Oxaliplatin, 5-fluorouracil and Leucovorin (FOLFOX-4) Combination Chemotherapy as a Salvage Treatment in Advanced Gastric Cancer

Young Saing Kim, M.D.[1]
Junshik Hong, M.D.[1]
Sun Jin Sym, M.D.[1]
Se Hoon Park, M.D.[2]
Jinny Park, M.D.[1]
Eun Kyung Cho, M.D.[1]
Jae Hoon Lee, M.D.[1]
Dong Bok Shin, M.D.[1]

Division of Hematology/Oncology, Department of Internal Medicine, [1]Gachon University Gil Hospital, Incheon, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence: Dong Bok Shin, M.D.
Division of Hematology/Oncology, Department of Internal Medicine, Gachon University Gil Hospital, 1198, Guwol-dong, Namdong-gu, Incheon 405-760, Korea
Tel: 82-32-460-8371
Fax: 82-32-460-3233
E-mail: dbs@gilhospital.com
Received September 14, 2009
Accepted October 19, 2009

Purpose
This study was designed to determine the efficacy and safety of FOLFOX-4 chemotherapy as a salvage treatment for patients with advanced gastric cancer (AGC).

Materials and Methods
The AGC patients with an ECOG performance status of 0~1 and progressive disease after prior treatments were registered onto this phase II trial. The patients received oxaliplatin (85 mg/m² on day 1), leucovorin (200 mg/m² on days 1 and 2) and 5-fluorouracil (400 mg/m² as a bolus and 600 mg/m² as a 22-hour infusion on days 1 and 2) every 2 weeks.

Results
For the 42 treated patients, a total of 228 chemotherapy cycles (median: 5, range: 1~12) were administered. Twenty-nine patients (69%) received FOLFOX-4 chemotherapy as a third-(50%) or fourth-line (19%) treatment. On the intent-to-treat analysis, 9 patients (21%) achieved a partial response, which was maintained for 4.6 months. The median progression-free survival and overall survival were 3.0 months and 6.2 months, respectively. The frequently encountered toxicities were neutropenia and gastrointestinal side effects, including anorexia. Although there was one possible treatment-related death, the toxicity profiles were generally predictable and manageable.

Conclusion
Salvage chemotherapy with FOLFOX-4 is an effective and tolerable regimen for those heavily pretreated AGC patients who have a good performance status.

Key words
FOLFOX-4, Salvage treatment, Stomach neoplasms

Introduction

Gastric cancer is the most common cancer and the third leading cause of cancer death in Korea (1,2). The majority of patients initially present with locally advanced or metastatic disease. Even those patients who are potentially curable have high rates of both local and distant recurrence. Combination chemotherapy was proven to produce a better quality of life and to increase overall survival when compared with the best supportive care for patients with advanced gastric cancer (AGC) (3-5). However, about half of patients do not respond to the current first-line chemotherapy and even the responders eventually show disease progression. After failure of first-line chemotherapy, many of these patients still have a good performance status and adequate organ function, and so they can be candidates for effective salvage treatments. However, a standard salvage treatment has not yet been established.

Oxaliplatin is a third generation platinum compound with the 1,2-diaminocyclohexane (DACH) carrier ligand. Oxaliplatin has shown efficacy against many tumor cell lines, including some that are resistant to cisplatin and carboplatin (6). In addition, it has demonstrated additive or synergistic activity, and especially when combined with 5-fluorouracil (FU) and even for treating 5-FU-resistant cell lines (7,8). A biweekly oxalipaltin plus infusional 5-FU

and leucovorin (LV) regimen had a significantly superior outcome for patients with metastatic colorectal cancer as compared to that of 5-FU/LV alone (9). In several phase II studies, FOLFOX-4 showed response rates of 38~43% and a manageable toxicity profile as a first-line treatment for patients with AGC (10,11).

