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Original Article

Retrospective analysis on the clinical efficacy of bevacizumab combined with FOLFOX4 in the first line treatment of metastatic colorectal cancer

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Objectives: The addition of bevacizumab to standard chemotherapy has been improved survival outcomes in patients with metastatic colorectal cancer. However, the combination of bevacizumab with oxaliplatin-based chemotherapy as first-line treatment showed limited survival benefit. The purpose of this study was to investigate the clinical efficacy and toxicity of the combination of bevacizumab to oxaliplatin and leucovorin (FOLFOX4) in the first-line treatment of patient with metastatic colorectal cancer.
Methods: Between December 2004 and September 2009, medical records of patients who were diagnosed with metastatic colorectal cancer and received the first line chemotherapy with bevacizumab and FOLFOX4, were retrospectively reviewed.
Results: A total of forty patients were analyzed. The median age of the patients was 55 years (range, 33-80), and 55% was male. The patients received a total of 206 cycles of therapy (median 4 cycles per patient; range 1 – 15 cycles). Of these 40 patients, none achieved complete response (CR) and 15 achieved a partial response (PR), for the overall response rate (ORR) 37.5% (95% CI, 22.5-52.5). Median progression free survival (PFS) was 6.9 months (95% CI, 3.4-10.5) and median overall survival (OS) was 22.6 months (95% CI, 17.3-27.8The most common grade 3 or 4 hematologic toxicity and non-hematologic toxicity were neutropenia (10.0%) and diarrhea (10.0%), respectively. Two patients experienced gastrointestinal perforation.
Conclusions: In this study, the combination bevacizumab with FOLFOX4 was associated with favorable OS, but did not showed favorable PFS and ORR.

Key Words: Bevacizumab, Colorectal cancer, FOLFOX

Metastatic colorectal cancer is a common cancer for which significant advances in treatment have been made. The integration of oxaliplatin or irinotecan to combination with 5-fluorouracil (5-FU) and leucovorin as front-line therapy for treatment of metastatic colorectal cancer has been associated with significant improvements in progression-free survival (PFS) and overall survival (OS), compared with 5-FU and leucovorin chemotherapy.[1-4]

In the last decade highly promising new molecular target agents, such as bevacizumab, cetuximab, or panitumumab, have been introduced into treatment of metastatic colon cancer for more improved outcomes.[5-7] The integration of bevacizumab, which is a recombinant, humanized

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monoclonal antibody against vascular endothelial grow factor, to 5-FU-based combination chemotherapy has clearly led to additional improvements of survivals in the both first-line and second-line treatment of patients with metastatic colorectal cancer.[5,8-10] Recently, however, the combination of bevacizumab to oxaliplatin-based regimen for the first-line treatment conferred only a marginal improvement of survival. The NO16966 trial, which is a large randomized phase III study to evaluate the efficacy of bevacizumab combined oxaliplatin based chemotherapy (capecitabine [CapeOX] or 5-FU/leucovorin [FOLFOX]) as the first-line chemotherapy, demonstrated that the addition of bevacizumab to oxaliplatin-based chemotherapy was associated with improved PFS, but did not reached statistical significance in overall survival.[5] Two meta-analyses showed, although the use of bevacizumab in first-line treatment for metastatic colon cancer was associated with improvement of survival outcomes, the advantage of survival was not evident when combined with oxaliplatin-based chemotherapy.[11,12] Consequently, there is some debate that oxaliplatin-based chemotherapy regimen may not be optimal partner for bevacizumab in practice or clinical trials.

This retrospective study was designed to investigate the clinical efficacy of bevacizumab combined to oxaliplatin and leucovorin (FOLFOX4) in patient with metastatic colorectal cancer.

MATERIALS AND METHODS

Patients

We obtained all the clinical data from the medical records retrospectively. Between December 2004 and September 2009, a total of 40 patients, who were newly diagnosed with metastatic colorectal cancer, was received the combination chemotherapy with FOLFOX4 plus bevacizumab. There were no limitations on the Eastern Cooperative Oncology Group (ECOG) performance status. The Institutional Review Board (IRB) of the Kosin Medical Center approved this retrospective study (91961-ABG-15-029).

Treatment schedule and toxicity and response assessment

FOLFOX4 chemotherapy was given every 2 weeks and consisted of intravenous (IV) oxaliplatin (85 ㎎/㎡) over 2 hours, IV leucovorin (200 ㎎/㎡) over 2 hours, followed by bolus 5-FU (400 ㎎/㎡) and infusion 5-FU (600 ㎎/㎡) over 22 hours, and 5-FU and leucovorin were repeated in day 2. Bevacizumab was administered IV 5 mg/kg over 30–90 minutes every 2 weeks, prior to FOLFOX4.

