A Phase II Study of Weekly Paclitaxel as Second-line Chemotherapy for Advanced Gastric Cancer (CCOG0302 Study)

YASUHIRO KODERA[1], SEIJI ITO[2], YOSHINARI MOCHIZUKI[2], SHINICHI FUJITAKE[3], KATSUMI KOSHIKAWA[4], YASUAKI KANYAMA[5], TAKANORI MATSUI[6], HIROSHI KOJIMA[6], TSUNENOBU TAKASE[7], NORIFUMI OHASHI[1], MICHITAKA FUJIWARA[1], JUNICHI SAKAMOTO[8] and AKIMASA NAKAO[1] for Chubu Clinical Cancer Group

[1]Department of Surgery II and [8]Young Leaders Program, Nagoya University Graduate School of Medicine, Nagoya, Aichi;
[2]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Aichi;
[3]Department of Surgery, Gamagori Municipal Hospital, Gamagori, Aichi;
[4]Department of Surgery, Komaki Municipal Hospital, Komaki, Aichi;
[5]Department of Surgery, Okazaki Municipal Hospital, Okazaki, Aichi;
[6]Department of Surgery, Aichi Cancer Center Aichi Hospital, Okazaki, Aichi,
[7]Department of Surgery, Aichi Kouseiren Kainan Hospital, Yatomi, Aichi, Japan

Abstract. *Background: Although paclitaxel was given triweekly in phase II trials prior to its approval for gastric cancer in Japan, it is currently more often delivered by a weekly schedule in the second-line setting. Patients and Methods: A phase II trial with response rate as the primary end-point was conducted. Patients with metastatic or unresectable gastric adenocarcinoma who had measurable lesions and had disease progression with the front-line chemotherapy were treated by weekly administration of paclitaxel at a dose of 80 mg/m^2. Results: Forty-five patients were accrued and 44 were assessable for response. Partial responses were observed in 7 patients (16%). Stable disease was documented in further 14 patients (48%). Median progression-free survival of all patients enrolled was 2.6 months and median overall survival was 7.8 months. Toxicity was mild and manageable, the most frequent ≥grade 3 toxicity being neutropenia occurring in 16% of the patients. Conclusion: With modest response rate, favorable toxicity profile, and progression-free or overall survival similar to those of more intense combination regimens, weekly paclitaxel remains a rational therapeutic option for gastric cancer refractory to the first-line chemotherapy.*

Correspondence to: Yasuhiro Kodera, M.D., Department of Surgery II, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. Tel: +81 52 7442250, Fax: +81 52 7442255, e-mail: ykodera@med.nagoya-u.ac.jp

Key Words: Gastric cancer, paclitaxel, phase II study, second-line chemotherapy.

Despite the declining incidence in Western Europe (1) and the United States (2), gastric carcinoma remains the second most common cause of cancer death worldwide with over 600,000 deaths per year (3). For patients with unresectable cancer, chemotherapy has been proven to significantly prolong survival over best supportive care, provided that the patients have a good performance status (4). Gastric cancer causes nutritional deficits that rapidly deprive patients of well-being, and tend to be disseminated *via* several pathways causing various clinical problems. Consequently, it is often difficult to control this disease by chemotherapy and survival of the patients tends to be brief, despite relatively high response rates reported from recent clinical trials (5). Nevertheless, there are numerous cytotoxic agents that are active against gastric cancer, and the experience with other types of cancer suggests benefit of using drugs in several successive lines to prolong overall survival (6).

Although several phase II trials have been conducted for patients with gastric carcinoma in the second-line setting (7-14), there is a shortage in the literature of trials evaluating activity of cytotoxic agents in patients pretreated with 5FU. Recently, weekly paclitaxel administration at a dose of 80 mg/m^2 has become a common practice for gastric cancer patients who failed treatments with the fluoropyrimidines in Japan (15), since this regimen was shown to be well-tolerated and active in various types of cancer (16-20). Weekly paclitaxel for gastric cancer has not

been formally evaluated in a clinical trial, however, and the authors conducted a multi-institutional phase II trial in the second-line setting to address this issue.