With this background, we conducted a phase II study to determine the effectiveness and safety of FOLFOX-4 when this is used as a salvage regimen for previously treated patients with advanced or metastatic gastric cancer.

Materials and Methods

1 Patient eligibility

All the study patients were required to fulfill the following eligibility criteria: (1) histologically proven gastric adenocarcinoma; (2) tumor progression after prior chemotherapy for metastatic or locally advanced disease; (3) >4 weeks had passed since undergoing prior chemotherapy; (4) no previous exposure to oxaliplatin; (5) measurable lesion that can be accurately measured in at least one dimension (longest diameter ≥ 1 cm with spiral CT); (6) age more than 18 years; (7) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1; (8) adequate bone marrow (absolute neutrophil count $\geq 1,500$/mL, platelet count $\geq 100,000$/mL); (9) adequate hepatic function [bilirubin level ≤ 1.25 upper limit of normal (ULN), hepatic transaminase ≤ 2.5 ULN; in the presence of hepatic metastases, bilirubin level ≤ 1.5 ULN and hepatic transaminase ≤ 5 ULN]; (10) adequate renal function (serum creatinine < 1.5 mg/dL) and (11) estimated life expectancy of at least 3 months. Patients were excluded from study if they had peripheral neuropathy of any grade, central nervous system metastases and an uncontrolled comorbid illness or other malignancy. This study protocol was reviewed and approved by the Gil Medical Center (Incheon, Korea) institutional review board. Written informed consent was obtained from all the patients.

2 Treatment schedule

The patients received oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1, and LV 200 mg/m^2 as a 2-hour infusion followed by bolus 5-FU 400 mg/m^2 and a 22-hour infusion of 5-FU 600 mg/m^2 on days 1 and 2. This treatment was repeated every 2 weeks. Treatment was continued until disease progression or unacceptable toxicity occurred or the patient declined further treatment.

The dose modifications were based on the hematologic parameters and the degree of non-hematologic toxicities. A physical examination, chest x-ray, complete blood counts and biochemical tests were performed before each chemotherapy cycle. The toxicity grading was based on the National Cancer Institute Common Toxicity Criteria (version 3.0). Chemotherapy was delayed until recovery if the neutrophils decreased to <1,500/mm^3 or the platelets decreased to < 100,000/mm^3 or for the patients with significant persisting non-hematologic toxicity. The dose of 5-FU was reduced by 25% when grade 3/4 diarrhea, stomatitis or dermatitis occurred. The oxaliplatin was reduced by 25% for the patients with grade 3/4 neutropenia. For the cases of persistent (14 days or longer) painful paresthesia or functional impairment, the oxaliplatin was omitted from the regimen until recovery.

3 Evaluation

The tumor responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST). The response was evaluated based on the findings of a computed tomography (CT) scan with each assessment being done using the same imaging technique as that at baseline. The clinical responses were assessed every 3 courses of chemotherapy or earlier in the case of clinical deterioration.

4 Statistical analysis

The primary end point of the study was the objective response rate. The secondary end points consisted of toxicity, progression-free survival (PFS) and overall survival (OS). Forty evaluable patients were required for a single-stage phase II clinical study with assuming that the expected overall response rate would be 25% and the threshold rate was 10% (alpha and beta-errors set at 0.1).

Survival analysis was performed by the Kaplan-Meier method. PFS was calculated from the date of the beginning of treatment to that of clinical progression. OS was defined as the interval between the date of the beginning of treatment and the date of death or the last follow-up appointment. Cox's proportional hazard method was used for assessing the independent prognostic factors. Statistical significance was calculated at the 95% confidence interval ($p < 0.05$). All the analyses were performed using SPSS for windows 15.0 (SPSS Inc., Chicago, IL).

