Irinotecan combined with 5-fluorouracil and leucovorin third-line chemotherapy after failure of fluoropyrimidine, platinum, and taxane in gastric cancer: treatment outcomes and a prognostic model to predict survival

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Abstract

Background The aim of this study was to evaluate the activity and safety of the combination chemotherapy of 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI regimen) after failure of fluoropyrimidine, platinum, and taxane in gastric cancer (GC) and to evaluate the prognostic factors for survival.

Methods Patients received biweekly FOLFIRI chemotherapy as third-line treatment. The FOLFIRI-1 consisted of irinotecan (180 mg/m² in a 2-h infusion) on day 1, and then leucovorin (200 mg/m² in a 2-h infusion) and 5-FU (a 400 mg/m² bolus, followed by 600 mg/m² in a 22-h continuous infusion) on days 1 and 2. FOLFIRI-2 consisted of irinotecan (180 mg/m² in a 2-h infusion) on day 1, and then leucovorin (400 mg/m² in a 2-h infusion) and 5-FU

(a 400 mg/m² bolus, followed by 2400 mg/m² in a 46-h continuous infusion) on day 1.

Results A total of 158 patients were included. The overall response rate was 9.6 % in patients with measurable lesions. The median progression-free survival (PFS) and overall survival (OS) were 2.1 months [95 % confidence interval (CI), 1.7–2.5] and 5.6 months (95 % CI, 4.7–6.5), respectively. The major grade 3/4 toxicity was myelosuppression (36.7 %). Good performance status (PS), fewer metastatic sites, and longer duration from the first-line to third-line chemotherapy were independent prognostic factors affecting both PFS and OS.

Conclusions The FOLFIRI regimen showed antitumor activity and tolerable toxicity profiles against advanced GC in the third-line setting. Patients with good PS, fewer metastatic sites and longer previous treatment duration might have the maximal benefit from third-line chemotherapy.

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Keywords Gastric cancer · Third-line chemotherapy · Irinotecan · FOLFIRI · Prognostic factor

Introduction

Although the incidence rates for gastric cancer (GC) have been steadily declining, it remains a major cause of cancer-related death in the world as well as in Korea [1, 2]. A surgical resection is the cornerstone of treatment in localized GC; however, local and distant relapses are common. For metastatic or relapsed gastric cancer (MRGC), palliative chemotherapy improves the symptoms and quality of life and prolongs overall survival (OS) in comparison to the best supportive care (BSC) alone [3]. However, the reported median progression-free survival (PFS) has been

only 4–7 months, and nearly all patients receiving first-line chemotherapy eventually progress. The median OS after the progression of first-line chemotherapy is only 2–4 months with BSC alone [4, 5]. Recently, two phase III trials comparing second-line chemotherapy with BSC alone showed OS benefit [4, 5], and many previous phase II or retrospective studies have shown similar OS results [6–10]. Therefore, second-line chemotherapy is currently considered a standard of care in MRGC patients with a good performance status (PS) after the failure of first-line therapy, and taxane- or irinotecan-based regimens are commonly used in clinical practice [4, 5, 10]. However, the response rate (RR) of second-line chemotherapy is low, and all patients suffer from disease progression. Many of these MRGC patients who failed second-line treatment still have a good PS and are candidates for third-line chemotherapy. Although the benefit of further chemotherapy has not been proven and there have been few data on third-line therapy, many oncologists, especially in Eastern Asian countries, provide third-line therapy to MRGC patients based on their belief in an OS benefit that originated from their clinical experiences. Considering the small amount of data on third-line chemotherapy and the possible benefits to MRGC patients, the selection of patients who may benefit most from third-line treatment is an important issue.

