial of weekly PTX plus cisplatin (CDDP), in which the recommended doses were set (80 and 25 mg/m², respectively) in a phase I trial [14, 15].

To evaluate the additional effects of 5-FU in combination with weekly PTX plus CDDP, we planned a phase I trial with combined weekly PTX, CDDP, and 5-FU for AGC. Intravenous bolus injection was selected as the method of administration for 5-FU in order to obtain the benefits of this treatment, which does not require hospitalization or a port system. As a result, recommended doses of PTX, CDDP, and 5-FU were set at 80, 25, and 600 mg/m², respectively, and a phase II clinical trial was established [16].

Methods

Study design and statistical methods

This was a multicenter, open-label, single-arm, phase II study conducted at 4 institutions in Japan. The primary endpoint was the RR of weekly combination therapy, and secondary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events.

On the basis of the results of previous clinical trials of 2-drug combination therapy including weekly PTX conducted in Japan [13, 15], and 3-drug combination therapy of DCF [docetaxel (DOC), CDDP, and 5-FU] reported by Ajani et al. [17], the present study was designed to reject an RR of less than 20% as a clinically meaningless RR and provide a statistical power of 80% for assessing an efficacy of 38% for the regimen with an alpha error of less than 5%. The required sample size was determined to be 44. PFS was measured from the date of registration to the date of documented progression or death from any cause. OS was defined as the time from registration until death from any cause. PFS and OS were updated 6 months after the registration of the final patient and the medians were calculated using the Kaplan–Meier method.

Patients

The patients enrolled in this study had histologically confirmed non-resectable (metastatic) or recurrent gastric cancers. Other criteria for inclusion were as follows: Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; measurable lesion(s); no history of treatment with taxanes, platinum-based compounds, or intravenous 5-FU (1 regimen of pre-treatment with oral 5-FU agents was allowed, and adjuvant chemotherapy of 6 months or more after completion was not considered prior treatment); adequate bone marrow, liver, and renal functions, as defined by white blood cell count between 4000 and 12,000/mm³, absolute neutrophil count >2000/mm³, platelet count >100,000/mm³, hemoglobin >8.0 g/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2 times institutional upper limits (<3 with liver metastasis), total bilirubin <1.5 mg/dl, creatinine <1.5 mg/dl; expected survival period of 3 months or more; no active cancer in other organs; and aged at least 20 years. Patients with severe organ dysfunction, history of hypersensitivity, inflammatory disease, massive ascites, and/or pleural effusion or brain metastasis were excluded from the study. The present study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the Institutional Review Boards of each institution, and all patients gave their written informed consent to participate in the study.

Treatment

Paclitaxel (PTX) at 80 mg/m² with 200 ml of 0.9% sodium chloride solution was administered by infusion over a period of 1 h followed by a bolus infusion of 5-FU at 600 mg/m² and a 2-h infusion of CDDP at 25 mg/m² with 500 ml of 0.9% sodium chloride solution. To prevent hypersensitivity reactions, pre-medication (intravenous dexamethasone at 16 mg; peroral diphenhydramine at 50 mg, and intravenous ranitidine at 50 mg or famotidine at 20 mg) was given 30 min before PTX administration. Each treatment cycle consisted of the administration of these agents once a week for 3 weeks (days 1, 8, and 15), and this treatment regimen was repeated every 4 weeks.

The decision to administer the combination therapy was based on the physical examination of the patient and data collected within 24 h, and the standards were set as follows: leukocytes >3000/mm³ (days 8, 15 >1500/mm³); neutrophils >1500/mm³ (days 8, 15 >1000/mm³); hemoglobin >8.0 g/dl; thrombocytes >75,000/mm³; AST and ALT <2 times institutional upper limits (<3 with liver metastasis); fever <38°C; PS 0–2; non-hematological toxicity Grade 0–2.