Results

1 Patients characteristics

A total of 42 patients were enrolled in the study between August 2004 and March 2007. The patient characteristics are listed in Table 1. The median age was 51 years (range: 32 to 75). Twenty-eight patients (67%) had an ECOG performance status of 1. The main metastatic sites were the peritoneum (60%), the abdominal lymph node(s) (52%)

Table 1. Patient characteristics (n=42)

	No.	%
Age		
Median, years	51	
Range	32 to 75	
Male gender	25	60
ECOG PS*		
0	14	33
1	28	67
Site(s) of metastatic disease†		
Peritoneum	25	60
Abdominal lymph node(s)	22	52
Liver	14	33
Lung and/or pleural effusion	8	19
Ovary	5	12
Neck lymph node	4	10
Bone	4	10
No. of metastatic sites		
1	13	31
2	15	36
≥3	14	33
Prior anticancer therapy		
Curative surgery	13	31
Palliative surgery	9	21
Adjuvant chemotherapy	12	29
Prior chemotherapy line(s)		
One	13	31
Two	21	50
Three	8	19
Prior chemotherapy drugs		
Fluoropyrimidines	38	91
Irinotecan	36	86
Cisplatin	25	60
Taxanes	15	36
Anthracyclines	3	7
Best response to prior chemotherapy		
Complete or partial response	21	50
Stable disease	12	29
Progressive disease	9	21

*Eastern Cooperative Oncology Group performance status, †Because the patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients.

and the liver (33%). Twenty-nine patients (69%) received FOLFOX-4 as more than their third-line treatment. Fluoropyrimidines and irinotecan were commonly used as prior chemotherapy regimens. Twenty-five patients (60%) had previously received cisplatin-based chemotherapy. Twenty-one patients (50%) had achieved a clinical response to their prior chemotherapy.
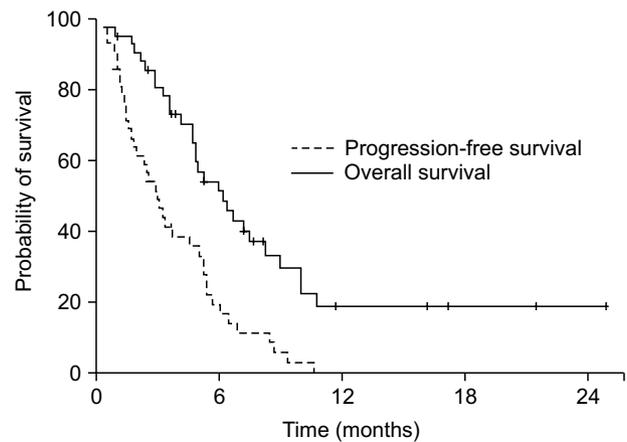
Fig. 1. Progression-free survival and overall survival.

2 Efficacy

Thirty-eight patients were evaluable for response. The response was not assessable in four patients due to follow-up loss (n=1), the patient's refusal for further treatment after the first cycle (n=1) and death of patients before the completion of the second cycle (n=2). According to the intent-to-treat principle, 9 partial responses were observed, giving an overall response rate of 21% [95% confidence interval (CI), 8 to 34%]. The median duration of the response was 4.6 months. Taking into account the 14 patients who had stable diseases, 23 patients (55%) achieved clinical benefit, which was defined as a partial response or stable disease. There was no significant difference in the response rate between the patients who had previously received platinum-based regimens vs. the patients who had not (29 vs. 16%, respectively, p=0.446). The main reasons for treatment discontinuation were disease progression (67%), patient refusal (14%) and toxicity (12%). After the median follow-up duration of 16.6 months, the median PFS and OS were 3.0 months (95% CI, 2.0 to 4.0 months) and 6.2 months (95% CI, 4.3 to 8.1 months), respectively (Fig. 1).

We conducted univariate analysis of the baseline characteristics such as age, gender, ECOG performance status, the response to previous therapy, the number of previous chemotherapy regimes the patient had undergone, having undergone previous cisplatin-based therapy and the number of organs with metastatic tumor.