Irinotecan (CPT-11) is an active agent that has been explored as a single agent or in combination for MRGC treatment. The single agent irinotecan showed a RR of 16 % for MRGC patients who had received prior chemotherapy [11]. Various regimens combining irinotecan with leucovorin and 5-fluorouracil (5-FU) in biweekly schedules, called FOLFIRI regimens, are widely used in GC as a salvage chemotherapy [6–9]; RR was reported to be 10–29 % and OS was reported to be 6.4–10.9 months in the second-line treatment [6–8]. Irinotecan-based regimens including FOLFIRI may be considered a third-line therapy in MRGC patients previously exposed to fluoropyrimidine, platinum, and taxane agents.

Based on this background, this study was conducted to evaluate the efficacy and safety of third-line FOLFIRI chemotherapy. The clinical parameters related to survival outcomes were also analyzed to be helpful in the selection of MRGC patients who may most benefit from third-line therapy.

Materials and methods

Patients

Patients with MRGC who had received FOLFIRI chemotherapy as third-line treatment at three institutions [Seoul National University Bundang Hospital, Seoul National University Hospital, and Seoul Metropolitan Government-

Seoul National University (SMG-SNU) Boramae Medical Center] between March 2003 and August 2011 were consecutively included in this retrospective study.

All patients had to meet the following criteria: histologically confirmed gastric or gastroesophageal junction adenocarcinoma with distant metastases or recurrent nonresectable disease after curative surgical resection; previous treatment failure of all following drugs—fluoropyrimidine (5-FU, capecitabine, TS-1, or uracil-tegafur), platinum (cisplatin or oxaliplatin), and taxane (docetaxel or paclitaxel); FOLFIRI treatment as third-line chemotherapy (no previous exposure to irinotecan); Eastern Cooperative Oncology Group (ECOG) PS ≤ 2 ; adequate bone marrow [absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$ and platelet count $\geq 75,000/\text{mm}^3$] and other organ functions; and no concurrent active malignancy other than GC. Data were collected from the electronic medical records. This study was approved by the Institutional Review Boards of each institution.

Treatment schedule

Two biweekly FOLFIRI regimens were used, as chosen by the attending physician. FOLFIRI-1 consisted of irinotecan (180 mg/m^2 in a 2-h infusion) on day 1, then leucovorin (200 mg/m^2 in a 2-h infusion) and 5-FU (a 400 mg/m^2 bolus, followed by 600 mg/m^2 in a 22-h continuous infusion) on days 1 and 2. FOLFIRI-2 consisted of irinotecan (180 mg/m^2 in a 2-h infusion) on day 1, then leucovorin (400 mg/m^2 in a 2-h infusion) and 5-FU (a 400 mg/m^2 bolus, followed by 2400 mg/m^2 in a 46-h continuous infusion) on day 1. An initial dose reduction (20–30 %) from the first cycle was conducted for some patients depending on patient PS, organ function, and other medical conditions.

Prophylactic antiemetic therapy was routinely given before chemotherapy. In cases of diarrhea, abdominal cramping, or symptoms of cholinergic syndrome that developed immediately after irinotecan infusion, atropine was administered. Loperamide was prescribed prophylactically, and patients were instructed to take loperamide if diarrhea developed. Chemotherapy was continued until documented disease progression, unacceptable toxicity, or patient refusal.

Dose modifications

Treatment was delayed for a minimum of 1 week if the ANC was $<1,500/\text{mm}^3$, platelet count was $<75,000/\text{mm}^3$, or nonhematological toxicities were not improved on the infusion day of FOLFIRI. Nonhematological toxicities (except alopecia) were required to be $\leq$ grade 1 before the next cycle could be started.

Dose modifications and treatment delays were conducted according to the extent of hematological and

nonhematological toxicities. Drug doses were reduced by 20 % for grade 4 neutropenia or thrombocytopenia, neutropenic fever, or other severe nonhematological toxicities $\geq$ grade 3 (except alopecia). An additional 20 % reduction of drug doses was indicated for recurrent febrile neutropenia, grade 4 neutropenia, grade 4 thrombocytopenia, or $\geq$ grade 3 nonhematological toxicities. If grade 2 nonhematological toxicities were repetitively developed and were not tolerable for the patients, a 20 % dose reduction was permitted at the discretion of attending physicians.

