ORIGINAL ARTICLE
**Journal of Digestive Cancer Reports** 6(1):25-31, 2018
ISSN 2288-1581
http://www.gicancer.or.kr

# Oxaliplatin and Leucovorin Plus Fluorouracil Combination Chemotherapy as a First-line versus Salvage Treatment in HER2-negative Advanced Gastric Cancer Patients

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**Background**: In Korea, stomach cancer is the second most common malignancy and the third leading cause of cancer-related deaths. the time of diagnosis is very important for treatment so early detection and surgery are currently considered the mainstay of treatment, when diagnosed advanced with tumor extension through the gastric wall and direct extension into other organs, with metastatic involvement. Recently, new drugs, drug combinations, and multimodal approaches have been used to treat this disease and In cancers over expressing or amplifying HER2, the combination of cisplatin-fluoropyrimidine-trastuzumab is considered to be the treatment of reference. but At present, the choice of treatment schedule for HER2-negative tumors is based on the medical institution's preferences and adverse effects profile. The aim of this study was to evaluate the effectiveness and safety of using FOLFOX regimen as a first-line therapy or a salvage therapy in the patients with HER2-negative advanced or metastatic gastric cancer.
**Methods:** We retrospective reviewed the patient medical record from March 2012 to July 2017. This study evaluated 113 patients. Sixty-eight patients were treated with the FOLFOX regimen for the first time (first-line group) and 45 patients were treated with the FOLFOX regimen as a second (35 patients) or third (10 patients) chemotherapy (salvage group).
**Results:** In the first-line group, the response rate was 54.9%. In the salvage therapy group, the response rate was 24.4% and The difference was statistically significant (p=0.205). The median TTP of the first-line group was 10.7 months (95% confidence interval [95% CI], 7.8-13.7 months) and that of salvage line group was 6.1 months (95% CI, 3.8-8.4 months). The median OS of the first-line group was 15.8 months (95% CI, 12.7-18.9 months) and that of the salvage therapy group was 10.2 months (95% CI, 8.2-11.9 months). drug toxicity was similar andtolerable between two groups.
**Conclusion:** In patients with unresctable metastatic gastric cancer, after failing to respond to first-line therapy, most patients have no alternative other than second-line therapy because the disease is highly progressive. if the performance status of the patient is good enough to be eligible to treatments beyond best supportive care. FOLFOX regimen can be a considerable therapeutic option for salvage treatment.

**Key Words**: HER2, Chemotherapy, Stomach, Adenocarcinoma

## INTRODUCTION

Gastric cancer is thesecond most common cancer and the fourth leading cause of cancer death in Korea.[1] With standard medical examinations, many gastric cancer cases are detected in the early stages. Nevertheless, many patients progress to unresectable advanced gastric cancer (AGC), and the prognosis of these patients are very poor. Combination chemotherapy was proven to produce a better quality of life (QOL) and to increase overall survival (OS) in AGC patients.[2-4] However, about 50% of patients do not respond to the current first-line chemotherapy and even the responders eventually show disease progression.[5] Accordingly, various second-line regimens have been investigated. Active and tolerable salvage chemotherapy can improve QOL and clinical outcomes in a certain proportion of selected patients.[6]

Received: Apr. 24, 2018, Accepted: Jun. 13, 2018
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Oxaliplatin is an innovative third-generation platinum compound that inhibits DNA replication.[7,8] Compared with cisplatin, oxaliplatin is considered to have a better safety profile and has higher antitumor effects.[9] A few studies have shown the favorable outcome and tolerability of the combination of oxaliplatin and 5-fluorouracil (5-FU) with leucovorinin patients with AGC, with fewer side effects than do other agents.[10-13]

There have not been many studies about using the FOLFOX regimen as a second-line treatment. Most studies on the FOLFOX regimen to date have assessed the efficacy and safety of using the regimen as a first-line therapy or a salvage therapy. We have conducted a single-institution retrospective study of patients with HER2-negative advanced or metastatic gastric cancer, to compare the efficacy and adverse events of the FOLFOX regimen as a first-line therapy or salvage treatment.