When these conditions were not met on day 1, the period of observation was extended by 1 week. Failure to meet these conditions after the 1-week extension or on day 8 or 15 meant that treatment was skipped on that day. Treatment doses in the next cycles were reduced for patients who developed Grade 4 leukopenia/neutropenia, febrile neutropenia or Grade 3 or higher non-hematological toxicity, and these dose regimens included Level-1 (PTX, CDDP, and 5-FU; 70, 20, and 500 mg/m², respectively) and Level-2 (60, 15, and 400 mg/m², respectively). Granulocyte colony-stimulating factor (G-CSF) was not administered prophylactically, but was permitted to be administered when Grade 4 leukopenia/neutropenia or febrile neutropenia developed.

The treatment protocol included 6 treatment cycles; however, treatment could be stopped when a complete response (CR) or partial response (PR) was confirmed. In addition, the treatment could be extended to 7 cycles or more on the basis of the judgment of the attending physician. However, administration was stopped under the following conditions: progressive disease (PD); decline in overall condition; treatment skipped twice in 1 cycle; withdrawal of consent or request for discontinuation; patient deemed unsuitable after registration or the attending physician deemed further treatment to be inappropriate. No restrictions were placed on follow-up treatments after the completion of this regimen.

Evaluation of response and toxicity

Pre-treatment evaluation included determination of baseline medical history, the physical condition of the patients, laboratory studies (complete blood cell counts, electrolytes, liver and renal function tests, and urinalysis), chest X-ray, abdominal computed tomography (CT), and electrocardiogram. CT or other imaging tests were also performed to examine the measurable lesion; these tests were repeated at the end of every treatment cycle or every 2 months in patients who stopped treatment before progression. The confirmed responses were classified by central review according to the Response Criteria in Solid Tumors version 1.0.

Toxicity was monitored and graded according to the Common Terminology Criteria for Adverse Events version 3.0. Patients underwent weekly laboratory tests and non-hematological toxicity tests during treatment.

Results

Patient characteristics

Between March 2006 and May 2009, a total of 46 patients with AGC were enrolled in the study. The characteristics of

the 46 patients are summarized in Table 1. Median age was 71 years (range 48–85 years); 36 patients (78%) were male, 15 patients (33%) had non-resectable cancer, and all patients had a good PS (0–1). Common metastatic sites included the lymph nodes (70%) and liver (24%). Eighteen patients had a history of pre-treatment with oral 5-FU agents [17 patients received S-1 (15 as adjuvant therapies and 2 as first-line therapies) and 1 received doxifluridine as an adjuvant therapy]. One patient withdrew consent before the start of treatment; therefore, only 45 patients were assessed for efficacy and toxicity.

Treatment delivery

A total of 237 cycles of weekly PTX, CDDP, and 5-FU were administered, with a median of 4.5 cycles per patient (range 1–24). Sixteen patients (36%) completed 6 treatment cycles, and the doses were reduced to Level-1 and Level-2 in 12 and 9 patients, respectively. Median relative dose intensity for PTX, CDDP, and 5-FU was 67%. One patient continued treatment past the 24th cycle. Treatment was discontinued for the other 44 patients for the following reasons: confirmation of PD in 25 patients, skipping the treatment more than once in a single cycle owing to

Table 1 Patient characteristics

Number of patients	46
Median age, years (range)	71 (48–85)
Gender	
Male	36
Female	10
Non-resectable (metastatic)	15
Recurrence	31
PS (ECOG)	
0	18
1	28
Prior chemotherapy	
None	28
S-1 (adjuvant/1st line)	17 (15/2)
Doxifluridine (adjuvant)	1
Histology	
Intestinal	22
Diffuse	23
Adenosquamous	1
Metastatic site	
Lymph node	32
Liver	11
Peritoneum	4
Others	3

PS (ECOG) Performance status (Eastern Cooperative Oncology Group)

Table 2 Tumor response

	No. of patients	CR	PR	SD	PD	NE	Response rate (95% CI)
Total	45	2	23	12	4	4	56% (41–70%)
Prior chemotherapy							
Yes	18	2	10	3	2	1	67% (41–86%)
No	27	0	13	9	2	3	48% (29–68%)

CR Complete response, PR partial response, SD stable disease, PD progressive disease, NE not evaluated, CI confidence interval

adverse events in 11 patients, decline in overall condition in 5 patients, completion of the planned 6 cycles of treatment in 2 patients, and upon request from the patient in one patient. Of these 44 patients, 30 received further lines of chemotherapeutic treatment and 2 received radiotherapy.

