Bevacizumab induced intestinal perforation in patients with colorectal cancer

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Purpose: Bevacizumab has been used as a promising drug for metastatic colorectal cancer in combination with chemotherapeutic agents. However, it has a few serious adverse effects, such as intestinal bleeding or perforation. The purpose of this study is to identify the clinical characteristics of intestinal perforation induced by bevacizumab in colorectal cancer patients.

Methods: From January 2007 to June 2018, a total of 488 patients underwent chemotherapy with bevacizumab for metastatic colorectal cancer. Medical records were reviewed retrospectively.

Results: Nine patients (1.8%) were identified with intestinal perforation induced with bevacizumab. The median age was 59 years (range, 36–68 years). The primary tumor site was the sigmoid colon in six patients, the rectum in three patients. The liver was the most common metastatic organ (7 patients). Perforation sites were primary tumor site of the colorectum in four patients and the small bowel in five patients. Intestinal perforation was developed after a median of 3 chemotherapy cycles (range, 1–15 cycles), and a median of 7 days (range, 3–32 days) after chemotherapy. One patient expired due to sepsis.

Conclusion: Bevacizumab induced intestinal perforation is a lethal adverse effect in patients with colorectal cancers. The characteristics of intestinal perforation varied according to perforation site, previous chemotherapy cycles, and clinical course. Careful monitoring is necessary with the use of bevacizumab in conjunction with chemotherapeutic agents.

Keywords: Colorectal neoplasms, Tumor, Intestinal perforation, Bevacizumab

INTRODUCTION

Bevacizumab, a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor, is an antiangiogenic agent approved for the treatment of multiple solid tumors. It has shown promise as a clinical agent against metastatic colorectal cancer, and particularly in combination with chemotherapy [1]. With increased use of bevacizumab, serious adverse effects are being reported more frequently, including hypertension, proteinuria, hem-

orrhage, thrombosis, fistula formation, and bowel perforation [2–4]. In two phase 3 trials of bevacizumab in colorectal cancer, intestinal perforation was an uncommon adverse event occurring at rates of only 1.5% and 1.1%, though serious and lethal. Here, the purpose of this study is to identify the clinical characteristics of intestinal perforation induced by bevacizumab in colorectal cancers.

METHODS

From January 2007 to June 2018, a total of 488 patients underwent chemotherapy with bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA, USA) with metastatic colorectal cancers. Medical records were reviewed retrospectively. The study was approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB 2019-01-013) and performed in accordance with the principles of the Declaration of Helsinki.

The use of chemotherapy was applied in patients younger than 75 years of age and having appropriate bone marrow, liver, and renal function (hemoglobin > 10 g/dL, leukocyte count > 4,000/mm³, platelets > 100,000/mm³, bilirubin < 2.0 mg, aspartate transaminase/alanine transaminase < 1.25 normal value, creatinine

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< 1.25 × normal value). The activity level was applied to patients with 0 to 2 using Eastern Cooperative Oncology Group criteria.

Bevacizumab was administered by intravenous infusion at 5 mg/kg in combination with irinotecan (FOLFIRI) at 130–180 mg/m² by 2-hour infusion with 5-fluorouracil at 400 mg/m² by bolus infusion followed by 600 mg/m² continuous infusion for 22 hours, and with leucovorin at 20 mg/m², every 2 weeks. With a FOLFOX regimen, bevacizumab was administered with oxaliplatin (FOLFOX) at 85 mg/m² by 2-hour infusion with 5-fluorouracil at 400 mg/m² by bolus infusion followed by 600 mg/m² continuous infusion for 22 hours, and with leucovorin at 20 mg/m².

For the patients with intestinal perforation induced by bevacizumab, clinical characteristics were reviewed such as perforation sites, surgery of intestinal perforation, postoperative complication, chemotherapy cycles, and interval between chemotherapy and intestinal perforation.

