Jpn J Clin Oncol 2008;38(3)176–181
doi:10.1093/jjco/hyn003

Multi-Center Phase II Study for Combination Therapy with Paclitaxel/Doxifluridine to Treat Advanced/Recurrent Gastric Cancer Showing Resistance to S-1 (OGSG 0302)

Hiroya Takiuchi[1], Masahiro Goto[1], Hiroshi Imamura[2], Hiroshi Furukawa[2], Motohiro Imano[3], Haruhiko Imamoto[3], Yutaka Kimura[4], Hideyuki Ishida[5], Kazumasa Fujitani[6], Hiroyuki Narahara[7] and Toshio Shimokawa[8]

[1]Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Osaka, [2]Department of Surgery, Sakai City Hospital, Sakai, Osaka, [3]Department of Surgery, Kinki University School of Medicine, Osakasayama, Osaka, [4]Department of Surgery, NTT West Osaka Hospital, Osaka, [5]Department of Surgery, Osaka Seamen's Insurance Hospital, Osaka, [6]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, [7]Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka and [8]Data Center of Osaka Gastrointestinal Cancer Chemotherapy Study Group, Osaka, Japan

Received September 7, 2007; accepted January 2, 2008; published online February 16, 2008

Background: A pre-clinical study demonstrated that paclitaxel induced thymidine phosphorylase in the tumor tissues. The combination of paclitaxel and doxifluridine is expected to exert extra anti-tumor effects. We evaluated the efficacy of this combination in patients with unresectable or recurrent gastric cancer who had been previously treated with S-1.
Methods: Registration was started to enroll 35 patients with advanced/recurrent gastric cancer, who were selected among those with measurable lesions fitting to response evaluation criteria in solid tumors, and with resistant to S-1 treatment. This regimen is consisted of paclitaxel, 80 mg/m^2, iv on days 1 and 8; and doxifluridine, 600 mg/m^2, po on days 1–14. The treatment was repeated every three weeks. Primary endpoint was response rate (RR); and secondary endpoints were overall survival (OS), progression free survival (PFS) and onset rate of adverse events.
Results: From September 2003 to March 2005, 35 patients were registered: including 28 men; 7 women; median age of 66 years (range, 49–75 years); and performance status (PS) levels were, zero with 21 and one with 14 patients. In 33 eligible patients, except two, clinical usefulness was evaluated resulting in RR of 18.2% (partial response, 6; stable disease, 15; progressive disease, 10; and not evaluable, 2 patients). Median survival time was 321 days and median PFS was 119 days. Severe adverse events were found in three patients to discontinue the present treatment.
Conclusions: The combination of paclitaxel and doxifluridine might be a treatment of choice as a second line chemotherapy for patient undergone S-1 treatment.

Key words: gastric cancer – paclitaxel – doxifluridine – second line chemotherapy – S-1

INTRODUCTION

The incidence of gastric cancer is still high, and it remains one of the leading causes of death in the world. Gastric cancer is moderately sensitive to systemic chemotherapy, and it has been used in an attempt to control cancer-related symptoms and prolong survival. Previous randomized studies have shown that systemic chemotherapy can prolong survival and improve the quality of life (1–3). However, we cannot recommend any specific regimens, although standard chemotherapy with cisplatin (CDDP) or 5-FU for unresectable or recurrent gastric cancer is performed throughout the world. In addition, practice standards differ among countries; in Asia, especially in Japan, continuous infusion of 5-FU, single therapy with a new oral fluoropyrimidine, S-1, or combination chemotherapy involving either of the two procedures is frequently employed as a first-line treatment. Two-phase III studies regarding single and combination therapies with S-1 are being conducted in Japan. Second-line chemotherapy for patients who are resistant to S-1 alone or combination therapy with S-1 should also be established.