## SUBJECTS AND METHODS

### 1) Eligibility Criteria

The eligibility criteria are as follows: histologically confirmed adenocarcinoma of the stomach; at least 1 measurable lesion; patient age between 18 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate hepatic, renal, and bone marrow function (neutrophil $\geq$1,500/$\mu$L, platelet $\geq$100,000/$\mu$L, serum creatinine $\leq$1.5 mg/dL, total bilirubin $\leq$1.25$\times$ upper limit of normal [ULN] in the absence of liver metastasis and serum transaminase $\leq$2.5$\times$ ULN); and no concurrent uncontrolled medical illness. Patients were excluded if they had a concurrent malignancy within the past 5 years, were treated with adjuvant chemotherapy, had no measurable lesion except peritoneal seeding, or died after chemotherapy due to a reason unrelated to the chemotherapy.

### 2) Treatment Protocol and Dose Modification

The treatment consisted of 100 mg/m$^2$ oxaliplatin and 100 mg/m$^2$ leucovorin administered as a 2-hour intravenous infusion, followed by 2,400 mg/m$^2$ 5-FU as a 46-hour continuo us infusion. The cycles were repeated every 2 weeks. The chemotherapy was continued unless the disease progressed, the patient developed severe grade 4 toxicity, the patient refused further treatment, or the physician decided to terminate the chemotherapy. Chemotherapy was delayed when neutrophil count was <1,500/mm$^3$ and/or platelet count <100,000 mm$^3$. The dose of all chemotherapy agents was reduced by 25 % in cases of grade 4 neutropenia, grade 3-4 thrombocytopenia lasting longer than 3 days, and poor general condition with an ECOG score of 2 or higher.

### 3) Patient Evaluation

Before each chemotherapy course, physical examination, routine hematology studies, chemistry, and chest X-ray were performed. We also excluded HER2-positive tumors (immunohistochemistry 3+ or 2+, and fluorescent in situ hybridization-positive), as they represent a different biological reality with standard treatment. Abdominal computed tomography scans of measurable lesions were performed after every 3 cycles. Responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), as follows: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The response rate was defined as the sum of CR and PR. The time to progression (TTP) was measured from the initiation of treatment until the progression of disease, and the OS was measured from the initiation of treatment until death. The toxicity of chemotherapy was graded according to the National Cancer Institute Common Toxicity Criteria.

### 4) Statistical Analysis

The response rates with respect to the categorial variables were compared using Fisher's exact test and $\chi$2 test. The TTP and OS were calculated according to the Kaplan-Meier method. All data were analyzed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). p-values of less than 0.05 were considered significant.

## RESULTS

### 1) Patient Characteristics

One hundred and twenty-two patients were enrolled in this retrospective study from March 2012 to July 2017. However, 3 patients were treated with adjuvant chemotherapy after gastrectomy, 5 patients had no measurable lesion except peritoneal seeding, and 1 patient died of a traumatic intracranial hemorrhage. Of the 122 patients, 113 were assessable for response. Sixty-eight patients were treated with the FOLFOX regimen for the first time (first-line group), whereas 45 patients were treated with the FOLFOX regimen as a

**Table 1.** Baseline characteristics of the patients (n=113)

| | First line group (n=68) | Salvage line group (n=45) | p-value |
|---|---|---|---|
| Age (year, median, range) | 61.93 (36–78) | 53.76 (30–73) | 0.013* |
| Sex (Male:Female) | 51:17 | 33:12 | 0.843 |
| Prior surgery (%) | | | 0.017* |
| None | 26 (38.2) | 18 (40.0) | |
| TG | 34 (50.0) | 13 (28.9) | |
| STG | 8 (11.8) | 14 (31.1) | |
| ECOG | | | 0.002* |
| 0 | 48 (70.6) | 19 (42.2) | |
| 1 | 13 (19.1) | 23 (51.1) | |
| 2 | 7 (10.3) | 3 (6.7) | |
| Histologic classification (%) | | | 0.287 |
| Adenocarcinoma (Moderately differentiated) | 20 (29.4) | 13 (28.9) | |
| Adenocarcinoma (Poorly differentiated) | 40 (59.8) | 20 (44.4) | |
| Signet ring cell type | 5 (7.4) | 6 (13.3) | |
| Other type | 3 (4.4) | 6 (13.3) | |
| Measurable lesion (%) | | | 0.268 |
| Lymph node | 43 (63.2) | 16 (35.6) | |
| Liver | 14 (20.6) | 14 (31.1) | |
| Bone | 1 (1.5) | 2 (4.4) | |
| Adrenal gland | 1 (1.5) | 0 (0.0) | |
| Pancreas | 0 (0.0) | 1 (2.2) | |
| Rectum | 1 (1.5) | 0 (0.0) | |
| Common bile duct | 0 (0.0) | 1 (2.2) | |
| Lung | 1 (1.5) | 1 (2.2) | |
| Ureter | 1 (1.5) | 2 (4.4) | |
| Ovary | 1 (1.5) | 2 (4.4) | |
| Colon | 1 (1.5) | 2 (4.4) | |
| Pleura | 0 (0.0) | 1 (2.2) | |
| Skin | 1 (1.5) | 0 (0.0) | |