Treatment was continued until tumor progression, unacceptable toxicity or refusal by patients. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTC-AE) of the National Cancer Institute (NCI), version 3.0. Only grade 3 or 4 toxicities were collected by retrospective medical record review. The dose and schedule of FOLFOX4 and bev-

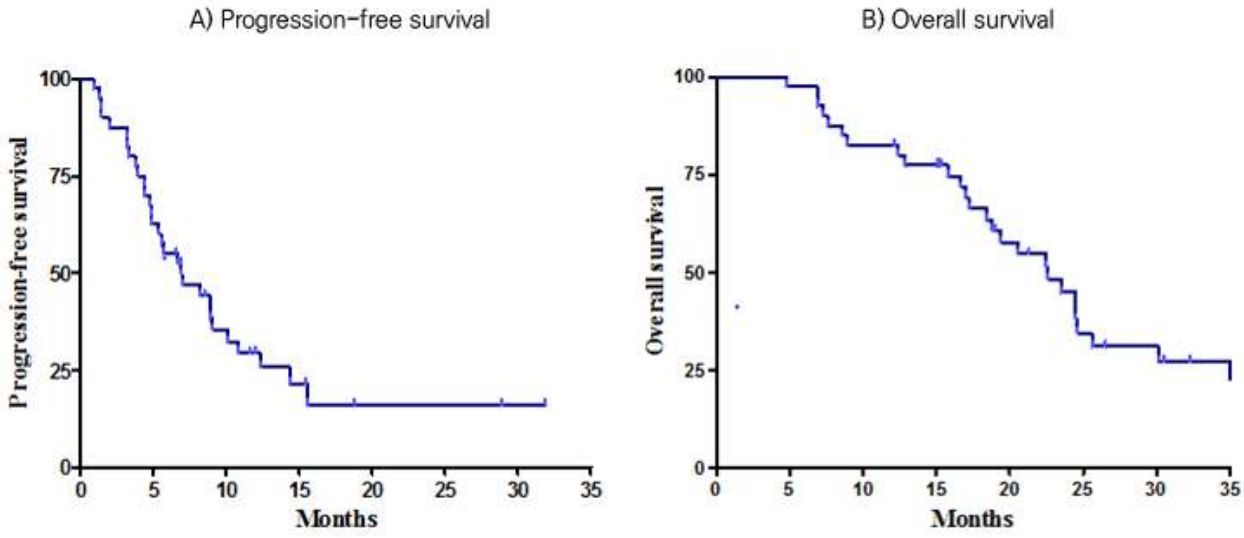

Fig. 1. Survival curves by the Kaplan-Meier method.

acizumab was modified according to the physician's discretion according to toxicity profiles. Tumor response was assessed every three cycles by Response Evaluation Criteria in Solid Tumor (RECIST) guideline. Progressive disease was defined as a 20% increase from tumor size at the time of best response after chemotherapy.

Statistics

The primary objective of this study was to investigate the efficacy of the combination of bevacizumab and FOLFOX4 as the first-line treatment in patients with metastatic colorectal cancer. Efficacy measures included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). OS was defined as the time from initiation of study therapy to date of death from any cause. PFS was defined as time from initiation of study therapy to date of progressive disease (PD) or death due to any cause. Patients who died without documented PD were considered to have had PD at the time of death. Survival curves were estimated using the Kaplan-Meier method (Fig. 1). A Cox proportional hazard model was used to determine factors independently prognostic for PFS and OS.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. The median age of the patients was 55 years (range, 33-80), and 55% of the patients were male. Most of the patients had good ECOG performance status scores of 0 or 1 (77.5%). Twenty one patients (52.5%) had primary colon cancer, and the most common metastatic organ was the liver (67.5%). Twenty five patients (62.5%) had history of prior resection of primary tumor, and 18 (45.0%) received adjuvant treatment.