Patients and Methods

Patient eligibility. Patients meeting the following criteria were considered as candidates for second-line chemotherapy: (i) patients with unresectable or metastatic gastric cancer who failed the first-line therapy (progressive disease confirmed by imaging studies), (ii) patients who had recurrence during or within 24 weeks from the termination of postoperative adjuvant chemotherapy, (iii) patients who had recurrence later than 25 weeks after the termination of adjuvant chemotherapy and failed one regimen, (iv) patients who responded to the neoadjuvant chemotherapy, recurred after surgery and failed one regimen, and (v) patients who did not respond to the neoadjuvant chemotherapy and had recurrent disease after the resection were considered eligible for this study. Prior treatments should not have included taxanes. An interval of at least 4 weeks from the previous treatment was required before administration of paclitaxel. Other eligibility criteria included: pathologically confirmed gastric adenocarcinoma, measurable disease, age <75 years, Cooperative Oncology Group performance status 0-2, and adequate organ functions defined as: total neutrophil count ≥2000/mm^3, platelet count ≥100000/mm^3, hemoglobin ≥8.0 g/dL, serum creatinine <1.5 mg/dL, total serum bilirubin <1.5 mg/dL, creatinine clearance >50 mL/min, serum AST, ALP twice the upper limit of normal or three times the upper limit of normal in the case of known liver metastases. Patients with another active neoplastic malignancy, a history of or active brain metastases, or uncontrolled intercurrent illness were excluded. Written informed consent was obtained from all participants after the nature of the study had been fully explained. The study had been approved by the institutional review board of Nagoya University Hospital and all other hospitals belonging to the Chubu Clinical Oncology Group that participated in this multi-institutional trial.

Pretreatment evaluation and treatment plan. At baseline, patients underwent a full medical history and physical examination. Laboratory assessment at baseline included CBC, serum biochemistry, serum tumor markers (CEA, CA19-9), and urinalysis. Patients underwent a baseline ECG and computed tomography (CT) scan of chest, abdomen and pelvis.

Patients received paclitaxel 80 mg/m^2 infused over 90 mins on days 1, 8, and 15 of every 28-day cycle. Premedication consisting of dexamethasone 20 mg *i.v.*, diphenydramine 25 mg *p.o.* and ranitidine 50 mg *i.v.* were given 30 mins before paclitaxel. Therapy was administered in an outpatient setting under medical supervision.

Evaluation on study and dose attenuation. All toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2.0). Patients were seen before treatment on days 1, 8, and 15 of each cycle. Paclitaxel was skipped if neutrophil count was <1000/mm^3 or platelet count <75000/ mm^3. No dose attenuation was allowed within a given cycle. Treatment was discontinued if the treatment had to be postponed for two successive weeks. Dose was reduced by 10 mg/m^2 when Grade 4 hematological toxicity or ≥Grade 3 non-hematological toxicity was observed. The treatment was discontinued when the dose had to be reduced to >60 mg/m^2 along these criteria. Patients were treated at the discretion of physicians when the treatment was discontinued or clinical response was not obtained.

Tumor assessments were performed after each cycle by CT scan according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (21) for the first 6 cycles and every 8 weeks thereafter. RECIST response definitions included complete response (CR: resolution of assessable lesions), partial response (PR: at least a 30% decrease in the sum of the longest diameter of target lesions), stable disease (SD: changes in the size of target lesions that do not fall into either PR or PD), and disease progression (PD: at least 20% increase in the sum of the longest diameter of target lesions). Progression of existing non-target lesions or finding of new lesions qualified as a definition of PD.

Biostatistics. The study was conducted according to Simon's two-stage optimal design, aiming to reject the hypothesis that the response rate (RR) is less than 10% with 5% significance. This study required 40 patients and accrual of 45 patients was planned considering dropouts. At the first stage, more than two responses out of the initial 22 patients were required to continue further patient accrual. The primary endpoint was RR. Secondary endpoints were overall survival (OS), progression-free survival (PFS), and toxicity. Survival analysis from the date of starting chemotherapy to death from any cause and PFS were carried out using the Kaplan-Meier method.

Results

Patient population. Forty-five patients were enrolled between October 2003 and July 2006. Patient demographics are shown in Table I. Eight patients had unresectable cancer, whereas 35 patients had either undergone non-curative resection or suffered from relapse following a gastrectomy and were pretreated with cytotoxic agents. Two other patients were pretreated with neoadjuvant chemotherapy which turned out to be ineffective, and had recurrent disease after surgery. First-line chemotherapy given was oral S-1 (22) in 34 patients, S-1 and cisplatin (23) in 7 patients, S-1 and irinotecan (24) in 2 patients, oral tegafur-uracil in one patient, and intravenous 5FU in one patient, which means that all patients enrolled could be considered as 5FU-refractory.

Responses and survival. One patient refused further therapy because of experiencing Grade 2 sensory disturbance after the first administration; the remaining 44 patients were evaluable for response. Partial responses were observed in 7 patients for a RR of 16%. Six out of 7 patients who responded had metastasis in the lymph nodes and the remaining patient had liver metastasis. Stable disease was documented in further 14 patients for a disease control rate of 48%. All 45 patients were included in the survival data, which were analyzed on an intent-to-treat basis. Median PFS of all patients enrolled was 2.6 months and median OS was 7.8 months (Figure 1).