RESULTS

Of the 488 patients, nine patients (1.8%) were identified with intestinal perforation induced by bevacizumab. The median age was 59 years (range, 36–68 years). Primary tumor site was the sigmoid colon in six patients, the rectum in three patients. The liver was the most common metastatic organ in seven patients. Six patients un-

Table 1. Characteristics of bevacizumab induced intestinal perforation in colorectal cancer

Characteristic	Patients (n = 9)
Sex (male:female)	6:3
Age (yr)	59 (36–68)
Primary tumor site (colon:rectum)	6:3
Metastasis site	
Liver	7
Lung	1
Peritoneum	3
Ovary	1
Resection of primary tumors (yes:no) ^{a)}	6:3
Perforation site (small bowel:colorectum) ^{b)}	5:4
Perforation at primary tumor sites	3
Concurrent chemotherapy regimen	
FOLFOX	4
FOLFIRI	5
Bevacizumab, total use (cycle)	3 (1–15)
Interval between chemotherapy and perforation (day)	7 (3–32)
Previous history of intestinal obstruction (yes:no)	4:5

Values are presented as median (range).

^{a)}Low anterior resection in 5 cases, sigmoidectomy in 1 case, colostomy in 1 case. ^{b)}The jejunum in 3 cases, the ileum in 2 cases, the sigmoid colon in 2 cases, the rectum in 1 case and anastomotic site in the rectum in 1 case.

derwent resection of primary tumor. Perforation sites were the colorectum in four patients, the small bowel in five patients (3 in the jejunum and 2 in the ileum). Primary tumor site perforation was in three patients. Intestinal perforation developed after a median of three chemotherapy cycles (range, 1–15 cycles; 3–4 cycles in 4 patients), and a median of 7 days (range, 3–32 days) after chemotherapy. Chemotherapy with bevacizumab was 3rd line in case 1 and 2nd line in case 8. Stoma formation was done in six patients (Table 1). Postoperative complications were anastomotic leakage in one patient, paralytic ileus in two patients. One patient expired due to sepsis.

In one patient, two events of intestinal perforation developed at 3-month intervals. There was no chemotherapy after the first event of intestinal perforation. The 2nd event of a colo-vesical fistula at the sigmoid colon developed. Hartmann's procedure and omentopexy were performed. The colo-vesical fistula developed after a total of 11 cycles of chemotherapy (FOLFIRI) with bevacizumab, 134 days after chemotherapy.

DISCUSSION

For bevacizumab induced intestinal perforation, the commonly suggested predisposing factors are peptic ulcer disease, diverticulitis, chemotherapy-induced colitis, a history of abdominal radiation, abdominal carcinomatosis and bowel obstruction [5-7]. Saif et al. [8] observed that the incidence of intestinal perforation seemed to be higher in patients with intact primary tumors, a recent history of sigmoidoscopy or colonoscopy, or previous adjuvant radiotherapy. The reported locations of perforation have included the stomach, small bowel and large bowel [3,4,7,9]. The large bowel is the most common site of bowel perforation after bevacizumab combination chemotherapy. In this study, perforation sites were the colorectum in four patients, the small bowel in five patients. Primary tumor site perforation was in three patients. Four patients had preoperative intestinal obstruction.

The pathophysiologic mechanism by which bevacizumab leads to bowel perforation is unknown. There are several possible mechanisms [10]. One possibility is that the perforations are tumor-related. In this case, subsequent chemotherapy with bevacizumab may lead to necrosis of the tumor in the bowel serosa and thus predispose the patient to developing bowel perforation. Another possibility is that bevacizumab could limit blood flow to the splanchnic vasculature via thrombosis or vasoconstriction. A marginal blood supply to an area of the bowel could potentially lead to bowel infarction and then perforation. Finally, delayed wound healing with bevacizumab may result in leakage from the anastomotic site after bowel operation. In this study, perforation sites

were the colorectum in four patients and the small bowel in five patients. Primary tumor site perforation was in three patients. In those cases, we assumed that tumor necrosis produced the intestinal perforation. Although the pathogenesis of the patient's intestinal perforation was not entirely understood, intestinal obstruction may be considered as the predisposing factor for bevacizumab-in-

duced intestinal perforation.

