

# Modified FOLFIRI as Second-Line Chemotherapy after Failure of Modified FOLFOX-4 in Advanced Gastric Cancer

Eun Kyoung Jeon, MD<sup>1</sup>  
 Sook Hee Hong, MD<sup>1</sup>  
 Tae Hee Kim, MD<sup>1</sup>  
 Seung Eun Jung, MD, PhD<sup>2</sup>  
 Ji Chan Park, MD<sup>1</sup>  
 Hye-Sung Won, MD<sup>1</sup>  
 Yoon-Ho Ko, MD<sup>1</sup>  
 Sang Young Rho, MD<sup>1</sup>  
 Young Seon Hong, MD, PhD<sup>1</sup>

<sup>1</sup>Division of Oncology, Department of Internal Medicine, <sup>2</sup>Department of Radiology, The Catholic University of Korea School of Medicine, Seoul, Korea

Correspondence: Young Seon Hong, MD, PhD  
 Division of Oncology, Department of Internal Medicine, The Catholic University of Korea School of Medicine, 505 Banpo-dong, Seocho-gu, Seoul 137-701, Korea  
 Tel: 82-2-2258-6042  
 Fax: 82-2-535-1682  
 E-mail: y331@catholic.ac.kr  
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## Purpose

The purpose of this study was to evaluate efficacy and toxicity of irinotecan, leucovorin and 5-fluorouracil (FOLFIRI) as second-line treatment after failure of oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) for advanced gastric cancer.

## Materials and Methods

Patients who received modified FOLFOX-4 as first-line treatment and then received sequential modified FOLFIRI for disease progression were included in this study. The modified FOLFIRI regimen consisted of irinotecan 150 mg/m<sup>2</sup> in a 90-minute intravenous infusion on day 1, leucovorin (LV) 20 mg/m<sup>2</sup> and 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup> as a bolus followed by 600 mg/m<sup>2</sup> as a 22-hour infusion on days 1 and 2 with the same dose of 5-FU/LV of modified FOLFOX-4 every 2 weeks.

## Results

A total of 32 patients received 126 courses of FOLFIRI chemotherapy. No complete response was achieved. Three patients (9.4%; 95% confidence interval [CI], 0 to 20.1%) achieved partial response, whereas 11 (34.4%; 95% CI, 17.0 to 51.8%) patients showed stable disease. Disease control rate (complete response, partial responses and stable diseases) was 43.8% (95% CI, 25.6 to 61.9%) and median follow up duration was 11.3 months (range, 2.23 to 37.9 months). Median time to progression was 2 months (95% CI, 1.49 to 2.51 months), and median overall survival from the start of FOLFIRI was 5.84 months (95% CI, 4.34 to 7.34 months). Toxicities were tolerable.

## Conclusion

Modified FOLFIRI as second-line chemotherapy after failure of the modified FOLFOX-4 in advanced gastric cancer was tolerable but showed a lower response rate. Further study about retrying 5-FU/LV with irinotecan after failure of the 5-FU/LV combined regimen is necessary in advanced gastric cancer.

## Key words

Stomach neoplasms, Chemotherapy, FOLFIRI

## Introduction

Gastric cancer is the most common cancer in Korea and is the second leading cause of cancer-related deaths [1]. Approximately 20-60% of patients who have undergone curative surgery for gastric cancer develop recurrent diseases [2], and they undergo palliative chemotherapy.

Palliative chemotherapy has been shown to improve quality of life

and overall survival (OS) compared to the best supportive care [3]. Different first-line treatments for advanced gastric cancer have response rates (RR) that range from 12-56%, with the median OS not exceeding 12 months [4,5]. There is no standard first-line treatment for advanced gastric cancer, yet a 5-fluorouracil (5-FU) and platinum-based regimen is usually administered.

Half of the patients receiving chemotherapy are unresponsive, and the majority of patients who initially responded eventually become unresponsive to the chemotherapy. These patients are candidates for

second-line chemotherapy. However, the efficacy and benefit of second-line chemotherapy for advanced gastric cancer has not been proven, and there is no currently established second-line regimen or treatment options. Nevertheless, most patients want to receive chemotherapy if they are able to.