Table I. *Patient demographics (n=45).*

	No.	%
Age, years	62 (45～75)	
Median (range)		
Gender		
Female	8	18
Male	37	82
ECOG performance status		
0	26	58
1	13	29
2	6	13
Organ involved		
Primary lesion	8	
Lymph nodes	32	
Liver	19	
Peritoneum	9	
Ovary	3	
Others	3	
Number of metastatic organs involved		
1	25	56
2	16	36
≥3	4	8
First-line regimen		
S-1	34	
S-1/cisplatin	7	
S-1/irinotecan	2	
UFT	1	
5FU	1	
Histological type		
Undifferentiated	20	44
Differentiated	23	53
Unrecorded	2	

Table II. *Grade 2 to 4 toxicity of the weekly paclitaxel treatment program (n=45).*

	No. of patients			%
	Grade 2	Grade 3	Grade 4	≥Grade 3
Leukocytopenia	5	5	3	18
Neutropenia (febrile)	11	5 (1)	2	16
Anemia	19	5	0	11
Thrombocytopenia	0	0	0	0
Asthenia/anorexia	3	4	1	11
Nausea/vomiting	2	2	0	4
Stomatitis	1	0	0	0
Diarrhea	0	1	0	2
AST/APT	1	1	0	2
Peripheral neuropathy	3	1	0	2
Arthralgia	1	0	1	2
Allergy	1	0	0	0
Dyspnea	0	1	0	2

Dose intensity and toxicity. The patients received a median of three (range 0～12) cycles. Dose reduction was required in 5 patients (11%) and administration was skipped during a cycle in 14 patients (40%). The most common cause of dose reduction was neutropenia which occurred in 4 of 5 patients. Treatment was relatively well-tolerated with a toxicity profile as shown in Table II.

Discussion

Paclitaxel as a single agent was administered tri-weekly at a dose of 210 mg/m^2 in two independent phase II trials performed in Japan prior to its approval by the Ministry of Health and Welfare (25, 26). In these trials, the objective responses were observed in 23～28% and the median duration of response ranged from 87～152 days for a population in which 30～50% of the patients were chemo-naïve. This agent given exclusively as second-line therapy in tri-weekly schedule at the dose of 225 mg/m^2 was also found to be active (13). More recently, however, this drug came to be widely used in a fractionated weekly schedule at 80 mg/m^2 in Japan, referring to the activity reported for other types of cancer (16-20). In ovarian cancer, weekly paclitaxel was active even for patients who had progressed on a less frequent paclitaxel dosing schedule (16), and there is a hypothesis that the benefit may derive from the increased exposure of cycling cancer cells to the agent when it is delivered on a weekly program. On the other hand, weekly administration of docetaxel, active as a single agent in a triweekly regimen for gastric cancer, turned out not to be as effective (10), and it was not reasonable to accept the dose-fractionated regimen unconditionally. The current phase II study reveals the first and long-awaited data testing the weekly regimen for advanced/metastatic gastric carcinoma as second-line therapy. Most patients who were entered this trial had been pretreated with S-1, a drug predominantly used in Japan in the first-line treatment for gastric carcinoma, and all patients can be considered as 5FU-refractory.

The current study aimed to reject the hypothesis that the RR is less than 10%, and fulfilled this expectation. The RR reported for the same agent in the tri-weekly schedule after failing PELF (5-FU, leucovorin, cisplatin, and epidoxorubicin) was higher at 22.2% (13), but the response in that and most other trials with high RR was evaluated using the previous WHO criteria and a direct comparison with the current study is inadequate. Although weekly administration could be considered dose-dense, a total dose of 240 mg per 4 weeks is not superior to the tri-weekly regimen in terms of dose intensity after all. Since PD by the RECIST criteria was a prerequisite for being enrolled into the study, some participants had to wait for their target lesions to grow sufficiently or to have a new lesion before