Scappaticci et al. [5] suggested that the use of bevacizumab within 28 days of operation could increase the risk of wound healing complications after primary cancer surgery in colorectal cancer patients. In this study, there was no intestinal perforation as wound healing complication. In this study, intestinal perforation was de-

Table 2. Case review of small bowel perforation induced with bevacizumab

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Male	Male	Male	Male
Age (yr)	48	68	36	67	65
Primary tumor locations	Sigmoid colon	Rectum	Rectum	Sigmoid colon	Sigmoid colon
Metastasis sites	Ovary, peritoneum	Liver, peritoneum	Liver	Liver	Liver
Surgery for primary tumor	Sigmoid colon resection	LAR	LAR	LAR	LAR
Perforation sites	Ileum	Jejunum	Ileum	Jejunum	Jejunum
Perforation at tumor sites	No	No	No	No	Yes
Perforation surgery	Small bowel resection & ileostomy	Primary closure & jejunum ostomy	Small bowel resection & ileostomy	Small bowel resection	Small bowel resection
Postoperative complications	None	Expired	None	Leakage	None
Bevacizumab concurrent chemotherapy regimen	FOLFOX	FOLFIRI	FOLFOX	FOLFIRI	FOLFIRI
Bevacizumab, total use (cycle)	1	4	3	11	3
Interval between chemotherapy and perforation (day)	7	3	4	32	11
Previous history of intestinal obstruction	No	No	No	No	Yes
Preoperative CEA	854.3	2,476	6.2	5.2	4.2

LAR, low anterior resection; CEA, carcinoembryonic antigen.

Table 3. Case review of the colorectum perforation induced with bevacizumab

Characteristic	Case 6	Case 7	Case 8	Case 9
Sex	Male	Female	Male	Female
Age (yr)	46	59	59	41
Primary tumor locations	Rectum	Sigmoid colon	Rectum	Sigmoid colon
Metastasis sites	Liver	Peritoneum	Liver, lung	Liver
Surgery for primary tumor	None	Colostomy	LAR	None
Perforation sites	Rectum	Sigmoid colon	Rectum	Sigmoid colon
Perforation at tumor sites	Yes	Yes	No ^{a)}	Yes
Perforation surgery	Hartmann's colostomy	Peritoneal irrigation & drainage	Ileostomy	Sigmoid colon resection & ileostomy
Postoperative complications	Paralytic ileus	Paralytic ileus	None	None
Concurrent chemotherapy regimen	FOLFIRI	FOLFOX	FOLFOX	FOLFIRI
Bevacizumab, total use (cycle)	2	14	15	3
Interval between chemotherapy and perforation	25	7	20	4
Previous history of intestinal obstruction	Yes	Yes	No	Yes
Preoperative CEA	1,082	6.8	12.8	12.4

LAR, low anterior resection; CEA, carcinoembryonic antigen.

^{a)}Rectum perforation at proximal site from the tumor site.

veloped with a median of three chemotherapy cycles (range, 1–15 cycles; 3–4 cycles in 4 patients) and a median of 7 days (range, 3–32 days) after chemotherapy (Tables 2 and 3).

In conclusion, intestinal perforation induced bevacizumab is uncommon, though a serious and fatal adverse effect. Although the pathophysiology is not completely understood, careful observation is imperative for those patients who are administered bevacizumab in combination chemotherapy. Awareness of signs and symptoms of peritonitis with abdominal pain, nausea, and vomiting is necessary, especially after 3–4 cycles and within 7–10 days after bevacizumab administration. If intestinal perforation is diagnosed, bevacizumab administration should be ceased immediately and then resuscitation and early surgical intervention should be undertaken.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 1997;57:4593-9.
2. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;21:60-5.
3. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25:1539-44.
4. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335-42.
5. Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* 2005;91:173-80.
6. Gordon MS, Cunningham D. Managing patients treated with bevacizumab combination therapy. *Oncology* 2005;69 Suppl 3:25-33.
7. Lordick F, Geinitz H, Theisen J, Sandler A, Sarbia M. Increased risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. *Int J Radiat Oncol Biol Phys* 2006;64:1295-8.
8. Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. *Ann Surg Oncol* 2007;14:1860-9.
9. Heinzerling JH, Huerta S. Bowel perforation from bevacizumab for the treatment of metastatic colon cancer: incidence, etiology, and management. *Curr Surg* 2006;63:334-7.
10. Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? *Gynecol Oncol* 2007;105:3-6.