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ORIGINAL PAPER

Bevacizumab plus FOLFIRI or FOLFOX as third-line or later treatment in patients with metastatic colorectal cancer after failure of 5-fluorouracil, irinotecan, and oxaliplatin: a retrospective analysis

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Abstract Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has shown clinical activity in metastatic colorectal cancer patients when used as either a first-line or second-line treatment. Here, we evaluated the efficacy and safety of bevacizumab plus FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) or FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) in metastatic colorectal cancer cases after failure to FOLFIRI and FOLFOX. Between October 2004 and February 2007, the data on 42 patients with metastatic colorectal cancer after failure of FOLFIRI and FOLFOX were reviewed retrospectively. All patients were treated with bevacizumab plus FOLFIRI or FOLFOX. The median patient age was 57.0 years. The ECOG performance status was 0 or 1 in 27 patients (64.3%). The number of previous chemotherapy regimens was $\geq$3 in 35 patients (83.3%). Thirty-nine patients were evaluable for response. Four patients had partial responses (PRs) and no patient had a complete response (CR), giving an overall response rate of 9.5%. Twenty-two patients (52.4%) had stable disease and 13 patients (31.0%) showed progressive disease. With a median follow-up time of 12.9 months (range 1.0–30.0 months), the median progression-free survival time and the median overall survival time were 5.3 and 9.5 months, respectively. Grade 3 or 4 neutropenia developed in 18 patients (42.9%), including febrile neutropenia in 4 patients (9.5%). Common non-hematologic toxicities were fatigue (21.4%), neuropathy (21.4%), and mucositis (21.4%). Grade 2 or 3 hypertension occurred in 4 patients (9.6%), and grade 1 or 2 proteinuria was seen in 16 patients (38.1%). The frequencies of adverse events related BV, such as bleeding, thrombosis, and gastrointestinal perforation, were within the ranges of previous reports. However, there were no treatment-related deaths. The combination of bevacizumab plus FOLFIRI or FOLFOX showed modest activity and was relatively tolerable in patients with metastatic colorectal cancer refractory to both FOLFIRI and FOLFOX.

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Introduction

Colorectal cancer (CRC) is the second leading cause of death from cancer in the United States [1]. In Korea, CRC is the fourth most common malignancy, with 10,000 new cases and 5,000 deaths each year, and the disease is increasing in incidence [2]. About 20% of CRC patients are diagnosed in metastatic stages and, even if curative surgery is performed, about 40% of patients will experience local or distant recurrences [3].

For decades, 5-fluorouracil (5-FU) was the sole active agent for metastatic CRC. The management of patients with metastatic CRC has changed dramatically over the last 5 years, especially, with the introduction of irinotecan and oxaliplatin. Irinotecan and oxaliplatin are widely used in combination with 5-FU and leucovorin as first-line and second-line treatments for metastatic CRC [4–6].

Bevacizumab (BV) is a recombinant human monoclonal antibody targeting vascular endothelial growth factor (VEGF), which is a key mediator of tumor angiogenesis [7, 8]. The addition of BV to IFL (irinotecan, bolus 5-FU, and leucovorin) was associated with a high response rate (RR) as well as a significant longer time to progression (TTP) and overall survival (OS) in CRC patients [9]. In a second-line setting, BV has also shown improved RR, progression-free survival (PFS), and OS, when combined with FOLFOX (oxaliplatin, 5-FU, and leucovorin). However, patients in the BV-only arm showed PFS rates lower than patients in the control (FOLFOX alone) arm (2.7 vs. 4.7 months) [10].

There are no standard treatments for patients with metastatic CRCs that have progressed after treatment with both irinotecan-based and oxaliplatin-based chemotherapy. In addition, there is little information on the use of BV combination chemotherapy in patients who were heavily pretreated with regimens including irinotecan and oxaliplatin. In this article, we report a retrospective survey of the efficacy and safety of BV plus FOLFIRI (irinotecan, 5-FU, and leucovorin) or FOLFOX in consecutive patients with metastatic CRCs that had refractory to both FOLFIRI and FOLFOX.