Efficacy and safety assessments

Complete blood counts and biochemical tests were repeated before each chemotherapy cycle. Chest X-rays and computed tomography (CT) scans were performed every three cycles or when disease progression was suspected; an abdominal CT including the pelvis was routinely conducted and the chest CT was carried out in selected cases in which the tumor extent had spread to the thoracic cavity or mediastinal or supraclavicular lymph nodes. Tumor responses were classified according to the response evaluation criteria defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0). Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Statistics

All patients who received at least one cycle of FOLFIRI treatment were included in efficacy or safety analyses. PFS was measured from the initiation of FOLFIRI chemotherapy until the time of the first occurrence of progression, death from any cause, or to the date of last follow-up if none of the preceding events had occurred. OS was determined by the interval from the first day of FOLFIRI treatment to death or the last day of follow-up visit. PFS and OS were obtained using the Kaplan–Meier method. The difference between the curves was analyzed using the log-rank test. After univariate analyses using the Kaplan–Meier method, variables that were significantly associated with poor survival time (variables with $P < 0.05$) were selected, and a Cox proportional hazards regression was conducted for multivariate analyses by the ‘enter’ method. SPSS for Windows, version 17.0 (SPSS, Chicago, IL, USA) was used for all statistical analysis.

Results

Patients

One hundred and fifty-eight patients were included in this study. Patient characteristics are listed in Table 1. All

Table 1 Patient characteristics

Characteristics	Number of patients	Percent (%)
Age (years), median (range)	59 (31–80)	
Number of patients		
Assessed for response (measurable)	136	86.1
Assessed for toxicity	158	100.0
Sex		
Male	102	64.6
Female	56	35.4
ECOG performance status		
0–1	112	70.9
2	46	29.1
Primary tumor location		
Upper 1/3 (cardia/fundus)	25	15.8
Mid 1/3 (body)	52	32.9
Lower 1/3 (antrum/pylorus)	56	35.4
Diffuse (entire stomach)	8	5.1
Unknown	17	10.8
Site of metastasis		
Liver	52	32.9
Lung	24	15.2
Peritoneum	86	54.4
Nodal, distant	81	51.3
Bone	14	8.9
Ovary	17	10.7
Number of metastatic sites		
1	60	38
2	70	44.3
≥ 3	28	17.7
Histology		
Adenocarcinoma, well differentiated	4	2.5
Adenocarcinoma, moderately differentiated	51	32.3
Adenocarcinoma, poorly differentiated	82	51.9
Signet-ring cell carcinoma	15	9.5
Unclassified	6	3.8
Disease status		
Initially metastatic	123	77.8
Recurrent	35	22.2
FOLFIRI regimen		
FOLFIRI-1	111	70.2
FOLFIRI-2	47	29.8
Previous chemotherapy		
Fluoropyrimidine		
5-Fluorouracil	86	54.4
Capecitabine	39	24.7
TS-1	44	27.8
Platinum		
Cisplatin	139	88.0
Oxaliplatin	80	50.6
Taxane		
Docetaxel	78	49.4
Paclitaxel	100	63.3

patients were previously treated with fluoropyrimidine, platinum, and taxane before third-line FOLFIRI chemotherapy. The median age was 59 years (range 31–80); 102 were men and 56 women. The median PFS from first-line chemotherapy to third-line FOLFIRI chemotherapy was 10.9 months [95 % confidence interval (CI), 9.9–11.9]. When calculating the PFS from first-line to third-line chemotherapy in individual patients, the interval from the starting date of first-line chemotherapy to the starting date of third-line FOLFIRI therapy was measured regardless of reasons for discontinuing previous first- or second-line chemotherapy whether tumor progression or other causes (i.e., toxicities); however, all patients had experienced tumor progression at the time of initiating FOLFIRI therapy. The main metastatic sites were the peritoneum, abdominal lymph nodes, and liver. The FOLFIRI-1 regimen was administered to 111 patients and the FOLFIRI-2 regimen to 47 patients.