New agents such as docetaxel and irinotecan are under study as second-line chemotherapy for gastric cancer. Irinotecan is a camptothecin analog that is converted *in vivo* to SN-38, which binds to the topoisomerase I-DNA complex and thereby disrupts DNA replication and cell division [6]. The mechanism of action of irinotecan is different from that of fluoropyrimidine, platinum and taxane, and irinotecan has no cross-resistance with these agents [7,8]. The objective RR of irinotecan is 13% for gastric cancer patients as a single agent [9]. In combination with 5-FU and leucovorin (LV), the overall RR was 22-42%, and the median OS was 7.6-14.0 months for patients with untreated gastric cancer [10-13]. As second-line chemotherapy, the overall RR of the modified irinotecan, LV and 5-fluorouracil (FOLFIRI) regimen was 10-29%, with the median time to progression (TTP) being 2.3-4 months and the median OS being 5-10.9 months [14-18].

We treated patients with advanced gastric cancer with the modified oxaliplatin, LV and 5-fluorouracil (FOLFOX) regimen as first-line therapy and then with the modified FOLFIRI regimen as second-line therapy. Our goal in this study was to evaluate the efficacy and toxicity of the modified FOLFIRI regimen following the modified FOLFOX regimen for patients with metastatic gastric cancer.

## Materials and Methods

### 1 Patient eligibility

We retrospectively reviewed all patients with gastric or gastroesophageal junction adenocarcinoma who received the modified FOLFOX-4 regimen as first-line treatment and the modified FOLFIRI regimen as second-line treatment for disease progression between January 2003 and August 2008 at Seoul St. Mary's Hospital. Patients with histologically confirmed and locally advanced, metastatic, or recurrent gastric cancer were eligible. Other eligibility criteria included the age range of 18 to 75 years, an Eastern Clinical Oncology Group (ECOG) performance status of 2 or less, adequate bone marrow and organ functions (an absolute neutrophil count  $\geq 1,500/\mu\text{L}$ , platelets  $\geq 75,000/\mu\text{L}$ , creatinine  $< 2.0$  mg/dL, serum bilirubin  $< 2.0$  mg/dL and serum transaminase levels  $< 2$  times the upper normal limit), no past or concurrent history of malignancy other than stomach cancer, except for curatively treated nonmelanoma skin cancer or *in situ* carcinoma of the cervix uteri. This study was reviewed and approved by Catholic Medical Center Institutional Review Board.

### 2 Treatment schedule

All patients received the modified FOLFOX-4 regimen, and this consisted of intravenous oxaliplatin 100 mg/m<sup>2</sup> in a 2-hour intravenous infusion on day 1, LV 20 mg/m<sup>2</sup> and 5-FU 400 mg/m<sup>2</sup> as a bolus followed by 600 mg/m<sup>2</sup> as a 22-hour infusion on days 1 and 2, every 2 weeks. As a second-line chemotherapy, the modified FOLFIRI regimen included irinotecan 150 mg/m<sup>2</sup> in a 90-minute intravenous infusion on day 1, LV 20 mg/m<sup>2</sup> and 5-FU 400 mg/m<sup>2</sup> as a bolus followed by 600 mg/m<sup>2</sup> as a 22-hour infusion on days 1 and 2, every 2 weeks. Atropine was not routinely used. All patients received adequate anti-emetic therapy prior to chemotherapy. Loperamide was prescribed prophylactically and the patients were instructed to take loperamide in case of developing diarrhea. Treatment was continued until documented disease progression, unacceptable toxicity or patient refusal.