Methods

Patients

Between October 2004 and February 2007, a total of 65 consecutive patients with metastatic CRC were treated with BV plus chemotherapy as a third or later-line treatment. To be eligible, patients had previously received at least one course of irinotecan-based chemotherapy and at least one course of oxaliplatin-based chemotherapy, and had histologically confirmed Stage IV CRC. Patients were included if progression to both FOLFOX and FOLFIRI was documented during prior chemotherapy or within 3 months thereafter. Other criteria for eligibility were (1) performance scores (PS) of 0, 1, or 2 on the Eastern Cooperative Oncology Group (ECOG) scale and (2) adequate hepatic [bilirubin <2.0 mg/dl, transaminases levels <3 times the upper normal limit (5 times for patients with liver metastasis), and serum albumin of >2.5 mg/dl], renal (creatinine <1.5 mg/dl), and bone marrow functions [absolute neutrophil count (ANC) >1,500/μl, hemoglobin >9.0 g/dl, and platelets >75,000/μl].

Forty-two of the sixty-five patients who received BV containing chemotherapy during this period were deemed to fit our eligibility criteria and were included in this analysis. Of the 23 excluded patients, 8 had no measurable disease, 8 did not have refractoriness both FOLFIRI and FOLFOX, 4 received other combination regimens with BV in third-line settings, and 3 did not have bone marrow or organ function that complied with the present criteria.

Study design and treatment

The Institutional Review Board of the Asan Medical Center approved this retrospective study. All patients had previously been intensively treated with combination chemotherapy. We therefore selected BV plus FOLFIRI to avoid cumulative oxaliplatin-induced neuropathy. In patients who had not tolerated irinotecan in previous treatments, we used BV plus FOLFOX.

Among the 42 patients, 18 patients received BV plus FOLFIRI and 24 patients received BV plus FOLFOX. BV (5 mg/kg) was administered intravenously (IV) on day 1 over 90 min, prior to administration of irinotecan and oxaliplatin. FOLFIRI consisted of irinotecan (150 mg/m^2) IV over 2 h, and leucovorin (200 mg/m^2) IV over 2 h, followed by a 5-FU (400 mg/m^2) IV bolus on day 1, and 5-FU (1,200 mg/m^2) by continuous IV over 22 h. FOLFOX consisted of oxaliplatin (85 mg/m^2) IV over 2 h, and leucovorin (200 mg/m^2) IV over 2 h, followed by a 5-FU (400 mg/m^2) IV bolus on day 1, and 5-FU (1,200 mg/m^2) by continuous IV over 22 h. Patients received BV plus FOLFIRI or BV plus FOLFOX once every 2 weeks. The treatment including BV plus FOLFIRI or FOLFOX was continued until progression.

Evaluation and statistical analysis

Our primary objective was to assess response rate, and secondary objectives were to evaluated OS, PFS, and

toxicity. Descriptive statistics were reported as proportion and medians. Tumor responses were assessed by RECIST criteria every 6–8 weeks [11]. Radiologic evaluation consisted of a chest X-ray and an abdominopelvic CT scan. PFS was defined as the time from the commencement of treatment to disease progression or death. OS was defined as the time from the commencement of treatment to death from any cause. Survival curves were estimated using the Kaplan–Meier method. Safety was assessed in terms of toxicity and evaluated based on the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. All analyses were performed using SPSS 12.0 for Windows.

Results

Patient characteristics

The median patient age was 57.0 years. The ECOG performance status was 0 or 1 in 64.3% of patients. The number of previous chemotherapy regimens was ≥3 in 35 patients (83.3%). Prior to this study, all patients had progressed during or shortly after FOLFIRI and FOLFOX. No patients were pretreated BV as a first- or second-line treatment (Table 1).

Response to treatment

The median number of cycles of BV treatment was 5.5 (range 1–26). Four patients had partial responses (PRs) and no patient had a complete response (CR), giving an overall response rate of 9.5%. Twenty-two patients had stable disease (SD) (52.4%), and thus the disease was controlled in 26 patients (61.9%) (Table 2).

Survival outcome

Of the 42 patients, 15 (35.7%) remained alive at a median follow-up time of 12.9 months (range 1–30 months). The median PFS was 5.3 months (range 1.0–13.6 months), the median OS was 9.5 months (range 1.0–25.7 months), and the 1-year OS rate was 31.5% (Fig. 1). Treatment failure was caused by disease progression (86.1%), inability to tolerate treatment (11.1%), or other reason (2.8%).