For reprints and all correspondence: Hiroya Takiuchi, Cancer Chemotherapy Center, Osaka Medical College Hospital, 2-7 Daigakucho, Takatsuki, Osaka, 569-8686 Japan. E-mail: in2028@poh.osaka-med.ac.jp

However, at this stage, no standard chemotherapy can be offered. No randomized controlled trial has suggested the benefit of second-line chemotherapy in comparison with supportive care alone. Previously, some phase II studies regarding second-line chemotherapy for gastric cancer have been performed (4–6). However, no study has published any pretreatment-matched data on second-line chemotherapy. In a recent phase III study of postoperative adjuvant chemotherapy involving stage II/III gastric cancer patients who underwent D2 dissection, the efficacy of S-1 was demonstrated in comparison with surgery alone (7). In the future, S-1 will comprise a standard regimen of postoperative adjuvant chemotherapy in Japan, and a regimen for relapse in patients treated with S-1 should also be developed.

Paclitaxel, a taxane anti-cancer drug, promotes microtubule assembly and then exhibits its anti-tumor effect by arresting the cell cycle in G2/M phase. This mechanism of action is different from other anti-cancer drugs, and non-cross resistance with them was suggested. Therefore, paclitaxel has been expected to provide a second-line therapy for gastric cancer. Doxifluridine (5'-DFUR; intermediate metabolite of capecitabine) and capecitabine are pro-drugs that are achieved and converted into 5-FU by thymidine phosphorylase (TP). A synergistic effect on inhibition of tumor growth has been reported when these agents are combined with paclitaxel (8,9). The results of a basic study demonstrated that administration of paclitaxel selectively induced TP in the tumor tissues and that the combination of paclitaxel and 5'-DFUR exerted more than additive effects. Consequently, concomitant use of these two drugs is expected to exert extra anti-tumor effects and to enhance the survival advantage, and can be regarded as a promising regimen as a second-line therapy for gastric cancer. In view of these beneficial effects, we conduct a phase II study in patients with unresectable or recurrent gastric cancer who failed S-1 treatment.

PATIENTS AND METHODS

Eligibility

All eligible patients had to fulfill the following eligibility criteria: (1) histologically confirmed unresectable or recurrent gastric cancer; (2) at least one measurable lesion according to the response evaluation criteria in solid tumors (RECIST); (3) patients who failed previous S-1 monotherapy; (4) age between 20 and 75 years old; (5) Eastern Cooperative Oncology Group performance status (PS) ≤ 2; (6) a life expectancy > 3 months; (7) adequate bone marrow function (absolute neutrophil count $\geq 2000/mm^3$ and platelet count $\geq 1\ 00\ 000/mm^3$); (8) adequate liver function (serum bilirubin $\leq 1.25 \times$ upper normal limit (UNL) of range set by the institution and serum transaminase $\leq 2.5 \times$ UNL (in cases of hepatic metastasis, $\leq 5 \times$ UNL)); (9) adequate renal function (serum creatinine $\leq 1.5 \times$ UNL); (10) no other severe medical conditions; (11) no other active malignancies; (12) no peripheral neuropathy; (13) no history using doxifluridine in adjuvant setting; and (14) provision of written informed consent.

Definition of S-1 Treatment Failure

Patients had to fulfill either of the following two conditions: (1) patients with unresectable or recurrent gastric cancer who received S-1 monotherapy in more than 4 weeks and confirmed tumor progression during the treatment period or after the treatment withdrawal; or (2) patients who have relapsed within 26 weeks after the completion of S-1 monotherapy in the adjuvant setting.

Treatment Schedule and Evaluation of Toxicity

Moriwaki et al. conducted a phase I clinical trial in order to study the feasibility of paclitaxel/doxifluridine combined therapy. Based on the results, we determined the dose and schedule of this study (10). The two drugs were administered as follows: paclitaxel (Taxol; Bristol-Myers Squibb Company, Tokyo, Japan) 80 mg/m^2 over 60 min iv infusion on day 1 and 8; doxifluridine (Fulturon; Chugai Pharmaceutical Company, Tokyo, Japan) 600 mg/m^2/day po on days 1–14. This treatment was repeated every three weeks (one cycle each) until disease progression or unacceptable toxicity was seen. The evaluation of disease status was planned every two cycles. Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC version 2.0). A new cycle of treatment could begin if the total leukocyte count was $\geq 2000/mm^3$, the neutrophil count was $1000/mm^3$, the platelet count was $\geq 75\ 000/mm^3$ and all relevant non-hematological toxicities were grade 1 or lower. Dose reductions were planned for diarrhea as follows: at grade 2 to keep the same dose level and to delay the treatment of one week, at grade 3 to delay the treatment of one week and to reintroduce paclitaxel at 70 mg/m^2 and doxifluridine 400 mg/m^2 /day, and for neutropenia as follows: at grade 3 to delay the treatment of one week, at grade 4 to delay the treatment of one week and to reintroduce paclitaxel at 70 mg/m^2 and doxifluridine 400 mg/m^2/day.