Drug delivery and toxicities

Of the 158 patients, 90 (57.0 %) received chemotherapy with initially reduced doses of FOLFIRI from the first cycle. Among them, 70 patients received chemotherapy with reduced doses of both irinotecan and 5-FU and 20 patients received FOLFIRI with a 5-FU dose reduction only. The causes of the initial dose reduction were previous chemotherapy-induced toxicities ($n = 34$) during the first- or second-line therapy, worsened PS ($n = 25$), older age ($n = 12$), combined comorbidities ($n = 7$), reduced body weight during prior chemotherapy ($n = 7$), and unknown reasons ($n = 5$). Of 68 patients who had initiated FOLFIRI with a full dosage, 37 (54.4 %) required a dose reduction during chemotherapy. Among the 90 patients who had received a reduced dose of FOLFIRI from the first cycle, 8 (8.9 %) patients required further dose reductions. The

median number of administered cycles of chemotherapy was 3 (range, 1–19 cycles; total, 768 cycles). Five patients stopped chemotherapy because of toxicities.

The frequencies of hematological and nonhematological adverse events are presented in Table 2. Myelosuppression was common. The frequencies of severe (grade ≥ 3) neutropenia and anemia were 36.7 and 6.3 %, respectively. Grade 3/4 nonhematological toxicities, which were not common, included stomatitis (1.9 %) and emesis (1.9 %). Febrile neutropenia had developed in two patients, and 5-FU-induced encephalopathy was seen in one patient. There was no treatment-related death.

Efficacy

The median duration of follow-up was 5.2 months (range, 0.5–40.5 months). One hundred thirty-six patients (86 %) had measurable target lesions. Of these 136 patients, 13 patients (9.6 %) achieved a partial response and 41 (30.1 %) had stable disease, showing an overall disease control rate of 39.7 % (Table 3). Twenty-two patients had no measurable lesion and thus the tumor response to chemotherapy was not evaluable. The median PFS was 2.1 months (95 % CI, 1.7–2.5) and the median OS was 5.6 months (95 % CI, 4.7–6.5). Survival curves are shown in Fig. 1.

Clinical parameters related to treatment outcomes

Median PFS and OS between the FOLFIRI-1 and FOLFIRI-2 regimens were not different [PFS 2.3 vs. 1.9 months ($P = 0.264$); OS 6.1 vs. 4.6 months ($P = 0.557$)]. Univariate analysis showed the PFS was significantly associated with a good PS (grade ≤ 1 vs. 2), fewer organs involved by metastasis (≤ 2 vs. ≥ 3), a higher hemoglobin level (≥ 10.0 vs. <10.0 g/dl) before the initiation of

Table 2 Treatment-related adverse events ($n = 158$)

	Grade 1 or 2		Grade 3		Grade 4	
	Number	%	Number	%	Number	%
Hematological						
Anemia	130	82.3	9	5.7	1	0.6
Neutropenia	47	29.7	35	22.2	23	14.6
Thrombocytopenia	31	19.6	3	1.9	–	–
Febrile neutropenia	–	–	2	1.3	–	–
Nonhematological						
Anorexia	42	26.6	–	–	–	–
Emesis	32	20.3	1	0.6	2	1.3
Stomatitis	15	9.5	3	1.9	–	–
Fatigue	36	22.8	2	1.3	–	–
Diarrhea	21	13.3	2	1.3	–	–
Neuropathy	9	5.7	1	0.6	–	–

Table 3 Efficacy analysis

Patients with measurable target lesions ($n = 136$) ^a	
Response to chemotherapy	
Complete remission	0 (0.0 %)
Partial remission	13 (9.6 %)
Stable disease	41 (30.1 %)
Progressive disease	82 (60.3 %)
Response rate	9.6 %
Disease control rate	39.7 %
All patients ($n = 158$)	
Progression-free survival (months), median (95 % CI)	2.1 (1.7–2.5)
Overall survival (months), median (95 % CI)	5.6 (4.7–6.5)