Efficacy

The response rate (CR + PR) was 56% [95% confidence interval (CI) 41–70%], with 2 patients showing a CR (Table 2). The RR among patients with lymph node metastasis was 59% (19/32), and that among patients with liver metastasis was 64% (7/11). The RR among patients with no prior treatment was 48%, and that among patients with a history of pre-treatment with oral 5-FU agents was 67%. The disease control rate [CR + PR + stable disease (SD)] was 82% (95% CI 71–93%). The median follow-up time was 332 days, during which the median PFS was 160 days (95% CI 145–214 days, event = 37) and the median OS was 552 days (95% CI 350–843 days, event = 22) (Figs. 1, 2).

Toxicity

Toxicities observed during treatment are listed in Table 3. Grade 3–4 major hematological adverse events observed in the patients were neutropenia (76%), leukopenia (38%), anemia (27%), and febrile neutropenia (22%). Seven of 10 patients who developed febrile neutropenia were 75 years old or more, and all patients recovered soon with the administration of G-CSF and antibiotics. Eight of these 10 patients could continue the treatment after recovery, with dose reduction, while two stopped treatment because of PD. Grade 3 major non-hematological adverse events observed were exacerbation of PS (16%) and anorexia (13%). Grade 4 non-hematological adverse events and treatment-related deaths were not observed.

Discussion

Although the median survival of AGC when left untreated is 3–4 months, the survival has been shown to improve

Fig. 1 Kaplan–Meier analysis of progression-free survival (PFS) for all 45 patients treated with paclitaxel, cisplatin, and 5-fluorouracil

Fig. 2 Kaplan–Meier analysis of overall survival (OS) for all 45 patients treated with paclitaxel, cisplatin, and 5-fluorouracil

with adequate chemotherapy. Whereas 5-FU had been and remains the core of chemotherapy for AGC, the advent of CDDP led to a new era of combination therapies such as CF (CDDP and 5-FU) and ECF (epirubicin, CDDP, and 5-FU) [18, 19]. Recently, the V325 study reported the superiority of DCF over CF in the United States, and the REAL2 trial reported the non-inferiority of EOX (epirubicin, oxaliplatin, and capecitabine) compared with ECF in European countries [20, 21].

In Japan, the non-inferiority of S-1 compared with 5-FU alone was shown in the JCOG9912 trial, thereby validating the introduction of S-1 in AGC treatment [22].

Table 3 Toxicity ($n = 45$)

Toxicity (CTCAE)	No. of patients				Grade 3–4 (%)
	Grade 1	Grade 2	Grade 3	Grade 4	
Hematological					
Leukopenia	2	20	13	4	38
Neutropenia	0	8	20	14	76
Hemoglobin	9	21	12	0	27
Thrombocytopenia	13	1	1	0	2
Febrile neutropenia	–	–	10	0	22
Non-hematological					
Anorexia	17	12	6	0	13
Nausea	5	4	0	0	0
Vomiting	2	1	1	0	2
Diarrhea	3	2	0	0	0
Stomatitis	9	2	0	0	0
Fatigue	15	19	2	0	4
Body weight loss	5	6	0	0	0
Exacerbation of PS	–	21	7	0	16
Neuropathy	14	3	0	0	0
Alopecia	24	4	–	–	–
AST	9	1	1	0	2
ALT	5	1	2	0	4
Creatinine	2	0	0	0	0

CTCAE Common Terminology Criteria for Adverse Events version 3.0, PS performance status, AST aspartate aminotransferase, ALT alanine aminotransferase

Furthermore, S-1 was also shown to be useful in postoperative adjuvant chemotherapy for stage II–III gastric cancer [23]. In the meantime, the superiority of S-1 plus CDDP over S-1 alone was shown in the SPIRITS trial, demonstrating again the effect of adding CDDP to the core treatment [24]. Thus, the S-1/CDDP combination is the current standard in Japan as first-line treatment for AGC. However, whether this combination is valid for a patient who was treated with adjuvant S-1 and was subsequently found to have recurrence remains unclear. According to Shitara et al., the RR of S-1-based secondary treatment in patients with a history of S-1 therapy is 0%; while this is based on a retrospective analysis, opinions regarding the re-introduction of S-1 are generally negative [25]. The establishment of a new regimen that is active against S-1-refractory recurrences and could also be used for AGC patients who are not capable of having oral food intake is warranted.