Safety and toxicity

The 42 patients received 297 cycles of chemotherapy. Grade 3 or 4 neutropenia developed in 18 patients (42.9%), including febrile neutropenia in 4 patients (9.5%). Common non-hematologic toxicities were fatigue (21.4%), neuropathy (21.4%), and mucositis (21.4%). Grade 2 or 3 hypertension occurred in 4 patients (9.6%) and grade 1 or 2 proteinuria was noted in 16 patients (38.1%). Deep vein thrombosis (DVT) and pulmonary embolism (PE) were observed in one patient, respectively. The patient who had DVT was treated without anticoagulation or any

Table 1 Baseline patient characteristics

	Total patients ($n = 42$)
Median age (range)	57 (34–76)
Sex (male/female)	22/20
ECOG Performance status	
0 or 1	27
2	15
Histologic differentiation	
Well	1
Moderate	33
Poorly	4
Others	4
Primary tumor site	
Colon/Rectum	23/19
Number of metastatic sites	
1	7
2	18
≥3	17
Sites of metastases	
Liver	32
Lung	15
Distant lymph node	19
Peritoneal seedings	13
Number of previous palliative chemotherapy regimens	
2	7
3	19
≥4	16
Prior treatment	
Irinotecan and oxaliplatin	42
BV	0

Note: BV, bevacizumab

Table 2 Responses to treatment

Response	Total patients ($n = 42$)	
	Number	%
Complete response (CR)	0	0.0
Partial response (PR)	4	9.5
Stable disease (SD)	22	52.4
Progressive disease (PD)	13	31.0
Not assessable	3	7.1
Objective response (CR + PR)	4	9.5
Disease control (CR + PR + SD)	26	61.9

intervention (grade 2). While the patient with PE (grade 4) was treated with low molecular weight heparin and bevacizumab was discontinued. Bleeding events (grade 2) developed in two patients (4.8%) and all of them had minor bleeding at suspicious site of locoregional recurrence. There were two reports (4.8%) of gastrointestinal perforation. The presentation of these events varied in type and severity, from the incidental finding of air to perforation with peritonitis and abscess. One case was asymptomatic and the other one that underwent the primary repair of small intestine was recovered without complication. However, there were no treatment-related deaths (Table 3).

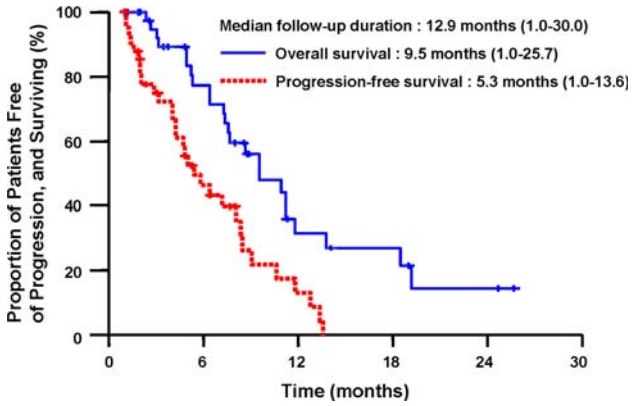

Fig. 1 Survival analysis of all patients

Table 3 Adverse events based on CTCAE version 3.0

Adverse events	Grades 1 or 2 (n^a)	Grades 3 or 4 (n^a)	All grade (n^a)
Hematologic			
Neutrophils	13	18	31
Febrile neutropenia	0	4	4
Platelets	3	0	3
Hemoglobin	9	2	11
Non-hematologic			
Nausea/vomiting	1	2	3
Diarrhea	2	1	3
Constipation	1	0	1
Mucositis	8	1	9
Neuropathy	6	3	9
Fatigue	6	3	9
Elevation of AST/ALT	10	0	10
Adverse events related BV			
Hypertension	2	2	4
Proteinuria	16	0	16
Thrombosis/thrombus/embolism	1	1	2
Bleeding	2	0	2
Gastrointestinal perforation	1	1	2

Note: BV, bevacizumab

[a] *n*, number of patients who had each adverse events

Discussion

This study demonstrated that the combination of BV with either FOLFIRI or FOLFOX was associated with an overall response rate of 9.5% in patients with metastatic CRC refractory to both FOLFIRI and FOLFOX. The median PFS and OS values were 5.3 and 9.5 months, respectively.