### 3 Dose modifications

Chemotherapy was delayed if the patient's granulocyte count was  $< 1,500/\text{mm}^3$  or the platelet count did not return to a minimum of  $75,000/\text{mm}^3$  on the day of infusion. Other toxicities (except alopecia) were required to be either grade 0 or 1 before another cycle was started. The 5-FU dosage was reduced by 20% in the next cycle if a related grade 3 or worse toxicity (mucositis and hand-foot syndrome) occurred. The dose of irinotecan was not reduced by the occurrence of mucositis or hand-foot syndrome. The dose of irinotecan and 5-FU were reduced by 20% for grade 4 neutropenia lasting 7 days or more, neutropenic fever, grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding requiring platelet transfusion, and grade 3/4 non-hematologic toxicities other than nausea and vomiting.

### 4 Assessment of efficacy and toxicity

Physical examination, chest X-rays, complete blood counts and biochemical tests were performed before each chemotherapy cycle. Computed tomography (CT) scans were performed every three cycles or when disease progression was suspected. The tumor response was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. If there was no measurable lesion, the evaluable lesion was assessed. The presence or absence of each lesion was noted throughout follow-up. The CT scans were reviewed by a single experienced radiologist (SEJ). The toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, ver. 3.0) at each cycle.

### 5 Statistics

Descriptive statistics were reported as proportions and medians. The TTP was measured from the first day of FOLFIRI treatment until the date of disease progression, the date of the last follow-up, or the date of

the decision to receive palliative care when no further imaging study had been performed. The OS was measured from the first day of FOLFIRI chemotherapy until death or the date of the last follow up. The TTP and OS were estimated by the Kaplan-Meier method. All the statistical analyses were performed using SPSS ver. 13.0 (SPSS Inc., Chicago, IL).

## Results

### 1 Patient characteristics

A total of 104 patients received modified FOLFOX-4 as first line chemotherapy for advanced or recurrent gastric cancer between January 2003 and August 2008 at Seoul St. Mary's Hospital. A total of 37 patients received modified FOLFIRI as second-line chemotherapy and 32 of these patients were eligible.

Patient characteristics are summarized in Table 1. The median age of the patients was 59 years (range, 33 to 72 years). The male to female ratio was 22 : 10. Thirteen (40.6%) of the patients had an ECOG performance status of 2. Thirty (93.8%) patients had metastatic disease and only 2 (6.2%) patients had locally advanced disease. Four patients (12.5%) had gastroesophageal junction adenocarcinoma. Ten (31.25%) patients had metastases in more than 3 organs, and the most common metastatic organ was peritoneum. The median hemoglobin level was 10.8 g/dL (range, 7.5 to 14.2 g/dL).

### 2 Treatment administration and toxicity

Patients received a total of 126 cycles of FOLFIRI chemotherapy, with a median of three cycles (range, 1 to 10 cycles) per patient. Dose reduction was applied in 29 cycles (23.0%) and the chemotherapy schedule was delayed in 20 cycles (15.9%), primarily due to hematological toxicity. The toxicities are listed in Table 2. No deaths due to toxicity occurred and the toxicities were tolerable. The most common toxicity was anemia in 27 (84.4%) patients. Grade 3 or 4 anemia occurred in 2 (6.2%) patients. Grade 3 or 4 neutropenia was observed in 7 (21.9%) patients. The non-hematologic toxicities consisted primarily of nausea and vomiting. Grade 1 or 2 diarrhea occurred in 2 (6.2%) patients.

### 3 Efficacy and survival

With the intent-to-treat analysis, the overall RR was 9.4% (Table 3). No patient had a complete response (CR), whereas 3 (9.4%; 95% confidence interval [CI], 0 to 20.1%) patients achieved partial responses (PR), and stable diseases (SD) were documented in 11 (34.4%; 95% CI, 17.0 to 51.8%) patients. The disease control rate (CR, PR and SD) was 43.8% (95% CI, 25.6 to 61.9%). Ten (31.2%; 95%

