Original Article

Bowel Perforation with Relevant Complications from Bevacizumab Plus FOLFIRI in the Treatment of Metastatic Colorectal Cancer

Yi-Chien Hsieh[1]
Wei-Chih Su[1]
Tsung-Kun Chang[1]
Cheng-Jen Ma[1]
Hsiang-Lin Tsai[1,2]
Yung-Sung Yeh[1,3,4,5]
Ching-Wen Huang[1,2,6]
Jaw-Yuan Wang[1,2,3,6]
[1]*Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University,*
[2]*Department of Surgery, Faculty of Medicine,*
[3]*Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University,*
[4]*Division of Trauma and Surgical Critical Care, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University,*
[5]*Department of Emergency Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University,*
[6]*Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Bevacizumab, a recombinant humanized monoclonal antibody blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF), is frequently using in treating metastatic colorectal cancer. Side effects of bowel perforation are relatively rare but fatal. This case series retrospectively reviewed the records of 213 patients with metastatic colorectal cancer receiving FOLFIRI with bevacizumab every two weeks in one single institute between Apr 2013 and Aug. 2017.

Thirteen cases of bowel perforation among 213 mCRC (6.1%) patients associated with bevacizumab use were diagnosed. 8 of 13 (61.5%) patients presented with pneumoperitoneum, 2 (15.3%) with necrotizing fasciitis, 2 of 13 (15.3%) with enterocutaneous fistula and 1 (7.6%) with intra-abdominal abscess formation. Under broad-spectrum antibiotic administration with early intervention of stoma creation or intra-abdominal drainage, these thirteen patients all recovered uneventfully.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2018;29:93-99*]

Key Words
Bowel perforation;
Bevacizumab;
FOLFIRI;
Metastatic colorectal cancer

Received: October 7, 2017. Accepted: January 29, 2018.

Correspondence to: Dr. Jaw-Yuan Wang, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, No. 100, Tzoyu 1st Road, Kaohsiung 807, Taiwan. Tel: 886-7-312-2805; Fax: 886-7-311-4679; E-mail: cy614112@ms14.hinet.net; jayuwa@cc.kmu.edu.tw

Bevacizumab, a monoclonal antibody that deactivates the vascular endothelial growth factor (VEGF), plays an important role in treating malignancies and is now widely used in patients with metastatic colorectal cancer (mCRC).[1] Several studies analyzed the efficacy of bevacizumab combined with different chemotherapy regimens consisting on drugs such as 5-FU, capecitabine, irinotecan and oxaliplatin. It has been reported that bevacizumab enhanced the effectiveness in patients with metastatic colorectal cancer (mCRC). Adverse effects of bevacizumab including hematological (anemia, neutropenia, thrombocytopenia), and non-hematological (hypertension, proteinuria, diarrhea, bleeding and spontaneous bowel perforation) have been reported.[2] Among them, spontaneous bowel perforation is relatively rare, but lethal major complication. It can be presented as fistula formation, necrotizing fasciitis, intra-abdominal abscess or pneumoperitoneum. Early recognition of these critical clinical finding and conservative treatment with empiric antibiotic with intervention of diverting stoma or intra-abdominal drainage may be successful treatment strategy for these patients.[3,4] We therefore retrospectively reviewed the whole cohort of patients with mCRC receiving bevacizumab as adjuvant or neoadjuvant target therapy in our institution, focus on the incidence, the duration among bevacizumab infusion and surgical intervention, and the managements of complications.

Materials and Methods

All mCRC patients who receiving systemic chemotherapy plus bevacizumab every two weeks in Kaohsiung Medical University Hospital from April 2013 to August 2017 were reviewed. All patients with a bevacizumab-associated bowel perforation were included. The diagnosis of bowel perforation was according to imaging finding, operative finding and clinical presentation. The clinical course of the cases include clinical symptoms, management of bowel perforation, duration between operation and Bevacizumab administration, the number of bevacizumab course and primary outcome were assessed.