As shown in Table 2, the performance status had a significant impact on both the PFS (p=0.024) and the OS (p=0.001). The PFS and OS for the patients with an ECOG of 0 were 5.1 and 10.8 months, respectively, and the PFS and OS for the patients with an ECOG of 1 were 2.5 and 4.9 months, respectively. Multivariate analysis (Table 3) also showed that the performance status was the only independent prognostic factor affecting both the PFS [hazard ratio (HR), 2.219; 95% CI, 1.090~4.518; p=0.028] and OS [HR, 5.407; 95% CI, 2.041 ~14.324; p=0.001].

Table 2. The prognostic factors by univariate anaylsis

Variables	No.	Median PFS* (months)	p-value	Median OS[†] (months)	p-value
Age					
<51	18	4.6		7.2	
≥51	24	2.5	0.200	5.0	0.784
Gender					
Female	17	2.4		4.9	
Male	25	3.4	0.418	7.5	0.116
ECOG PS[†]					
0	14	5.1		10.8	
1	28	2.5	0.024	4.9	0.001
Response to previous therapy					
Yes	21	3.4		7.2	
No	21	2.9	0.590	4.9	0.703
Number of previous chemotherapies					
1	13	2.5		3.6	
2 or 3	29	3.3	0.292	6.7	0.252
Previous cisplatin-based therapy					
No	17	4.6		8.3	
Yes	25	2.6	0.253	5.0	0.084
Number of metastatic organs					
1	13	2.9		7.2	
≥2	29	3.3	0.380	5.0	0.784

*progression-free survival, [†]overall survival, [†]Eastern Cooperative Oncology Group performance status.

Table 3. The multivariate analysis of the prognostic factors according to the Cox model

Survival	Variables	Hazard ratio	95% CI*	p-value
Progression-free survival	ECOG PS[†]			
	0	1		
	1	2.219	1.090~4.518	0.028
Overall survival	ECOG PS			
	0	1	2.041~14.324	0.001
	1	5.407		
	Sex			
	Female	1		
	Male	0.416	0.182~0.948	0.037

*confidence interval, [†]Eastern Cooperative Oncology Group performance status.

3 Safety

Forty-two patients received a total of 228 cycles of chemotherapy, with a median number of five cycles per patient (range: 1 to 12). The frequencies of the treatment-related hematological and non-hematological toxicities are listed in Table 4. The most common hematological toxicity was grade 3/4 neutropenia, which occurred in 17 patients (40%). Febrile neutropenia was observed in three patients (7%), but this was successfully treated without administering hematopoietic growth factors. Gastrointestinal toxicities were the most common non-hematological toxicities, while severe gastrointestinal toxicities were uncommon: grade 3/4 anorexia, nausea and stomatitis were observed in three (7%), two (5%) and one (2%) patients, respectively. Ten patients (24%) experienced grade 1/2 peripheral neuropathy, but there were no cases of grade 3/4 peripheral neuropathy. One patient died of pneumonia 11 days after the first cycle, and this was considered likely to be treatment-related. Mean relative dose intensities of oxaliplatin and 5-FU were 82% and 83%, respectively. Dose reduction was required in 73 cycles (32%). Treatment was delayed due to toxicities in 52 cycles (23%) of chemotherapy.

Table 4. The worst toxicities in the evaluable patients (n=42)

	Grade 1 or 2	Grade 3 or 4
Hematological		
Neutropenia	13 (31%)	17 (40%)
Thrombocytopenia	6 (14%)	3 (7%)
Anemia	8 (19%)	10 (24%)
Febrile neutropenia	–	3 (7%)
Non-hematological		
Nausea	24 (57%)	2 (5%)
Vomiting	16 (38%)	–
Stomatitis	3 (7%)	1 (2%)
Diarrhea	8 (19%)	–
Anorexia	22 (52%)	3 (7%)
Fatigue	13 (31%)	4 (10%)
Peripheral neurotoxicity	10 (24%)	–
Constipation	9 (21%)	–
Skin	8 (19%)	–