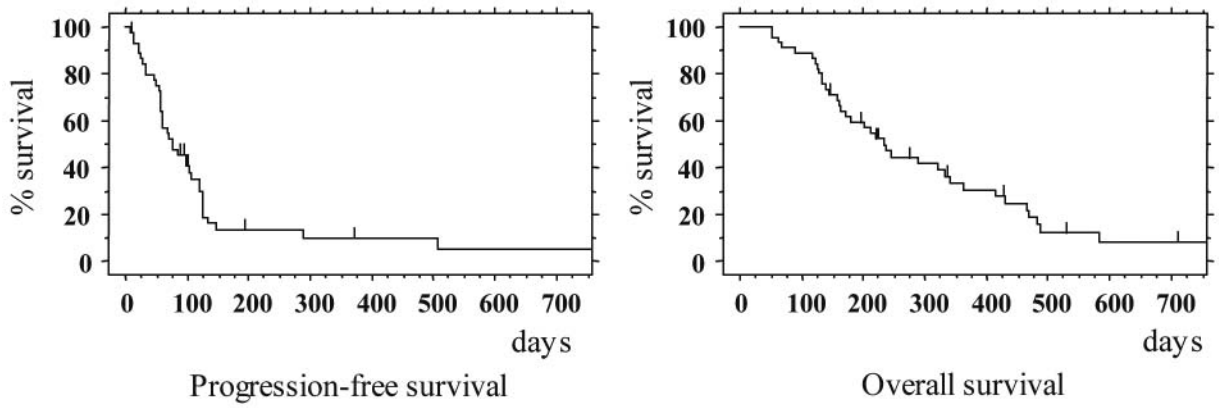

Figure 1. *Progression-free survival and overall survival of patients with pretreated advanced/metastatic gastric cancer, treated with weekly administration of paclitaxel.*

becoming eligible. Given the rapid tumor growth clinically observed in advanced gastric cancers, current practice in Japan is focused on a prompt shift to other available drugs when a treatment failure in a particular therapy is suggested. The stringent eligibility criteria employed in the current study protocol now seems rather outdated, and may have influenced the results.

The results in terms of survival time were considered reasonable, given the results of other phase II trials. Kim *et al.* (7) reported on modified FOLFIRI regimen (5FU, leucovorin, and irinotecan) administered in patients pretreated with taxane and cisplatin, achieved time to progression of 2.5 months and OS of 7.6 months, and considered this regimen as moderately active. Conversely, the current study evaluated activity of a taxane for patients pretreated with 5FU-containing regimens, but PSF and OS observed were identical at 2.6 months and 7.8 months. OS evaluated in other phase II studies for the second-line treatment of gastric cancer ranged from 3.5 to 8 months (10-13), and from 5.8 to 7.8 months in trials testing a combination of docetaxel and cisplatin for patients pretreated with a 5FU-based regimen (8, 9). Thus, use of combination therapies that generated higher RR did not translate into a marked difference in survival. This finding has much in common with those of several trials testing first-line treatments in gastric cancer and may denote limits of treatments with cytotoxic agents alone.

Weekly administration was moderate in terms of bone marrow suppression, with ≥grade 3 neutropenia occurring in 16% of the patients as opposed to 37% and 88% reported in the tri-weekly schedule, while thrombocytopenia was minimal and rare. Grade 3 anemia was seen in 5 patients, but this can be attributed to the waning nutritional status of pretreated and mostly gastrectomized patients. Non-hematological ≥grade 3 toxicity was rarely observed.

Conclusion

Weekly paclitaxel in the second-line setting was not superior to a tri-weekly schedule and other regimens in terms of RR. Toxicity was mild and manageable, however, with decreased incidence of ≥grade 3 bone marrow toxicity when compared to the tri-weekly paclitaxel, while OS and PFS seems to be similar to more intense combination regimens. These findings suggest that weekly paclitaxel remains a rational therapeutic option for gastric cancer refractory to 5FU or S-1. While a small number of responders do benefit considerably from this treatment, investigators may in future opt for improving survival data by exploring combinations with molecular targeting agents (27).

References

1 Ekstrom AM, Hansson LE, Signorello LB and Lindgren A: Decreasing incidence of both major histologic subtypes of gastric carcinoma-a population-based study in Sweden. Br J Cancer *83*: 391-396, 2000.

2 Hundahl SA, Menck HR, Mansour EG and Winchester DP: The National Cancer Data Base report on gastric carcinoma. Cancer *80*: 2333-2341, 1997.

3 Pisani P, Parkin DM, Bray F and Ferlay J: Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer *83*: 18-29, 1999.

4 Murad AM, Santiago FF, Petroianu, Rocha PR, Rodrigues MA and Rausch M: Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer *72*: 37-41, 1993.

5 Ichikawa W and Sasaki Y: Correlation between tumor response to first-line chemotherapy and prognosis in advanced gastric cancer patients. Ann Oncol *17*: 1665-1672, 2006.

6 Grothey A and Sargent D: Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardlesss of whether doublet or single-agent therapy is used first line. J Clin Oncol *23*: 9441-9442, 2005.