Data are presented as mean±SD or number (%).
ECOG, Eastern Cooperative Oncology Group.
*Statistical significance.

second (35 patients) or third (10 patients) chemotherapy (salvage group). The median age of the enrolled patients was 61.9 years in the first-line group and 53.7 years in the salvage group. The first-line group received an average of 6.5 chemotherapy sessions, and the salvage therapy group received an average of 10.3 sessions, including previous treatments. The first-line group had more subjects who scored 0 or 1 on the ECOG performance status scale. The most common location of the measurable lesion in both groups was the lymph node, seen in 43 patients in the first-line group and 16 patients in the salvage therapy group. There were no histological differences between the 2 groups, and the first-line group had a more frequent history of gastrostomy (Table 1). Among the 43 patients in the salvage group, 27 patients had previously been treated with a cisplatin-based chemotherapy (Table 2).

**Table 2.** Previous chemotherapy

| Previous Regimen | No. of patient | Total cycle | % |
|---|---|---|---|
| FOLFIRI | 23 | 110 | 53.5 |
| TCF | 22 | 125 | 51.2 |
| TS-1+Cisplatin | 2 | 5 | 4.7 |
| ELF | 2 | 9 | 4.7 |
| FP | 2 | 8 | 4.7 |

FOLFIRI, Irrinotecan, Leucovorin, 5-FU; TCF, Docetaxel, Cisplatin, 5-FU; ELF, Etoposide, Leucovorin, 5-FU; FP, Cisplatin, 5-FU.

#### 2) Response

The median follow-up duration was 18.9 months (range, 2.5-99.0 months). In the first-line group, there were 11 cases of CR, 26 cases of PR, 10 cases of SD, and 21 cases of PD, and the response rate was 54.9%. In the salvage therapy group, there was 1 case of CR, 10 cases of PR, 9 cases of SD and 25 cases of PD, and the response rate was 24.4% (Table 3). The difference was statistically significant. The median TTP of the first-line group was 10.7 months (95% confidence interval [95% CI], 7.8-13.7 months) and that of salvage line group was 6.1 months (95% CI, 3.8-8.4 months) (Fig. 1). The median OS of the first-line group was 15.8 months (95% CI, 12.7-18.9 months) and that of the salvage therapy group was 10.2 months (95% CI, 8.2-11.9 months) (Fig. 2).

**Table 3.** Treatment Response Rate

| Response | No. of patients (%) | | p-value |
|---|---|---|---|
| | First line group (n=68) | Salvage line group (n=45) | |
| CR | 11 (16.2) | 1 (2.2) | 0.009* |
| PR | 26 (38.7) | 10 (22.2) | |
| SD | 10 (14.7) | 9 (20.0) | |
| PD | 21 (30.9) | 25 (55.6) | |
| CR+PR | 37 (54.9) | 11 (24.4) | |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Statistical significance.

#### 3) Toxicity

In terms of hematological toxicity in the first-line group, we observed 7 cases of grade 1-2 leukopenia (10.4%) and 2 cases of grade 3-4 leukopenia (3.0%), and there were no cases of neutropenia. In addition, there were 8 cases of grade 1-2 anemia and 9 cases of grade 1-2 thrombocytopenia. On the other hand, in the salvage therapy group, we observed 6 cases of grade 1-2 leukopenia and 1 case of grade 3-4 leukopenia. Additionally, there were 2 cases of grade 1-2 anemia and 7 cases of grade 1-2 thrombocytopenia. The common nonhematological toxicities in both groups included grade 1-2 nausea and vomiting, and 1 case of grade 3-4 neuropathy was observed in the first-line group (Table 4).

## DISCUSSION

When gastric cancer is detected in the early stages, a complete recovery can be expected in >90% of the cases. However, in locally advanced or metastatic gastric cancer, even with anticancer chemotherapy, only approximately 10% of the patients survive after 2 years, showing a poor prognosis.[14]

Patients with HER2 positive are recommended to receive chemotherapy with herceptin.