Discussion

Chemotherapy has been shown to improve patient survival as compared with best supportive care (BSC) alone for patients with AGC (3-5). However, most patients eventually develop progressive disease. Many patients and physicians request further treatment after failure of the first-line chemotherapy. However, there is no established second-line therapy and the benefit of second-line chemotherapy is not yet clear. A previous study by De Vita et al. (11) suggested that salvage chemotherapy for AGC patients might have a beneficial effect on survival: the patients (n=36) who received a second-line treatment showed a significant better median OS than the patients (n=25) who received only BSC after failing the first-line treatment (12.7 vs. 9.4 months, respectively; p=0.0026). To date, many phase II trials have assessed the activity of second-line chemotherapy on the basis of the radiological response alone. The assessment of symptomatic benefits is also important since chemotherapy for AGC is mainly focused on palliation. Several trials have reported the improvement of disease-related symptoms from second-line therapy (12-16). Furthermore, symptomatic benefits were achieved even in patients who showed no objective response (13,15,16). The first randomized phase III tiral in Germany has recently demonstrated irinotecan as 2nd-line chemo-therapy significantly improved OS and tumor-related symptoms compared with BSC (17). Although only a small number of patients (n=40) was evaluated due to poor accrual, second-line chemotherapy can be considered to be a proven option for treating gastric cancer.

This phase II study was designed to assess the activity and safety of the FOLFOX-4 regimen for previously treated patients with AGC. In our study, the response rate (RR) was 21% and the median OS was 6.2 months. These results are comparable with those reported by other phase II trials that have evaluated different FOLFOX regimens (18, 19). Kim et al. (18) reported a 26% RR with a median OS of 7.3 months for previously platinum-treated patients. Seo et al. (19) reported a 23% RR with a median OS of 8.0 months with using a modified FOLFOX-6 regimen as salvage therapy. In other phase II trials using some new drugs such as irinotecan and taxanes, the RR has ranged from 14% to 29% with the overall survival ranging from 5.2 to 8.0 months (12,13,20,21).

The most common toxicity in our study was neutropenia. Grade 3/4 neutropenia and febrile neutropenia developed in 40% and 7% of patients, respectively. However, in another phase II study using a different FOLFOX regimen, grade 3/4 neutropenia was observed only 15% of the patients (19). A possible explanation for the relatively frequent incidence of neutropenia is that patients in our study were heavily pretreated. Many patients (69%) received the FOLFOX-4 regimen as a third- or fourth-line treatment. On the other hand, peripheral neuropathy was seen in a minority of patients. The incidence of grade 1/2 neuropathy was 24% without any severe neuropathy. It might be explained by the relatively low cumulative dose of oxaliplatin (median 440 mg/m^2, range 85~1,014 mg/m^2) our study patients received because chronic neuropathy is cumulative and it is most commonly seen in patients who have received total doses $\geq$ 540 mg/m^2 (22).

Salvage chemotherapy is not appropriate for all patients. Therefore, the proper selection of patients who are likely to benefit from salvage chemotherapy is important. In our previous study with mitomycin C plus S-1 second-line chemotherapy (23), the patients with a poor performance status (ECOG 2) demonstrated significantly lower survival compared with that of the patients with a good performance status (ECOG 0 or 1). So, we confined the candidates for this phase II study to the patients with an ECOG of 0 or 1. Wilson et al. (24) has suggested that second-line therapy is more likely to be effective in platinum-naive patients. However, in our study, the cisplatin-naive patients did not show a significantly better response and longer survival. The performance status (ECOG 0 vs. 1) was found to be the only independent prognostic factor for both PFS and OS. This might suggest that oxaliplatin has no cross-resistance with cisplatin, and the patients with a good performance status could be good candidates for salvage FOLFOX-4 therapy.

Conclusion

In current study, we have shown that FOFOX-4 might be a modestly effective regimen with tolerable toxicities for the previously treated patients with AGC. Especially, this regimen can be considered a treatment option for those heavily-treated AGC patients with a good performance status.