**Table 1.** Patient characteristics

Characteristics	No. of patients (%)
Gender	
Male	22 (68.75)
Female	10 (31.25)
Median age (range, yr)	59 (33-72)
ECOG performance status	
0	8 (25)
1	11 (34.4)
2	13 (40.6)
Extent of disease	
Metastatic	27 (84.4)
Recurrent	3 (9.4)
Locally advanced	2 (6.2)
Operation	
Curative	3 (9.4)
Palliative	2 (6.2)
Primary site	
Unknown	1 (3.1)
Gastroesophageal junction	4 (12.5)
Body	27 (84.4)
Metastatic number	
0	1 (3.1)
1	6 (18.8)
2	15 (46.9)
≥3	10 (31.2)
Metastatic lesion	
Liver	6 (18.8)
Peritoneum	21 (65.6)
Bone	7 (21.9)
Measurable lesion	
No measurable	10 (31.25)
Measurable	22 (68.75)
Differentiation	
Well	0 (0)
Moderate	9 (28.1)
Poor	19 (59.4)
Unknown	4 (12.5)
Median complete blood count (range)	
Hemoglobin (g/dL)	10.8 (7.5-14.2)
White blood cell ( $\times 10^9/L$ )	5,450 (2,980-16,990)
Plate count ( $\times 10^9/L$ )	197 (81-462)

ECOG, Eastern Clinical Oncology Group.

CI, 14.3 to 48.2%) patients had progressive diseases (PD). The tumor responses were not evaluated in 8 (25%) patients; 6 patients showed clinical progression with aggravation of their performance status, while 2 patients were lost to follow-up. Nineteen (59.4%) patients received third line chemotherapy after failure of FOLFIRI regimen.

The median follow up duration was 11.3 months (range, 2.23 to 37.9 months). The median TTP for the FOLFIRI regimen was 2 months (95% CI, 1.49 to 2.51 months) (Fig. 1). The median OS was 5.84

**Table 2.** Toxicity profiles of FOLFIRI (per patient)

	NCI-CTCAE grade (%)				
	G1	G2	G3	G4	All
Non hematologic toxicities					
Nausea	5 (15.6)	6 (18.8)	3 (9.4)	0	14 (43.8)
Vomiting	3 (9.4)	6 (18.8)	2 (6.2)	0	11 (34.4)
Diarrhea	1 (3.1)	1 (3.1)	0	0	2 (6.2)
Hepatotoxicity	6 (18.8)	0	0	1 (3.1)	7 (21.9)
Hematologic toxicities					
Neutropenia	5 (15.6)	7 (21.9)	0	7 (21.9)	19 (59.4)
Anemia	11 (34.4)	13 (40.6)	1 (3.1)	2 (6.2)	27 (84.4)
Thrombocytopenia	3 (9.4)	2 (6.2)	1 (3.1)	0	6 (18.8)
Febrile neutropenia	0	0	0	0	0

FOLFIRI, irinotecan, leucovorin and 5-fluorouracil; NCI-CTCAE ver. 3.0, National Cancer Institute-Common Toxicity Criteria for Adverse Events ver. 3.0.

**Table 3.** Efficacy of FOLFIRI

Response	No. of patients (%)	95% confidence interval
Complete response	0 (0)	-
Partial response	3 (9.4)	0-20.1
Stable disease	11 (34.4)	17.0-51.8
Progressive disease	10 (31.2)	14.3-48.2
Not assessable	8 (25)	-

FOLFIRI, irinotecan, leucovorin and 5-fluorouracil.

months (95% CI, 4.34 to 7.34 months) (Fig. 2).