According to the Toga study, 594 HER2-positive patients were compared with those who received conventional chemotherapy with trastuzumab and conventional chemotherapy. Median overall survival was better at 13.8 versus 11.1 months

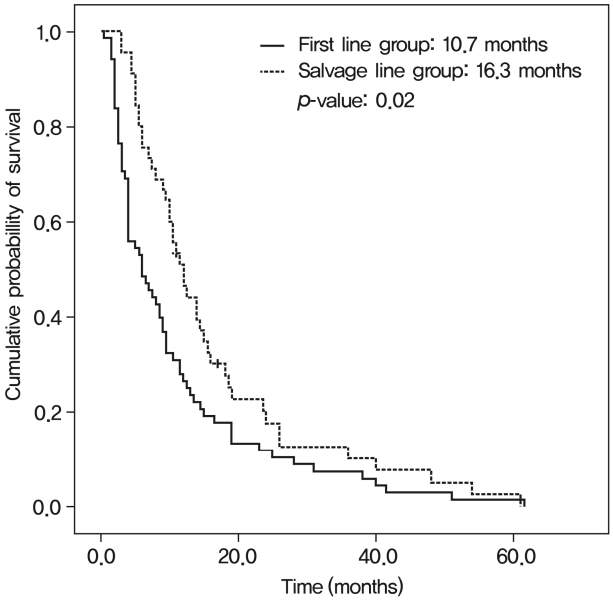


**Fig. 1.** Analysis of time to progression.

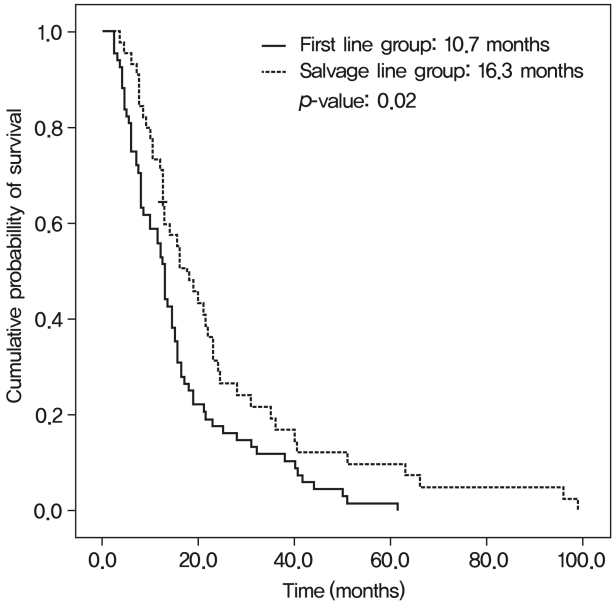


**Fig. 2.** Analysis of overall survival.

**Table 4.** Toxicity of Chemotherapy

| | First line group (n=68, 373 cycle) | | Salvage line group (n=45, 193 cycle) | |
|---|---|---|---|---|
| | Grade 1-2 No. (%) | Grade 3-4 No. (%) | Grade 1-2 No. (%) | Grade 3-4 No. (%) |
| Hematologic | | | | |
| Leukopenia | 7 (10.4) | 2 (3.0) | 6 (13.3) | 0 (0.0) |
| Febrile neutropenia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.2) |
| Anemia | 8 (11.9) | 1 (1.5) | 2 (4.4) | 0 (0.0) |
| Thrombocytopenia | 9 (13.2) | 2 (2.9) | 7 (15.6) | 2 (4.4) |
| Non-hematologic | | | | |
| Nausea | 22 (32.8) | 1 (1.5) | 12 (26.7) | 1 (2.2) |
| Vomiting | 21 (30.9) | 1 (1.5) | 11 (24.4) | 1 (2.2) |
| Diarrhea | 0 (0.0) | 1 (1.5) | 0 (0.0) | 0 (0.0) |
| Neuropathy | 3 (4.5) | 1 (1.5) | 2 (4.4) | 0 (0.0) |
| Mucositis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