Endpoints and Evaluation of Treatment

Primary endpoint was response rate (RR). Tumor response was evaluated every two cycles by means of CT scan or MRI. Measurable lesions were assessed according to the RECIST. Secondary endpoints were overall survival (OS), progression free survival (PFS), time to treatment failure (TTF) and incidence of adverse events. Intention-to-treatment (ITT) analysis was used to evaluate patients for response, survival and toxicity.

Table 1. Patient characteristics

Patien characteristics ($n = 35$)	
Gender: males/females	28/7
Age: median (range), years	66 (49–75)
ECOG Performance status (PS): 0/1/2	21/14/0
Histology: differentiated/undifferentiated/ohter	22/12/1
Primary lesions: present/absent	10/25
Metastatic leasions: liver/lymph node/peritoneum/lung/ others	16/24/8/3/6
Prior S-1 treatment: adjuvant/advance	6/29
Median duration of S-1 administration for advanced/ recurrent disease, days	118
Efficacy of S-1monotherapy: effective/ineffective/ unknow	2/24/3

n, number of patients; ECOG, Eastern Cooperative Oncology Group.

Statistical Analysis

If over three patients among 18 patients have objective response, this study is regarded to be adequate to proceed further and to enroll more 18 patients assuming *P*0 of 15%, *P*1 of 35%, alpha error of 0.05 and beta error of 0.20 based on Simon two-stage phase II design. Thirty-five eligible patients were required to evaluate the activity of this combination. The planned duration of accrual was 2 years, and planned follow-up time was 6 months after the last patient registration. The duration of objective responses, TTP and OS were calculated from the date of starting chemotherapy until last follow-up or death. Survival was calculated employing the Kaplan–Meier product-limit analysis for the estimation of incomplete data.

RESULTS

Patients Characteristics

Thirty-five patients were enrolled into the trial from September 2003 to March 2005. All patients had developed progressive disease while receiving S-1 monotherapy in the first-line treatment or within 26 weeks after the completion of S-1 monotherapy in the adjuvant setting. Thirty-three patients were eligible for efficacy. Two patients were ineligible in terms of insufficient duration of S-1 treatment (< 4 weeks) and history of doxifluridine administration in adjuvant setting. Patients main clinical characteristics are listed Table 1. There were 28 males and 7 females with a median age of 66 years, with many patients being with in good general condition. All patients had an adenocarcinoma with a predominance of differentiated forms (62.9%). The metastatic sites of disease were: liver (45.7%), lymph-nodes (68.6%), peritoneum (22.9%), lung (8.6%) and other sites (17.1%). Six patients had relapsed early after adjuvant treatment with S-1. The doses of paclitaxel and doxifluridine were reduced in eight patients (22.8%), in line with the dose reduction criteria. Treatment administration was also delayed for a median of seven days (range 1–14 days) in 20 of 166 cycles.

Table 2. Overall response rate

Eligible patients ($n = 33$)	n	%	95%Cl
Overall response	6	18.2	7.0 to 35.5
Complete response (CR)	0		
Partial response (PR)	6		
Stable disease (SD)	15	45.5	28.1 to 63.7
Progressive disease (PD)	10	30.3	15.6 to 48.7
Not evaluable (NE)	2		
Disease control*	21	63.6	45.1 to 79.6

*Overall response and stable disease.
CI, confidence interval

Efficacy

According to an ITT analysis, the objective response rate (ORR) was 18.2% (6/33). Fifteen patients showed stable disease (SD), 10 patients progressed and disease control rate (PR + SD) was 63.6% (21/33) (Table 2). Median PFS was 119 days [95% confidence interval (CI), 89.7–148.3]

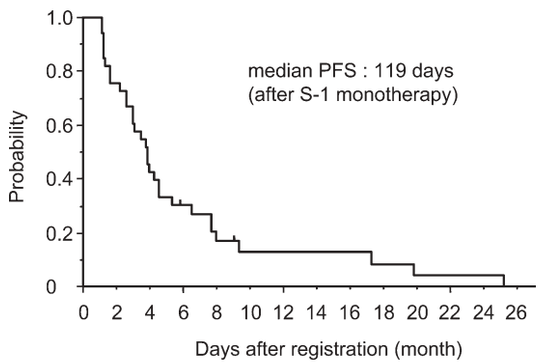

Figure 1. Progression-free survival (PFS).