The addition of another drug, as in the recent trend in Western countries, could be a solution. Indeed, DCF was superior to CF in every endpoint, including PFS (5.6 months), OS (9.2 months), and RR (37%). However, DCF was shown to be problematic because of adverse events, with Grade 3–4 neutropenia observed in 82%,

febrile neutropenia in 29%, Grade 3–4 stomatitis in 21% and diarrhea in 19% [20]. In addition, the effect of docetaxel in pretreated patients had not been documented. We therefore turned to PTX, which had been explored more extensively in the second-line setting. The RR of weekly PTX reached 20% when administered as a single agent, but increased to about 40% when it was combined with either 5-FU or CDDP [8, 9, 13, 15]. Recently, 2 studies reported on the combination of weekly PTX, CDDP, and 5-FU (c.i.v.). The RRs in these studies were 48% and 50% [26, 27], and were close to the RR achieved in the present study. In addition, the incidences of Grade 3–4 neutropenia in these weekly regimens (3 and 21%) were lower than the incidence for the same three-drug combination given every 3 weeks (54%) [28].

In the present trial, we combined a 5-FU bolus with weekly PTX plus CDDP and observed an additional effect, achieving an RR of 56%. Rather surprisingly, the combination was active in patients who had been pretreated with oral 5-FU agents, including S-1. 5-FU is known for having two modes of action; one of them is time-dependent and is exerted mainly by continuous infusion or oral administration, whereas the other is concentration-dependent and is exerted by bolus administration. There is a possibility that cancer that had become refractory to oral 5-FU agents remained sensitive to the concentration-dependent action of 5-FU.

Despite the use of weekly administration in the present study, hematological toxicities were frequent and comparable to those of the V325 study. This was partly because of the way 5-FU was administered and the background of the patients. While the bolus 5-FU inhibited additional gastrointestinal toxicities, it led to enhanced bone-marrow suppression. In addition, the median age of the patients enrolled in the present trial was higher, at 71 years, when compared with the ages of the patients in the other 3-drug trials (median age 51–62 years), and most of our patients who developed febrile neutropenia were over 75 years of age. Nevertheless, these toxicities were managed without difficulties through dose modifications and alterations in the treatment schedule.

On the other hand, our treatment regimen was associated with a low incidence of subjective adverse events despite being a triplet regimen. While median PFS was 160 days, which is no better than that reported for other existing clinical trials, the median OS was extremely good, at 552 days. As well as the fact that our study population had favorable characteristics, with a low rate of peritoneal metastasis and a high rate of recurrent cases with a small tumor volume, the low incidence of subjective adverse events may have contributed to enhance the OS time. Few patients experienced a decline in general condition during the present treatment and, consequently, further lines of

treatment were delivered to several of the patients after termination of the protocol treatment.

In conclusion, the results of the present phase II trial show that the combination of weekly PTX plus CDDP and bolus 5-FU is effective against AGC. While adequate attention to neutropenia and febrile neutropenia is required, especially for elderly patients, we consider that the adverse events observed with this combination therapy are within the permissible range. We believe that this regimen is promising as a first-choice therapy for AGC, especially in patients who have difficulties with oral ingestion or those who have received prior treatment with oral 5-FU. We intend to further investigate the usefulness of this combination in a randomized controlled trial.

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Conflict of interest The authors declare no conflict of interest.