References

1. Korea National Statistical Office. Annual report on the cause of death statistics (based on vital registration); 2007.

2. Ministry Health and Welfare. Annual report of Korea central cancer registry (published in 2008). Available from URL:http://www.ncc.re.kr

3. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden 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. 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.

5. 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.

6. Rixe O, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol. 1996;52:1855-65.

7. Becouarn Y, Agostini C, Trufflandier N, Boulanger V. Oxaliplatin: available data in non-colorectal gastrointestinal malignancies. Crit Rev Oncol Hematol. 2001;40:265-72.

8. Bleiberg H, de Gramont A. Oxaliplatin plus 5-fluorouracil: clinical experience in patients with advanced colorectal cancer. Semin Oncol. 1998;25(2 Suppl 5):32-9.

9. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938-47.

10. Cavanna L, Artioli F, Codignola C, Lazzaro A, Rizzi A, Gamboni A, et al. Oxaliplatin in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic gastric cancer (MGC). Am J Clin Oncol. 2006;29:371-5.

11. De Vita F, Orditura M, Matano E, Bianco R, Carlomagno C, Infusino S, et al. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. Br J Cancer. 2005;92:1644-9.

12. Assersohn L, Brown G, Cunningham D, Ward C, Oates J, Waters JS, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol. 2004;15:64-9.

13. 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.

14. Park SH, Lee WK, Chung M, Bang SM, Cho EK, Lee JH, et al. Quality of life in patients with advanced gastric cancer treated with second-line chemotherapy. Cancer Chemother Pharmacol. 2006;57:289-94.

15. Sencan O, Buyukcelik A, Yalcin B, Boruban MC, Akbulut H, Demirkazik A, et al. The symptomatic benefit (the clinical benefit response) from the second-line chemotherapy in patients with advanced gastric adenocarcinoma. Eur J Cancer Care (Engl). 2008;17:26-32.

16. Stathopoulos GP, Rigatos SK, Fountzilas G, Polyzos A, Stathopoulos JG. Paclitaxel and carboplatin in pretreated advanced gastric cancer: a phase II study. Oncol Rep. 2002;9:89-92.

17. Thuss-Patience PC, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B, et al. Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: A randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol. 2009;27:abstr. 4540.

18. Kim DY, Kim JH, Lee SH, Kim TY, Heo DS, Bang YJ, et al. Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol. 2003;14:383-7.

19. Seo HY, Kim DS, Choi YS, Sung HJ, Park KH, Choi IK, et al. Treatment outcomes of oxaliplatin, 5-FU, and leucovorin as salvage therapy for patients with advanced or metastatic gastric cancer: a retrospective analysis. Cancer Chemother Pharmacol. 2009;63:433-9.

20. Chun JH, Kim HK, Lee JS, Choi JY, Lee HG, Yoon SM, et al. Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. Jpn J Clin Oncol. 2004;34:8-13.

21. Jo JC, Lee JL, Ryu MH, Sym SJ, Lee SS, Chang HM, et al. Docetaxel monotherapy as a second-line treatment after failure of fluoropyrimidine and platinum in advanced gastric cancer: experience of 154 patients with prognostic factor analysis. Jpn J Clin Oncol. 2007;37:936-41.

22. Cersosimo RJ. Oxaliplatin-associated neuropathy: a review. Ann Pharmacother. 2005;39:128-35.

23. Park SH, Kim YS, Hong J, Park J, Nam E, Cho EK, et al. Mitomycin C plus S-1 as second-line therapy in patients with advanced gastric cancer: a noncomparative phase II study. Anticancer Drugs. 2008;19:303-7.

24. Wilson D, Hiller L, Geh JI. Review of second-line chemotherapy for advanced gastric adenocarcinoma. Clin Oncol (R Coll Radiol). 2005;17:81-90.