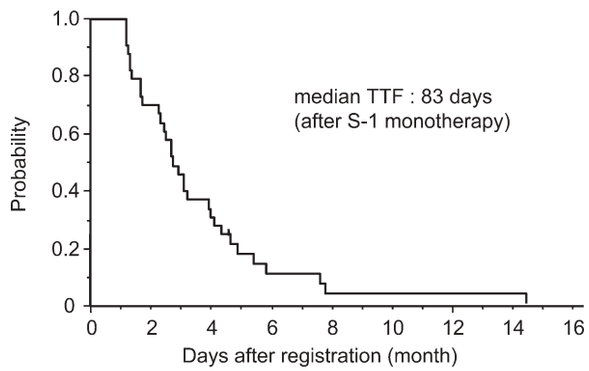

Figure 2. Time to treatment failure (TTF).

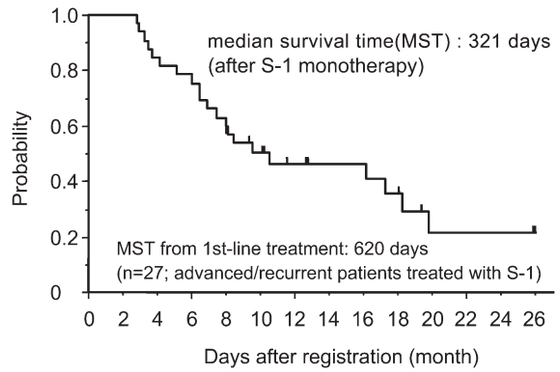

Figure 3. Overall survival.

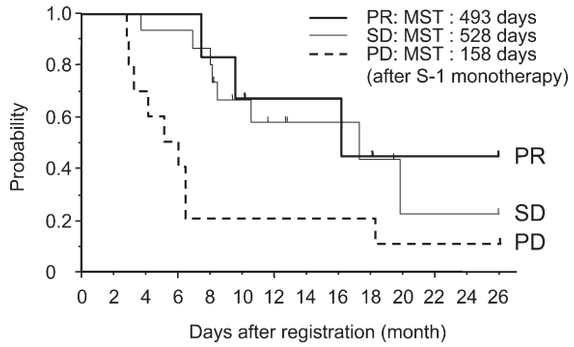

Figure 4. OS of the patients according to response. PR, partial response; SD, stable disease; PD, progressive disease.

(Fig. 1), and median TTF was 83 days (95% CI, 65.2–100.8) (Fig. 2). Median survival time (MST) was 321 days (95% CI, 49.2–592.8) (Fig. 3). The MST was 493, 528 and 158 days in PR, SD and PD patients, respectively (Fig. 4). The median follow-up period was 290 days (range: 182–792 days). According to information from the off-treatment forms at the failure of this regimen, at least 24 patients (72.7%) received third-line chemotherapy regimens: 17 patients in irinotecan-containing regimens.

Toxicity

The median number of treatment cycles was four (range 1–20). All patients were evaluable for toxicity (Table 3). No toxic deaths were observed. Hematological toxicity was mainly presented by neutropenia that was recorded in 21 patients (60%) but it was severe (grade 3) only in eight cases (22.9%). Only one patients (2.9%) experienced febrile neutropenia. Anemia was observed in 33 patients (94.3%) whereas grade 3–4 was only 17.1%; thrombocytopenia was of grade 1 in two patients (5.7%) whereas no major grade was observed. The most frequent non-hematological toxicity was anorexia (40%). Peripheral neuropathy was grade 3 in only one patient (2.9%).