7 Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, Park JO, Kim K, Kim WS, Jung CW, Park YS, Im YH and Park K: Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. Br J Cancer *92*: 1850-1854, 2005.
8 Park SH, Kang WK, Lee HR, Park J, Lee KE, Lee SH, Park JO, Kim K, Kim WS, Chung CW, Im YH, Lee MH, Park CH and Park K: Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen. Am J Clin Oncol *27*: 477-480, 2004.
9 Kim H, Park J-H, Bang S-J, Kim DH, Cho HR, Kim GY and Min YJ: A phase II study of docetaxel and cisplatin in patients with gastric cancer recurring after or progressing during 5FU/platinum treatment. Jpn J Clin Oncol *35*: 727-732, 2005.
10 Graziano F, Catalano V, Baldelli AM, Giordani P, Testa E, Lai V, Catalano G, Battelli N and Cascinu S: A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. Ann Oncol *11*: 1263-1266, 2000.
11 Assersohn I, Brown G, Cunningham D, Ward C, Oates J, Waters JS, Hill ME, and Norman AR: Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol *15*: 64-69, 2004.
12 Kim DY, Kim JH, Lee, S-H, Kim TY, Heo DS, Bang YJ and Kim NK: Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol *14*: 383-387, 2003.
13 Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET and Catalano G: Phase II study of paclitaxel in pretreated advanced gastric cancer. Anti-Cancer Drugs *9*: 307-310, 1998.
14 Polyzos A, Tsavaris N, Kosmas C, Polyzos K, Giannopoulos A, Felekouras E, Nikiteas N, Kouraklis G, Griniatsos J, Safioleas M, Stamatakos M, Pikoulis G, Papachristodoulou A and Gogas H: Subsets of patients with advanced gastric cancer responding to second-line chemotherapy with docetaxel-cisplatin. Anticancer Res *26*: 3749-3754, 2006.
15 Hironaka Y, Zenda S, Boku N, Fukutomi A, Yoshino T and Onozawa Y: Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer *9*: 14-18, 2006.
16 Markman M, Hall J, Spitz D, Weiner S, Carson L, Van Le L and Baker M: Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. J Clin Oncol *20*: 2365-2369, 2002.
17 Perez EA, Vogel CL, Irwin DH, Kirshner JJ and Patel R: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol *19*: 4216-4223, 2001.
18 ten Tije AJ, Smorenburg CH, Seynaeve C, Sparreboom A, Schothorst KL, Kerkhofs LG, van Reisen LG, Stoter G, Bontenbal M and Verweij J: Weekly paclitaxel as first-line chemotherapy for elderly patients with metastatic breast cancer. A multicentre phase II trial. Eur J Cancer *40*: 352-357, 2004.
19 Yasuda K, Igishi T, Kawasaki Y, Kato K, Matsumoto S, Katayama S, Sako T, Shigeoka Y, Suyama H, Sugitani A, Yamamoto M, Hitsuda Y and Shimizu E: Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. Oncology *66*: 347-352, 2004.
20 Yamamoto N, Tsurutani J, Yoshimura N, Asai G, Moriyama A, Nakagawa K, Kudoh S, Takada M, Minato Y and Fukuoka M: Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res *26*: 777-782, 2006.
21 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Glabbeke MV, van Oosterom AT, Christian MC and Gwyther SG: New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst *92*: 205-216, 2000.
22 Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y and Taguchi T: Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1M tegafur-0.4M gimestat-1M otastat potassium) in advanced gastric cancer patients. Eur J Cancer *34*: 1715-1720, 1998.
23 Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsuyama Y and Gotoh M: Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer *89*: 2207-2212, 2003.
24 Takiuchi H, Narahara H, Tsujinaka T, Gotoh M, Kawabe S, Katsu K, Iishi H, Tatsuta M, Fujitani K, Furukawa H, Taguchi T and Osaka Gastrointestinal Cancer Chemotherapy Study Group: Phase I study of S-1 combined with irinotecan (CPT-11) in patients with advanced gastric cancer (OGSG0002). Jpn J Clin Oncol *35*: 520-525, 2005.
25 Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, Miyata Y and Taguchi T: Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol *12*: 1133-1137, 2001.
26 Yamaguchi K, Tada M, Horikoshi N, Otani T, Takiuchi H, Saitoh S, Kanamaru R, Kasai Y, Koizumi W, Sakata Y, Taguchi T and Paclitaxel Gastric Cancer Study Group in Japan: Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. Gastric Cancer *5*: 90-95, 2002.
27 Shah MA, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, Tse A, Trocola R, Schwartz L, Capanu M, Schwartz GK and Kelsen DP: Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol *24*: 5201-5206, 2006.

Received February 2, 2007
Revised April 3, 2007
Accepted April 23, 2007