CI confidence interval

^a Patients without measurable lesions ($n = 22$) were excluded **Fig. 1** Progression-free survival (PFS) and overall survival (OS) for all patients ($n = 158$)

FOLFIRI, disease status (recurrent GC after curative surgery vs. initial distant metastasis at the time of GC diagnosis), and a longer duration from the first-line to third-line chemotherapy (≥ 10.9 vs. < 10.9 months). Regarding OS, the results of the univariate analyses were similar except for the disease status and serum albumin level. Patients with a higher serum albumin level (≥ 4.0 vs. < 4.0 g/dl) before the initiation of FOLFIRI showed a longer OS ($P = 0.008$), and the disease status was not related to the OS ($P = 0.115$) in univariate analyses (Table 4). In multivariate analyses using a Cox proportional hazards regression model, a good PS, fewer metastatic sites, and a longer duration from the first-line to third-line

chemotherapy were independently related to both prolonged PFS and OS (Table 5).

Then, we constructed a prognostic model by incorporating all these three clinical parameters [EGOG PS (grade ≤ 1 vs. 2), number of organs involved by metastasis (≤ 2 vs. ≥ 3), and time from first-line to third-line chemotherapy (≥ 10.9 vs. < 10.9 months)]. Patients were subcategorized into three groups: low-risk group, patients with no adverse factor ($n = 51$); intermediate-risk group, patients with one adverse factor ($n = 71$); and high-risk group, patients with two or more adverse factors ($n = 36$). The survival curves according this classification are shown in Fig. 2a, b. The median PFS for low-, intermediate-, and high-risk groups were 4.5, 1.8, and 1.6 months ($P < 0.001$), and the median OS for low-, intermediate-, and high-risk groups were 10.3, 5.2, and 2.9 months, respectively ($P < 0.001$).

Discussion

At the present time, although there have been some studies on salvage chemotherapy for MRGC in which chemotherapy regimens were used as second- or third-line treatments [9, 12–14], studies specifically focused on third-line chemotherapy have been scarce [15, 16]. To our knowledge, this report is one of the largest studies about third-line palliative chemotherapy and the first study on third-line FOLFIRI therapy in MRGC patients. In our study, 158 patients who had been previously exposed to fluoropyrimidine, platinum, and taxane were included. The median PFS and OS were 2.1 and 5.6 months, respectively, and the toxicities were tolerable.

Combination chemotherapy containing fluoropyrimidine plus platinum is globally recognized as the standard first-line treatment in MRGC [17–21]. Based on two recent phase III trials [4, 5], second-line chemotherapy is currently considered a standard of care in MRGC patients after first-line therapy failure. As the benefit of second-line therapy was proven, it is time to investigate the effect of third-line chemotherapy and to find the selection criteria for MRGC patients who may gain maximal benefit from third-line therapy.

In the third-line setting, there have been only a few studies. Most of them reported the combined results of second-line and third-line chemotherapy together and contained a small number of patients in the third-line setting [12–14]. The reported median PFS was 2.1–5.6 months and the median OS was 6.1–7.6 months in those studies. Regarding studies on third-line chemotherapy using a single regimen, there was only one retrospective study [16]. Shimoyama et al. [16] reported the efficacy of third-line weekly paclitaxel in 85 patients with MRGC who were refractory to all three drugs (fluoropyrimidine, irinotecan, and cisplatin);

Table 4 Univariate analysis for progression-free survival (PFS) and overall survival (OS)