DISCUSSION

In several phase III studies of gastric cancer conducted in the twentieth century, the MST was approximately 7 months (11,12). However, it was slightly prolonged to nine to ten months in phase III studies reported in the twenty first century (13,14). As a background factor, the appearance of some new anticancer agents (oral fluoropyrimidines, irinotecan and taxanes) has increased choices of first- and second-line therapies. The TTP or PFS of a conventional first-line therapeutic regimen with 5-FU and CDDP was approximately 4 months. In a recent phase III study, the TTP of 5-FU + CDDP was also approximately 4 months, with no marked difference. However, the MST in the 5-FU + CDDP group in a recent phase III study was prolonged by about 2 months in comparison with previous phase III studies, which was possibly associated with the effects of second-line or later therapy. Based on the background, the results of some phase II studies regarding second-line regimens have been published (4–6). Most of these phase II studies outside of Japan included 5-FU- or CDDP-based regimen-resistant patients. In Japan, S-1 monotherapy or S-1 + CDDP is frequently employed as a first-line treatment in clinical practice. It is important to establish second-line treatment for patients who are resistant to these therapies. In this study, we investigated patients who were resistant to S-1 monotherapy to unify the first-line treatment.

In pre-clinical studies, paclitaxel in combination with doxifluridine showed a synergistic activity (9). Based on the results of these experiments, Moriwaki et al. reported the results of a phase I study regarding combination therapy with paclitaxel and doxifluridine for gastric cancer (10). In their study, 22 of 28 patients were pretreated with 5-FU or S-1. The RR was 42%; the rates were 40 and 43% in the patients without and with pretreatment, respectively, suggesting the usefulness of this therapy as a second-line treatment for 5-FU-resistant patients. Based on the study results, we examined the efficacy and safety of combination therapy with paclitaxel and doxifluridine in S-1 monotherapy-resistant patients. In this study, the RR was 18.2–95% CI, 7.0–35.5, below the threshold of the expected RR. However, disease control rate (CR+PR+SD) was achieved in 63.6%. PFS was approximately 4 months, and the MST was 321 days. In several previous phase II studies, the RR ranged from 20 to 32% and the disease control rate ranged from 42.6 to 63%. The PFS ranged from 2.5 to 3.7 months, and the MST ranged from 5.2 to 7.8 months. Our results in this study were comparable to those for some second-line regimens previously reported. The main grade 3 or higher adverse events included neutropenia in 22.9% of our patients, leukopenia in 11.7% and anorexia in 8.6%. This second-line regimen may be safe under poor treatment conditions.

Concerning paclitaxel, two phase II studies were conducted in Japan, and 15 (22.7%) of 66 patients who had undergone chemotherapy responded to this agent (15,16). Based on the results of these phase II studies, we expected

Table 3. Adverse events.

Adverse events (n =35)	Grade				All grade	≥Grade 3
	1	2	3	4		
Hematological events						
Anemia	14	13	5	1	94.3%	17.1%
Leukopenia	5	10	4		54.3%	11.4%
Neutropenia	7	6	8		60.0%	22.9%
Lymphopenia		2			5.7%	–
Thrombocytopenia	2				5.7%	–
Non-hematological events						
Alkaline phosphatase	1		3		11.4%	8.6%
Alopecia	9	12			60.0%	–
Nail chages	1				2.9%	–
Dermatosis	1				2.9%	–
Nausea	7	2			25.7%	–
Anorexia	8	3	3		40.0%	8.6%
Stomach heaviness	1				2.9%	–
Diarrhea	9	1			28.6%	–
Constipation	2				5.7%	–
Taste disturbance	3				8.6%	–
Stomatitis	3				8.6%	–
Glossitis	1				2.9%	–
Peripheral neuropathy	7	2	1		28.6%	2.9%
Arthralgia	2				5.7%	–
Muscle pain	2				5.7%	–
Back pain	1				2.9%	–
Lumbago	1				2.9%	–
Bile reflux	1				2.9%	–
Fatigue	11	2	1		40.0%	2.9%
Lightheadedness		1			2.9%	–
Lightheadedness upon standing	1				2.9%	–
Common cold symptom	1				2.9%	–
Shortness of breath	1				2.9%	–
Fever	2	1			8.6%	–
Febrile neutropenia			1		2.9%	2.9%
Infection with grade 3 or 4 neutropenia			1		2.9%	2.9%
Epistaxis	1				2.9%	–
Edema	2				5.7%	–
Tearing	1				2.9%	–