Table 1. Patient characteristics (n = 40)

Characteristic	Data
Age, years [median (range)]	55 (33-80)
≤ 60 years	28 (70.0)
〉 60 years	12 (30.0)
Gender [n (%)]	
Male	22 (55.0)
Female	18 (45.0)
Site of primary tumor [n (%)]	
Colon	21 (52.5)
Rectum	19 (47.5)
ECOG PS [n(%)]	
0-1	31 (77.5)
≥ 2	9 (22.5)
Number of metastatic site [n (%)]	
1 site	21 (52.5)
≥ 2 sites	19 (47.5)
Site of metastasis [n (%)]	
Liver	27 (67.5)
Lung	13 (32.5)
Peritoneum	3 (7.5)
Lymph nodes	7 (17.5)
Bone	12 (30.0)
Prior resection of primary tumor [n (%)]	25 (62.5)
Prior adjuvant treatment [n (%)]	18 (45.0)
Initial CEA level(ng/mL) [median(range)]	29.5 (0.8-2359.0)
〈 3.5 ng/mL	4 (10.0)
≥ 3.5 ng/mL	36 (90.0)

ECOG: Eastern Cooperative Oncology Group
PS: performance status
CEA: carcinoembryonic antigen

Treatment and Toxicity profile

The 40 patients received a total of 206 cycles of chemotherapy with bevacizumab plus FOLFOX4. The median of cycles was 4 (range, 2-13), 14 patients (35.0%) received more than 6 cycles of chemotherapy. Five patients (12.5%) discontinued chemotherapy due to toxicities. Ten patients (75%) received second-line chemotherapy after disease progressed.

The most common grade 3 or 4 hematologic toxicity and non-hematologic toxicity were neutropenia (10.0%) and diarrhea (10.0%), respectively. Febrile neutropenia and peripheral neuropathy more than grade 3 were not observed. However, two patients (5.0%) experienced gastrointestinal perforation and 1 patient died from that.

Table 2. Toxicity profile (According to NCI-CTCAE1)version3.0)

	Grade III or IV [n(%)]
Hematologic	
Anemia	0
Neutropenia	4(10.0)
Thrombocytopenia	0
Febrile neutropenia	0
Non-hematologic	
Nausea	0
Anorexia	1(2.5)
Diarrhea	4(10.0)
Peripheral neuropathy	0
GI bleeding	0
GI perforation	2(5.0)
Hypertension	0
Proteinuria	1(2.5)

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
GI: gastrointestinal

Tumor response & Survival

All 40 patients had measurable lesions and were assessable for response. None of these patients achieved a complete response (CR), and 15 patients had partial response (PR), for the overall response rate (ORR) 37.5% (95% CI, 22.5-52.5). Eighteen patients had stable disease (SD), and the disease control rate (CR+PR+SD) was 82.5% (95% CI, 70.0-92.5) (Table 2).

The median duration of follow-up was 32.3 months (95% CI, 29.7-34.8 months). The median PFS and OS were 6.9 (95% CI, 3.4-10.5 months) and 22.6 months (95% CI, 17.3-27.8 months), respectively. The 1-year survival rate was 82.5%, and the 2-year was 44.8%.

DISCUSSION

Unprecedented advances in survival have been recognized during past decade with systemic chemotherapy in patients with metastatic colorectal cancer. The combination chemotherapy of three active drugs (5-FU/leucovorin/irinotecan or oxaliplatin) demonstrated significant advantages in survival,[13] and the corporation of molecular target agents in first-line treatment has shown more improved outcomes.[5-7] Our study was to evaluate the efficacy and safety of the combination chemotherapy of bevacizumab and FOLFOX4 in metastatic colorectal cancer patients as front-line chemotherapy. Although our study did not show favorable ORR and median PFS, median OS of 22.6 months was comparable with the results of others studies of the combination of bevacizumab with oxaliplatin-based regimen.

Bevacizumab was initially studied in colorectal

Table 3. Tumor responses and results of treatment

Responses	[n %)]	95% CI
Complete response	0 (0)	-
Partial response	15 (37.5)	22.5-52.5
Stable disease	18 (45.5)	30.0-62.5
Progressive disease	7 (17.5)	7.5-30.0
Overall response rate	15 (37.5)	22.5-52.5
Disease control rate	33 (82.5)	70.0-92.5