References

- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74–108.
- Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare. Vital statistics of Japan 2006. Tokyo: Health and Welfare Statistics Association; 2008.
- Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer*. 1993;72:37–41.
- Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer*. 1995;71:587–91.
- Glimelius B, Ekström K, Hoffman K, Graf W, Sjöden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol*. 1997;8:163–8.
- Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of taxol in patients with advanced gastric carcinoma. *Cancer J Sci Am*. 1998;4:269–74.
- Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET, et al. Phase II study of paclitaxel in pretreated advanced gastric cancer. *Anticancer Drugs*. 1998;9:307–10.
- Emi Y, Yamamoto M, Takahashi I, Orita H, Kakeji Y, Kohnoe S, et al. Phase II study of weekly paclitaxel by one-hour infusion for advanced gastric cancer. *Surg Today*. 2008;38:1013–20.
- Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, et al. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). *Anticancer Res*. 2007;27:2667–71.
- Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. *Gastric Cancer*. 2006;9:14–8.
- Shimoyama R, Yasui H, Boku N, Onozawa Y, Hironaka S, Fukutomi A, et al. Weekly paclitaxel for heavily treated advanced or recurrent gastric cancer refractory to fluorouracil, irinotecan, and cisplatin. *Gastric Cancer*. 2009;12:206–11.
- Sakamoto J, Matsui T, Kodera Y. Paclitaxel chemotherapy for the treatment of gastric cancer. *Gastric Cancer*. 2009;12:69–78.
- Ninomiya M, Kondo K, Matsuo K, Hirabayashi N, Kojima H, Kobayashi M, et al. Multicenter phase II trial of combination chemotherapy with weekly paclitaxel and 5-fluorouracil for the treatment of advanced or recurrent gastric carcinoma. *J Chemother*. 2007;19:444–50.
- Nagata N, Kobayashi M, Kojima H, Kondo K, Hirabayashi N, Matsui T, et al. Phase I study of paclitaxel and cisplatin for patients with advanced or recurrent gastric cancer. *Hepatogastroenterology*. 2005;52:1905–10.
- Nagata N, Kimura M, Hirabayashi N, Tuburaya A, Murata T, Kondo K, et al. Phase II study of weekly paclitaxel and cisplatin combination therapy for advanced or recurrent gastric cancer. *Hepatogastroenterology*. 2008;55:1846–50.
- Hara T, Omura K, Hirano M, Asada Y, Munemoto Y, Sakamoto J. A phase I study of paclitaxel, cisplatin, and fluorouracil (TCF) for advanced gastric cancer. *Cancer Chemother Pharmacol*. 2007;59:631–6.
- Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol*. 2005;23:5660–7.
- Lacave AJ, Barón FJ, Antón LM, Estrada E, De Sande LM, Palacio I, et al. Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. *Ann Oncol*. 1991;2:751–4.
- Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol*. 1997;15:261–7.
- Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24:4991–7.
- Cunningham D, Starling N, Rao S, Iveson N, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med*. 2008;358:36–46.
- Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol*. 2009;10:1063–9.
- Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357:1810–20.
- Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol*. 2008;9:215–21.
- Shitara K, Muro K, Ura T, Takahashi D, Yokota T, Sawaki A, et al. Chemotherapy for gastric cancer that recurs after adjuvant chemotherapy with S-1. *Jpn J Clin Oncol*. 2008;38:786–9.
- Honecker F, Kollmannsberger C, Quetzs D, Haag C, Schroeder M, Spott C, et al. Phase II study of weekly paclitaxel plus 24-h continuous infusion 5-fluorouracil, folinic acid and 3-weekly

- cisplatin for the treatment of patients with advanced gastric cancer. *Anticancer Drugs*. 2002;13:497–503.
27. Gu Y, Shu Y, Xu Q. A study of weekly paclitaxel plus 5-fluorouracil and cisplatin for patients with advanced or recurrent inoperable gastric cancer. *Biomed Pharmacother*. 2009;63:293–6.
28. Hwang J, Cho SH, Shim HJ, Lee SR, Ahn JS, Yang DH, et al. Phase II study of paclitaxel, cisplatin, and 5-fluorouracil combination chemotherapy in patients with advanced gastric cancer. *J Korean Med Sci*. 2008;23:586–91.