	PFS		OS	
	95 % CI	P	95 % CI	P
Age (≥ 70 vs. < 70 years)	4.3 vs. 2.0	0.084	7.5 vs. 5.1	0.070
Gender (male vs. female)	2.4 vs. 2.0	0.077	5.9 vs. 5.1	0.410
PS (grade 0/1 vs. ≥ 2)	2.5 vs. 1.2	< 0.001	6.9 vs. 2.7	< 0.001
Hemoglobin level (≥ 10.0 vs. < 10.0 g/dl)	2.5 vs. 1.8	0.047	6.2 vs. 3.6	0.021
Serum albumin level (≥ 4.0 vs. < 4.0 g/dl)	3.4 vs. 1.9	0.330	8.1 vs. 4.4	0.008
Number of organs involved by metastasis (≤ 2 vs. ≥ 3)	2.3 vs. 1.7	0.020	6.2 vs. 3.5	0.007
Disease status (relapsed vs. initially metastatic)	4.3 vs. 1.9	0.023	7.9 vs. 5.1	0.115
FOLFIRI-1 vs. FOLFIRI-2	2.3 vs. 1.9	0.264	6.1 vs. 4.6	0.557
PFS from first to third-line chemotherapy (≥ 10.9 vs. < 10.9 months)	3.5 vs. 1.7	0.003	7.8 vs. 4.4	< 0.001

PFS progression-free survival, OS overall survival, CI confidence interval, PS performance status

Table 5 Cox proportional hazard regression model

	PFS			OS		
	HR	95 % CI	P	HR	95 % CI	P
Performance status ($\geq$ grade 2 vs. 0/1)	1.7	1.18–2.45	0.004	1.8	1.27–2.66	0.001
Hemoglobin level (< 10.0 vs. ≥ 10.0 g/dl)	1.2	0.87–1.72	0.250	1.3	0.88–1.79	0.212
Serum albumin level (< 4.0 vs. ≥ 4.0 g/dl)	–	–	–	1.5	0.99–2.29	0.058
Number of organs involved by metastasis (≥ 3 vs. ≤ 2)	1.6	1.04–2.54	0.034	1.6	1.03–2.50	0.034
Disease status (initially metastatic vs. relapsed)	1.4	0.95–2.05	0.090	–	–	–
PFS from first- to third-line chemotherapy (< 10.9 vs. ≥ 10.9 months)	1.5	1.09–2.10	0.012	1.7	1.22–2.43	0.002

PFS progression-free survival, OS overall survival, HR hazard ratio, CI confidence interval

Fig. 2 Progression-free survival and overall survival curves according to the risk groups: **a** progression-free survival; **b** overall survival

median PFS and OS were 3.5 and 6.7 months, respectively, and the overall RR was 23.2 %. In another study using various regimens as the third-line therapy, median PFS and OS were 2.6 and 6.4 months, respectively, and the RR was 10.3 % [15].

There has been no study of third-line FOLFIRI treatment in MRGC. Because several prior studies on second-line ($\pm$ later-line) FOLFIRI chemotherapy showed

favorable efficacy and tolerable toxicities [6–9, 22], we explored whether third-line FOLFIRI would be beneficial for MRGC patients. In our study, as expected, third-line FOLFIRI showed tolerable toxicity profiles as in the second-line setting [6–8] and similar efficacy to previously reported studies on third-line therapy in MRGC [15, 16].

Selecting MRGC patients who may gain maximal benefit from third-line treatment is an important issue. Several