and progression-free survival was also better at 6.7 vs 5.5.[15] Patients with HER2 negative are treated with conventional chemotherapy. Among the chemotherapeutic agents used in these cases, we aimed to compare the efficacy of the FOLFOX regimen (a combination of oxaliplatin, 5-FU, and leucovorin) as a first-line therapy or a salvage therapy in this study. Combination therapies with oxaliplatin generally show a high efficacy. Aphase II study of a regimen of oxaliplatin, folic acid, and 5-FU as a first-line therapy showed 4.3% CR, 41.3% PR, a response rate of 45.6%, aprogression-free survival (PFS) of 6.2 months, and an OS of 9.8 months.[16] However, the reported incidence of peripheral neuropathy in this study was high, at 43.5%. The results of a different study using oxaliplatin, conducted at our institution, showed a response rate of 43%, a PFS of 4 months, and an OS of 8.3 months; grade 3-4 leukopenia and grade 3-4 neutropenia each occurred in 13.3% of the cases, showing a similar efficacy to that in the aforementioned study.[17] In the current study, we used 100 mg/m$^2$ oxaliplatin, 100 mg/m$^2$ leucovorin, and 2,400 mg/m$^2$ 5-FU, and obtained a response rate of 54.9%, a PFS of 10.7 months, and an OS of 15.8 months, showing vastly improved results compared with previous studies. It is unclear why the PFS and OS, in addition to the response rate, were improved in this study; however, this may be attributed to the difference in the composition of the subject population. Compared with the previous study conducted at our institution,[17] there were more cases of metastasis to the lymph node, and the patients were younger than those in the study by Zhao et al.[16] Grade 1-2 leukopenia occurred in 10.4% of the cases and grade 3-4 leukopenia occurred in 3%. Non-hematological toxicity events included grade 1-2 nausea in 32.8% of the cases and grade 1-2 vomiting in 30.9%. Grade 1-2 peripheral neuropathy was observed in 4.5% of the patients. Because this was a retrospective study based on medical records, and records of adverse events may have been omitted, we cannot conclude that the incidence of neuropathy was lower than in other studies. In previous studies on FOLFOX in Korea,[18-20] the incidence of peripheral neuropathy varied widely, from 7.3% to 39.1%, and the difference is believed to be due to the retrospective nature of these studies.

After failing to respond to first-line therapy, most patients have no alternative other than second-line therapy because the disease is highly progressive. Furthermore, the performance status of the patient is often good enough to be eligible to treatments beyond best supportive care. Therefore, a few studies have investigated second-line chemotherapy in AGC. Clinical studies of second-line chemotherapy in AGC patients have different results. Agents for second-line chemotherapy include taxanes, irinotecan, oral 5-FU (capecitabine or S-1), platinum agents (cisplatin, carboplatin, or oxaliplatin), epirubicin, and mitomycin C. In this study, we administered the FOLFOX regimen based on oxaliplatin. The treatment protocol was identical to the first-line therapy. A study conducted in Korea that administered the FOLFOX regimen to patients who did not react to other chemotherapy reported 0 CR, 22.6% PR, a median PFS of 3 months, and a median OS of 8 months.[21] In other oxaliplatin-based phase II studies, the response rate was 4%, the median PFS was 2.5 months, and the OS was 6.6 months.[22] The reason that the results of the current study were significantly better than those of previous studies may be that the first-line chemotherapy protocol used before the salvage therapy was different. Furthermore, the differences between the study by Jeong et al.[22] and the current study may stem from the differences in the dose and method of administration of oxaliplatin. We observed grade 1-2 leuko-

penia in 13.3% of the cases and grade 1-2 thrombocytopenia in 15.6% of the cases, and these results were similar to those of the previous reports. In terms of nonhematological toxicity, nausea and vomiting were common, similar to the first-line treatment group, and peripheral neuropathy was present in 2% of the cases. We believe that the differences in the incidences of neuropathy compared with the study by Seo et al.[22] are also due to the limitation of retrospective studies. It is encouraging that in the current study, we were able to see an increase in the response rate at the 100 mg/m$^2$ dose, compared with previous studies that used 85 mg/m$^2$, without an increase in adverse events. Furthermore in our study 27 out of 45 patients received cisplatin-based chemotherapy previously. In these patients, FOLFOX also seemed to be effective. Therefore, whatever prior chemotherapy regimen, FOLFOX can be good choice for salvage treatment. There are almost no studies comparing the use of the FOLFOX regimen as a first-line therapy with using it as a second- or third-line therapy for HER2-negative tumors. The FOLFOX regimen can be efficacious as a first-line or a salvage therapy for AGC; however, the response rate was much higher when it is used as a first-line treatment than a salvage treatment since there was no response to other chemotherapy agents. Therefore, in patients who did not respond to the first-line chemotherapy, we cannot expect a significantly improved response from chemotherapy with a different agent. The median TTP and OS of the salvage group was better than those reported in the previous studies, and this is believed to support previous studies indicating that salvage treatment is more efficacious than best supportive care. Since the response rate is not as closely associated to patient survival as median OS, and gastric cancer often progresses to a non-measurable disease, it is significant that our results show a large improvement in median OS. If we include patients who were excluded from the current analysis owing to a lack of measurable lesions such as a peritoneal seeding, we may be able to predict a greater extension in OS. According to the genetic analysis by Keam et al.,[23] AGC patients with a 6-bp deletion in the 3'UTR of thymidylate synthase gene responded better to FOLFOX-6. Thus, future research is necessary to assess whether this genetic variation is also associated with the response to salvage therapy.