The combination of 5-FU/leucovorin with either irinotecan or oxaliplatin has been widely used as a first-line or second-line chemotherapy regimen in patients with metastatic CRC [4–6]. When combinations of these three standard drugs have failed, however, there are few accepted treatment options. Only a few studies on third-line or later treatment in patients with metastatic CRC pretreated with 5-FU/leucovorin, irinotecan, and oxaliplatin have been published (Table 4). Mitomycin-based chemotherapy or capecitabine single agent treatment showed minimal activities in these settings [12–15]. In contrast, cetuximab combined with irinotecan has shown promising activity after failure of both irinotecan-based and oxaliplatin-based chemotherapy. In these studies, the response rates were 20–25% and median TTP and OS values were 4.7–5.5 months and 9.8–10.4 months, respectively [16, 17]. Recently, two randomized phase III trials of monoclonal antibody against epidermal growth factor receptor were reported in patients with chemotherapy-refractory metastatic CRC: The results from cetuximab monotherapy in third-line patients has shown a statistically significant improvement in OS compared with best supportive care (BSC) [18]. In a study by Van Cutsem et al. [19], significant improvement of median PFS was shown for treatment with panitumumab compared with BSC alone in patients with chemo-refractory CRC.

Although the response rate was low in the present study, our PFS and OS data were comparable to those of previous cetuximab studies [16, 17, 20]. As the majority of our patients had received three or more previous courses of chemotherapy, and as 15 (35.7%) patients had poor performance status (ECOG $\geq$ 2), the results of the current study are encouraging. A small pilot study showed that the combination of BV plus FOLFIRI resulted in modest efficacy with an objective response rate of 28.5%, a median TTP of 7.0 months, and a median OS of 12.1 months, in patients with metastatic CRC that had progressed after irinotecan and oxaliplatin chemotherapy [21]. These findings are comparable to those of our study. The TRC-0301 study showed, however, that the combination of BV and 5-FU/leucovorin was associated with a low objective

Table 4 Summary of data from third-line clinical trials in patients with metastatic colorectal cancer after failure of irinotecan, oxaliplatin, and 5-fluorouracil

Study and treatment [Reference]	No. of patients	RR (%)	Median TTP (months)	Median OS (months)
S-1 [26], phase II	28	14.3	3.0	13.8
MMC and Raltitrexed [15], phase II	21	No response	2.3	5
MMC and Capecitabine [12], phase II	21	4.8	2.6	6.8
Capecitabine [13], phase II	28	7	4	6
Capecitabine [14], phase II	20	No response	2.8	6.1
BV and 5-FU/LV [22], phase II	100	4	3.5[a]	9
Cetuximab and Irinotecan [17], phase II	55	25.4	4.7	9.8
Cetuximab and Irinotecan [16], phase II	65	20	5.5	10.4
Cetuximab versus	287	6.6	1.9[a]	6.1
Best supportive care [18], phase III	285	No response	1.8[a]	4.6
Panitumumab versus	231	10	1.9[a]	–
Best supportive care [19], phase III	232	No response	1.7[a]	–

Note: No., number; RR, response rate; TTP, time to progression; OS, overall survival; MMC, Mitomycin-C; BV, bevacizumab; 5-FU/LV, 5-fluorouracil/leucovorin

[a] Median progression-free survival

response (1%), a low PFS (3.5 months), and a low OS (9.0 months) [22]. These data suggest that a BV-containing regimen may bring about disease stabilization in only some patients. The between-study discrepancy may be related to differences in patient selection and the combinations of chemotherapy used.

It is interesting to note that four of our patients showed PRs. All four of these patients had earlier demonstrated resistance to chemotherapy with both FOLFIRI and FOLFOX. The PRs can be partly explained by the "normalization" of the vasculature by BV treatment, with resultant decreases in tumor interstitial pressures, which in turn enhanced the delivery of the drugs co-administered with BV [23]. In patients with breast cancer, eight patients who were refractory to cyclophosphamide and methotrexate treatment crossed over to a regimen of BV with cyclophosphamide. One patient showed PR and five patients revealed SD. Taken together, the data support the finding that BV may circumvent resistance to cytotoxic agents in patients with tumors resistant to such drugs [24]. No patient in the present study were pretreated with BV-containing regimens because BV was not reimbursed at the study period as a first- or second-line treatment in Korea.

The safety profile seen in this study was similar to those observed in previous studies featuring BV-containing regimens. The frequencies of BV-related adverse events, such as hypertension, thrombosis, or bowel perforation, were within the ranges of previous reports [9, 10, 22, 25].

In conclusion, these data demonstrate that the addition of BV to FOLFIRI or FOLFOX provides interesting PFS and OS for patients with metastatic CRCs refractory to both irinotecan- and oxaliplatin-based chemotherapy. A large-scale prospective study is needed to determine the value of combinations of BV with other chemotherapy, in third-line and later-line settings, and the present study serves to emphasize the importance of such work.

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