CI: confidence interval

cancer, and approved by US Food and Drug Administration (FDA) in 2004 as first-line treatment of metastatic colorectal cancer. The pivotal trial demonstrated that the combination of bevacizumab to irinotecan, 5-FU, and leucovorin improved median OS from 15.6 months to 20.3 months ($P < 0.001$).[9] Subsequently, in the NO16966 phase III trial, 1401 patients with metastatic colorectal cancer were randomized to receive FOLFOX or CapeOX, with bevacizumab or placebo. Median PFS was significantly increased when bevacizumab was added to FOLFOX or CapeOx (9.4 months in bevacizumab group vs. 8.0 months in placebo group, HR 0.83, 97.5% CI 0.72-0.95, $P = 0.0023$), however, there was no significant OS improvement (21.3 months in bevacizumab group vs. 19.9 months in placebo group, HR 0.89, 97.5% CI 0.76-1.03, $P = 0.077$). The authors suggested that no difference in OS between two groups potentially was influenced by higher early withdrawal rate in bevacizumab group because of unacceptable toxicities.[5] However, two meta-analyses demonstrated that the bevacizumab in first-line treatment chemotherapy in metastatic colorectal cancer improved overall survival (Macedo et al., HR 0.84, 95% CI 0.77-0.91, and Meyerhardt et al., HR 0.85, 95% CI 0.78-0.93) but the survival benefit was diminished in oxaliplatin-based regimen (Macedo et al., HR 0.89, 95% CI 0.79-1.00, and Meyerhardt et al., HR 0.96, 95% CI 0.66-0.97).[11,12] Therefore, the addition of bevacizumab to oxaliplatin-based chemotherapy as first line chemotherapy has not evidently shown overall survival benefit. Consequently, further studies are required to confirm of the combination of bevacizumab and oxaliplatin-based regimen as the first-line chemotherapy.

Nevertheless, the addition of bevacizumab to first-line chemotherapy has improved survival to almost 2 years. In a pooled analysis of 25 published trials, the combination of bevacizumab to oxaliplatin-based chemotherapy as first-line treatment demonstrated that median PFS and OS were 10.3 (range, 7.8-13.8 months) and 23.7 months (range 17.2-32.0 months), respectively.[14] These results were comparable to those of a 29 pooled analysis of the combination of bevacizumab to irinotecan/5-FU/leucovorin (FOLFIRI)

that demonstrated median PFS and OS were 10.8 (95% CI, 8.9-12.8 months) and 23.7 months (95% CI, 18.1-31.6 months), respectively.[15] Our study showed similar median OS of 22.6 months with these results. However, it is unclear if this survival is due to the additional effect of bevacizumab, because median PFS of 6.9 months was lower than results of other studies. Because of small number of patients in this study and a retrospective nature, we should caution to interpret these results.

VEGF is a diffusible, homodimeric glycoprotein produced by healthy and neoplastic cells, and is a key promoter of angiogenesis under both physiological and pathological conditions, including tumor progression.[16] Because of the important role of VEGF in vascular function and physiological angiogenesis, its inhibition by bevacizumab has been noted to cause serious adverse events, including wound dehiscence, bleeding, thromboembolic events, bowel perforation, and neutropenia.[17] A recent meta-analysis of 16 randomized control trials showed that bevacizumab in combination with chemotherapy in patients with a variety of advanced solid tumors was associated with a higher incidence of treatment-related mortality than chemotherapy alone, with relative risk of 1.33 (95% CI, 1.02-1.73, P = 0.04). In that study, the most common causes of death were hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal track perforation (7.1%).[18] Another meta-analysis of 17 randomized trial to determine the risk of gastrointestinal perforation associated with bevacizumab reported that the addition of bevacizumab significantly increased the risk of gastrointestinal perforation compared with chemotherapy alone (Relative risk: 2.14, 95% CI 1.19-3.85, P = 0.011) and the incidence of gastrointestinal perforation was 0.9% (95% CI, 0.7-1.2) among patients receiving bevacizumab, with a mortality or 21.7% (95% CI, 11.5-37.0). Among patients with various tumor types, notably, the relative risk was 3.10 (95% CI, 1.26-7.63, P = 0.013) for colorectal cancer.[19] The risk of gastrointestinal perforation in patients with colorectal cancer may be enhanced because of predisposing gastrointestinal toxicity (e.g. bowel perforation) from chemotherapy regimens and/or pelvic radiation in patients with an intact tumor, and bevacizumab-induced changes in tumor vasculature.[20-22] In our study, two of a total of 40 patients (5.0%) experienced gastrointestinal perforation, and one of both was died from that event. However, both patients had no history of previous pelvic irradiation. Because gastrointestinal perforation is a fetal outcome in patients who are receiving with bevacizumab containing chemotherapy, clinicians need to pay for this complication to occur.

In conclusion, our results showed that the addition of bevacizumab to FOLFOX4 as first-line chemotherapy was associated with favorable overall survival in patients with metastatic colorectal cancer. However, because PFS of our study was not comparable with that of other studies, the definitive role of bevacizumab should be explored further investigations.

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