## Discussion

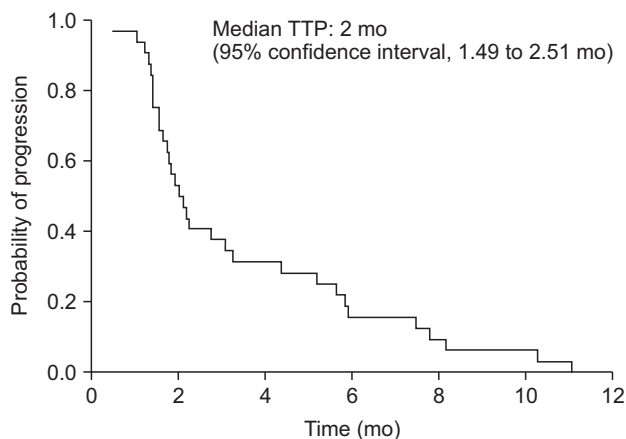
This study assessed the efficacy and toxicity of the FOLFIRI regimen as second-line treatment after failure of the modified FOLFOX-4 regimen. The treatment was well-tolerated. The most predominant grade 3 or 4 toxicity was neutropenia. Febrile neutropenia was not seen. There was no grade 3 or 4 diarrhea, and only 3 patients (8.1%) had grade 1 or 2 diarrhea. This low rate of diarrhea, as compared with that of other irinotecan based studies, could be explained by the low dose of irinotecan and the ethnic differences of uridine diphosphate glucuronosyltransferase 1 (UGT1A1). Irinotecan is bio-transformed into its active metabolite SN-38, and SN-38 is inactivated by UGT1A1 through glucuronidation. Depending on the number of TA insertions in the TATAA element of the 5' promoter region, the genotype of the UGT1A1\*28 allele is named as the wild-type (6/6), the heterozygous genotype (6/7) and the homozygous genotype (7/7). The patients carrying the heterozygous or homozygous genotype experienced a decreased expression of the UGT1A1 enzyme, resulting in a lower rate of SN-38 glucuronidation. The association between the UGT1A1 gene polymorphism and increased toxicity in patients who received irinotecan-based chemotherapy is well known [6]. Liu et al.

[19] showed the predominance of the UGT1A1 (6/6) genotype in Asians (76%) compared with 46% in Caucasians [19]. A high rate of grade 3 or 4 toxic diarrhea (48.9%) was reported at 180 mg/m<sup>2</sup> irinotecan in French patients [11], but this was 10% at 125 mg/m<sup>2</sup> in American patients [10], and 6% at 180 mg/m<sup>2</sup> in Korean patients [15].

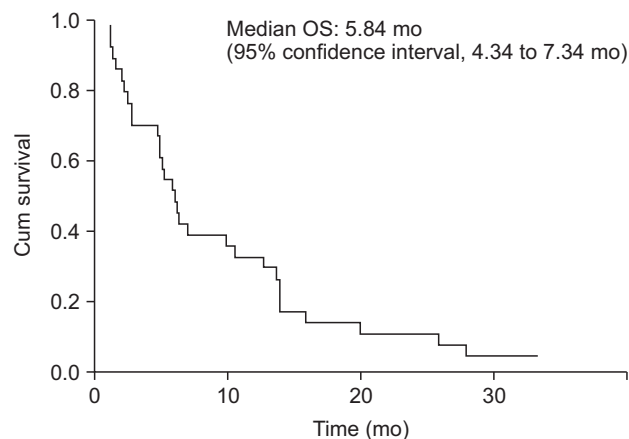
There is no standard first-line treatment for advanced gastric cancer, yet a 5-FU and platinum based regimen is usually administered and a modified FOLFOX-4 regimen is one of the commonly used regimens. Several phase II studies have reported the efficacy of the modified FOLFIRI regimen as a second-line or salvage regimen after failure of a 5-FU combined regimen (Table 4), for which the response rate was 10-29%. The TTP was 2.3-4 months and the OS was 5-10.9 months. Our study showed a lower overall RR but had similar disease control rate (CR, PR and SD) and similar OS with the other studies. This study included 10 (31.3%) patients without measurable lesions. These patients only had evaluable lesions and were evaluated for only SD or PD responses, resulting in a low RR.

Based on the results of the phase III study [20], we used a low dose of LV. Jäger et al. [20] compared the therapeutic effects and toxicity of high-dose LV/5-FU versus low-dose LV/5-FU for treating colon cancer. The high dose LV/5-FU was not superior to the low-dose LV/5-FU, yet the RR and OS were comparable, but the treatment-related toxicity was higher in the high dose LV/5-FU group.