that the combination of paclitaxel and doxifluridine would be administered as an optional extra. Unfortunately, our results could not positively suggest the usefulness of additional treatment with another fluoropyrimidine agent, doxifluridine, in patients pretreated with S-1. However, in Japan, postoperative adjuvant chemotherapy with S-1 may be performed in stage II/III gastric cancer patients after D2 dissection based on the results of the ACTS-GC trial (7). No prospective study of S-1 involving recurrent cancer patients has been conducted, and currently, combination therapy with paclitaxel and doxifluridine may be a treatment choice in clinical practice with respect to the disease control rate and mild toxicity. In the future, a clinical study of S-1 involving recurrent cancer patients will be performed with reference to the results of this study.

Acknowledgement

Investigators who participated in this study were Yasushi Nakane, Kansai Medical College, Osaka, Japan; Suguru Morimoto, Yao Municipal Hospital, Osaka, Japan; Takao Tamura, Kobe University, Hyogo, Japan; Akinori Hara, Saiseikai Suita Hospital, Osaka, Japan; Hiroki Fukunaga, Saiseikai Senri Hospital, Osaka, Japan; Shigemi Matsumoto, Kyoto University, Kyoto, Japan. We are indebted to the physicians and all other co-medical staff who contributed to this study. We also thank Ms Akiko Hotta and Ms Hiroko Maruyama at the OGSG data center for their excellent secretarial assistance.

Conflict of interest statement

None declared.

References

1. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with best supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;71:587–91.
2. Murad A, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-FU, doxorubicin and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37–41.
3. Grimelius B, Ekström K, Hoffman K, Graf W, Sjödén 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.
4. Kunisaki C, Imada T, Yamada R, Hatori S, Ono H, Otsuka Y, et al. Phase II study of docetaxel plus cisplatin as a second-line combined therapy in patients with advanced gastric carcinoma. *Anticancer Res* 2005;25:2973–7.
5. Kim H, Park JH, Bang SJ, Kim DH, Cho HR, Kim GY, et al. A phase II study of docetaxel and cisplatin in patients with gastric cancer recurring after or progressing during 5-FU/platinum treatment. *Jap J Clin Oncol* 2005;35:727–32.
6. Giuliani F, Molica S, Maiello E, Battaglia C, Gebbia V, Di Bisceglie M, et al. Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). *Am J Clin Oncol* 2005;28:581–5.
7. Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, et al. Randomized phase III trial comparing S-1 monotherapy versus surgery alone for stage II/III gastric cancer patients (pts) after curative D2 gastrectomy (ACTS-GC study). Abstract No 8. Gastrointestinal Cancers Symposium 2007.
8. Sawda N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. Introduction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. *Clin Cancer Res* 1998;4:1013–9.

9. Sawada N, Nose T, Ishikawa T, Yutaka T. Enhancement of antitumor activity of 5′-deoxy-5-fluorouridine (Furtulon) by taxane in human gastric cancer xenografts. *Oncol Rep* 2005;14:53–7.
10. Moriwaki T, Hyodo I, Nishina T, Hirao K, Tsuzuki T, Hidaka S, et al. A phase I study of doxifluridine combined with weekly paclitaxel for metastatic gastric cancer. *Cancer Chemother Pharmacol* 2005;56:138–44.
11. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with advanced gastric cancer: JCOG study 9205. *J Clin Oncol* 2003;21:54–9.
12. Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, et al. Final results of a randomized phase III trial of sequential high-dose Methotrexate, fluorouracil, and doxorubicin versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 2000;18:2648–57.
13. 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.
14. Cunningham D, Rao S, Starling N, Iveson T, Nicolson M, Coxon F, et al. Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric (OG) cancer: The REAL 2 trial. Abstract No: 4017 *Proc Am Soci Clin Oncol* 2006;25.
15. Yamaguchi K, Tada M, Horikoshi N, Otani T, Takiuchi H, Saitoh S, et al. Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. *Gastric Cancer* 2002;5:90–5.
16. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, et al. 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* 2001;12:1133–7.