## CONCLUSION

In conclusion, the combination of oxaliplatin, 5-FU, and leucovorin is a safe and efficacious regimen as a first-line therapy as well as a salvage therapy for HER2-negative tumors.

## REFERENCES


1. https://www.cancer.go.kr/lay1/S1T654C656/contents.do
2. Glimelius B, Ekstrom K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997;8:163-168.
3. 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; 71:587-591.
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. Dickson JL, Cunningham D. Systemic treatment of gastric cancer. Eur J Gastroenterol Hepatol 2004;16:255-263.
6. Baek SK, Kim SY, Jeong JH, Cho KS, Yoon HJ. Second-line chemotherapy for advanced gastric cancer in Korea. Gastric cancer 2012;15:345-354.
7. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.
8. Arnould S, Hennebelle I, Canal P, Bugat R, Guichard S. Cellular determinants of oxaliplatin sensitivity in colon cancer cell lines. Eur J Cancer 2003;39:112-119.
9. Kollmannsberger C, Rick O, Derigs HG, et al. Activity of oxaliplatin in patients with relapsed or cisplatin-refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol 2002;20:2031-2037.
10. Louvet C, Andre T, Tigaud JM, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002;20:4543-4548.
11. Al-Batran SE, Atmaca A, Hegewisch-Becker S, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol 2004;22:658-663.
12. De Vita F, Orditura M, Matano E, 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;92:1644-1649.
13. Luo HY, Xu RH, Zhang L, et al. A pilot study of oxaliplatin, fluorouracil and folinic acid (FOLFOX-6) as first-line chemotherapy in advanced or recurrent gastric cancer. Chemotherapy 2008;54:228-235.
14. Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. The Lancet 2010;376 (9742):687-697.
15. Janunger KG, Hafstrom L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. Eur J Surg 2002;168:597-608.

16. Zhao JG, Qiu F, Xiong JP, et al. A phase II study of modified FOLFOX as first-line chemotherapy in elderly patients with advanced gastric cancer. Anticancer Drugs 2009;20:281-286.
17. Kang SH, Kim JI, Moon HS, et al. Oxaliplatin and leucovorin plus fluorouracil versus irinotecan and leucovorin plus fluorouracil combination chemotherapy as a first-line treatment in patients with metastatic or recurred gastric adenocarcinoma. Korean J Gastroenterol 2010;55:26-32.
18. Lee HH, Hur H, Kim SH, Park AR, Kim W, Jeon HM. Outcomes of modified FOLFOX-6 as first line treatment in patients with advanced gastric cancer in a single institution; retrospective analysis. Cancer Res Treat 2010;42:18-23.
19. Kim YJ, Goh PG, Kim ES, et al. Comparison of the toxicities and efficacies of the combination chemotherapy regimens in advanced gastric cancer patients who achieved complete response after chemotherapy. Korean J Gastroenterol 2011;58:311-317.
20. Kim HS, Kim JH, Kim HJ, et al. Oxaliplatin, 5-fluorouracil and leucovorin (modified FOLFOX-6) as first-line chemotherapy for advanced gastric cancer patients with poor performance status. Oncol Lett 2012;3:425-428.
21. Seo HY, Kim DS, Choi YS, 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;63:433-439.
22. Jeong J, Jeung HC, Rha SY, et al. Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. Ann Oncol 2008;19:1135-1140.
23. Keam B, Im SA, Han SW, et al. Modified FOLFOX-6 chemotherapy in advanced gastric cancer: Results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. BMC Cancer 2008;8:148.