studies analyzed the prognostic factors for MRGC patients undergoing second-line chemotherapy. A good PS was the most important prognostic factor of second-line chemotherapy in nearly all studies [6, 23–25]; in addition, a higher hemoglobin level [23–25], longer PFS from first-line chemotherapy [6, 23, 25], and a lower number of metastatic sites [6, 25] were reported as independent prognostic factors for OS. Shim et al. [15] reported a prognostic factor analysis of third-line therapy; poor PS (ECOG PS ≥ 2), low serum albumin level (< 4.0 g/dl), poor histological grade, and shorter PFS following second-line chemotherapy (< 2.7 months) were factors related to poor survival outcome. In our report, poor PS (ECOG PS ≥ 2), the increased number of organs involved by metastasis (≥ 3), and shorter PFS from first-line to third-line chemotherapy (< 10.9 months) were independent factors for poor prognosis in multivariate analysis. In the analysis of Shim et al. [15], various regimens were included as third-line treatment, but our study included patients treated with FOLFIRI alone. In our study, a higher serum albumin level (≥ 4.0 g/dl) was associated with prolonged OS in univariate analysis but did not have statistical significance in multivariate analysis, although there was a trend ($P = 0.058$). In the Shim et al. analysis, the proportion of poor ECOG PS (≥ 2) was more than our study (48.3 vs. 29.1 %). Because the serum albumin level may reflect the patients' general medical status as well as nutritional condition, Shim's study might have had more patients with a low serum albumin, and this could thus make a difference with statistical significance. In the study by Shim et al., the PFS of second-line chemotherapy revealed statistical significance ($P = 0.033$), but PFS of first-line chemotherapy was not a factor related to survival outcome in multivariate analysis ($P = 0.624$). In our study, PFS from first-line to third-line treatment was independently related to survival outcome in univariate and multivariate analyses (Tables 4, 5). In separate analyses putting PFS of second-line therapy into univariate and multivariate analyses instead of PFS from first-line to third-line treatment, PFS of second-line therapy was a factor independently related to survival outcomes (both PFS and OS) also in our study (data not shown). However, we chose to put PFS from first-line to third-line treatment into multivariate analysis or the prognostic model as we considered PFS from first- to third-line therapy more appropriate than PFS of second-line therapy, because PFS during all previous treatments was thought to reflect the overall disease course of individual patients, considering heterogeneous tumor characteristics, different sequences of previously used chemotherapeutic agents, different previous chemotherapy regimens, etc.

Our study has potential limitations because of its retrospective nature. More than half of the patients ($n = 90$)

received initial reduced doses of FOLFIRI from the first cycle and, among 68 patients who had initiated full-dose FOLFIRI, about half of the patients ($n = 37$) experienced a dose reduction during chemotherapy. Considering the favorable safety profiles in our patient population could be achieved with those dose reductions, the appropriate dosage of third-line FOLFIRI therapy in MRGC patients needs to be further investigated in future studies. It is also questionable whether 5-FU in FOLFIRI is necessary in patients who were already exposed to fluoropyrimidine. In vitro studies have shown that irinotecan downregulates thymidylate synthase expression in tumor cells, leading to synergy between irinotecan and 5-FU [26, 27]. In metastatic colorectal cancer (CRC), fluoropyrimidine is usually reintroduced and combined with another drug in second-line therapy even after first-line fluoropyrimidine-based chemotherapy. The 5-FU/leucovorin/oxaliplatin (FOLFOX) regimen showed superior RR and time to progression compared with oxaliplatin alone after front-line irinotecan plus bolus 5-FU/leucovorin therapy in metastatic CRC patients [28]. However, there are few reports about the benefits of reintroducing fluoropyrimidine in combination with a newly introduced drug as salvage palliative treatment in MRGC patients. Considering more toxicities are related to combination treatment, studies about the necessity of reintroducing fluoropyrimidine in combination with other chemotherapeutic agents to MRGC patients are also required [6]. In addition, the prognostic model using three clinical parameters we presented needs to be validated in future well-designed prospective studies.

Nevertheless, our study has importance. The present study included the largest number of MRGC patients for the efficacy analysis of third-line treatment using a homogeneous regimen (FOLFIRI). Moreover, data collection was performed at three institutions, and thus our study is thought to reflect the real clinical situation of third-line chemotherapy in MRGC patients. As studies about parameters associated with treatment outcomes of third-line therapy in MRGC are scarce, the clinical parameters we have identified would be helpful in designing randomized clinical trials on the efficacy of third-line chemotherapy in MRGC patients.

In conclusion, our study showed that the FOLFIRI regimen has antitumor activity and tolerable toxicity profiles and thus would be a good choice as third-line chemotherapy. Especially, it would be more beneficial for patients with good PS, few organs involved by metastasis, and longer PFS from previous chemotherapy.

Conflict of interest Dr. Keun-Wook Lee and Dr. Yung-Jue Bang received honoraria for lecturing from Pfizer. Dr. Yung-Jue Bang has acted as an advisor to Pfizer and received research grants from Pfizer. The other authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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