A low dose of irinotecan and the same dose of the prior failed regimen (5-FU/LV) with same infusion-method could also be reasons for the low RR and shorter TTP. Also, a synergistic effect of irinotecan and 5-FU/LV is controversial. In some studies, combining irinotecan with 5-FU/LV showed synergistic effects after failure of 5-FU/LV [21-23]. However, the FOLFIRI regimen as the second-line therapy had a lower response rate than the RR of second-line FOLFOX with the same dose of 5-FU/LV in advanced colon cancer [24]. In addition, the efficacy of irinotecan alone was comparable to that of 5-FU/LV and irinotecan after failure of 5-FU/LV [25]. Therefore, after failure of FOLFOX, irinotecan single chemotherapy, combination of irinotecan with other doses of 5-FU/LV can be considered.



**Fig. 1.** Time to progression (TTP) curve.



**Fig. 2.** Overall survival (OS) curve.

**Table 4.** Phase II studies on irinotecan, 5-FU, and LV combination chemotherapy for advanced gastric cancer

	Previous chemotherapy	No. of previous chemo-regimen	Regimen	RR (%)	SD (%)	TTP (mo)	OS (mo)
Lorizzo et al. [16]	Not restricted, fluoropyrimidine based, regimen (71.43%) included, no FOLFOX	1	I 180 mg/m <sup>2</sup> D1 LV 200 mg/m <sup>2</sup> bolus D1 5-FU 400 mg/m <sup>2</sup> bolus, 2,400 mg/m <sup>2</sup> over 46 hr	21	21	4	5
Assersohn et al. [15]	Not restricted, fluoropyrimidine based, regimen (97.4%) included, no FOLFOX	1	I 180 mg/m <sup>2</sup> D1 LV 125 mg/m <sup>2</sup> bolus D1 5-FU 400 mg/m <sup>2</sup> bolus, 1,200 mg/m <sup>2</sup> over 48 hr	29	34	3.7	6.4
Seo et al. [14]	Not restricted, fluoropyrimidine based, regimen (75%) included, modified FOLFOX (29%) included	1	I 180 mg/m <sup>2</sup> D1 LV 200 mg/m <sup>2</sup> bolus D1, 2 5-FU 400 mg/m <sup>2</sup> bolus, 600 mg/m <sup>2</sup> over 22 hr D1, 2	18	29	3.2	9.1
Kim et al. [18]	Fluoropyrimidine based regimen	≥ 1	I 150 mg/m <sup>2</sup> D1 LV 20 mg/m <sup>2</sup> bolus D1, 2 5-FU 3,000 mg/m <sup>2</sup> over 48 hr	18.2	18.2	2.3	5.1
Kim et al. [17]	Not restricted, modified FOLFOX (52.6%) included	≥ 1	I 150 mg/m <sup>2</sup> D1 LV 20 mg/m <sup>2</sup> bolus D1, 2 5-FU 400 mg/m <sup>2</sup> bolus, 600 mg/m <sup>2</sup> over 22 hr D1, 2	10	36.7	3.3	10.9
This study	Modified FOLFOX	1	I 150 mg/m <sup>2</sup> D1 LV 20 mg/m <sup>2</sup> bolus D1, 2 5-FU 400 mg/m <sup>2</sup> bolus, 600 mg/m <sup>2</sup> over 22 hr D1, 2	9.1	34.4	2	5.84

5-FU, 5-fluorouracil; LV, leucovorin; RR, response rate; SD, stable diseases; TTP, time to progression; OS, overall survival; I, irinotecan; D, day.

## Conclusion

The modified FOLFIRI regimen as second-line therapy after failure of the modified FOLFOX-4 regimen in patients with advanced gastric

cancer was tolerable, but our study showed a lower response rate than that of other studies on second-line FOLFIRI after failure with various first-line chemotherapy strategies. Re-administration of failed 5-FU/LV with the same dose and with the same infusion method in the modified FOLFIRI regimen could be one of the reasons for this.



Further study on retrying 5-FU/LV with irinotecan after failure of the 5-FU/LV combined regimen in advanced gastric cancer patients is necessary.

## Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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