Results

There are 213 mCRC patients receiving FOLFIRI with bevacizumab every two weeks in one single institute between Apr 2013 and Aug. 2017. 132 patients underwent neoadjuvant treatment and 81 patients underwent first-line treatment. Thirteen cases of bowel perforation among 213 mCRC (6.1%) patients associated with bevacizumab use were diagnosed. Patients' characteristics are presented as Table 1. Among the 13 cases, seven patients developed perforation treated as the neoadjuvant setting (5.3%), six patients developed perforation after the resection of primary tumor treated as the first-line setting (7.4%). Seven of 12 (58.3%) patients had perforation at the tumor site, 5 patients (38.5%) occurred perforation at the anastomosis site and 1 (7.6%) had perforation site proximal to the tumor. Among the 5 patients occurred perforation at the anastomosis site, 2 of them had bevacizumab administration 5 weeks after previous surgery, 2 had bevacizumab infusion 6 weeks after surgery.

Of these patients, 8 of 13 (61.5%) patients presented with pneumoperitoneum, 2 (15.3%) patients presented with necrotizing fasciitis, two presented with enterocutaneous fistula and one (7.6%) with intra-abdominal abscess formation. Moreover, 2 patients had lumen stenosis at initial diagnosis and underwent intraluminal self-expanding metallic stents placement before Bevacizumab administration. One of the patients had perforation event after 1st course of bevacizumab administration. The interval between stent placement and perforation event was one month while another was two months after 4th course of bevacizumab infusion.

We performed diverting stoma for 12 patients and broad-spectrum antibiotic treatment for all thirteen cases. The patient who did not underwent stoma creation suffered from severe small intestine adhesion and peritoneal carcimomatosis. The family refused stoma creation after risk explanation. Subsequent intra-abdominal drainage was performed for four patients. For two patients with necrotizing fasciitis, fasciotomy was also undergone. Under the conservative treatment, these thirteen patients all recovered uneventfully. Treatment and outcomes are presented as

Table 1.

Patient Age/gender	Tumor location	TNM Stage	Metastatic site	Surgical procedure	Total bevacizumab cycles
1 67/F	Rectum	T3N2aM1a, IVA	Lung	Low anterior resection	Neoadjuvant, 5 Adjuvant, 7
2 71/F	Sigmoid colon	T3N0M1a, IVA	Liver	No surgery	Neoadjuvant, 2
3 44/F	Rectosigmoid colon	T4aN2bM1a, IVA	Liver	No surgery	Neoadjuvant, 1
4 48/F	Rectosigmoid colon	T3N1M1a, IVA	Liver	No surgery	Neoadjuvant, 4
5 41/M	Ascending and sigmoid colon	T4bN2aM1b, IVB	Liver, peritoneum	No surgery	Neoadjuvant, 5
6 75/M	Rectosigmoid colon	T4aN2bM1b, IVB	Liver, lung	No surgery	Neoadjuvant, 2
7 50/F	Ascending colon	T4bN1aM1a, IVA	Lung, peritoneum	No surgery	Neoadjuvant, 17
8 62/M	Cecum	T3N2bM1b, IVB	Liver	No surgery	Neoadjuvant, 11
9 64/M	Rectosigmoid colon	T3N1M1a, IVA	Liver	Low anterior resection	Adjuvant, 3
10 75/F	Sigmoid colon	T3N1bM1b, IVB	Liver, peritoneum	Anterior resection	Adjuvant, 1
11 79/M	Sigmoid colon	T4bN1M1a, IVA	Lung	Anterior resection	Adjuvant, 6
12 73/F	Transverse colon	T3N2bM1a, IVA	Liver	Transverse colectomy	Adjuvant, 1
13 79/F	Descending colon	T3N1bM1a, IVA	Liver	Left hemicolectomy	Neoadjuvant, 7 Adjuvant, 7

Table 2. The 30-day mortality rate is 7.7% (1 of 13 patients). The patient who died within 30 days after bowel perforation is due to bilateral lung metastasis with respiratory failure. The death could not be directly attributed to bowel perforation.

Discussion

The combination of chemotherapy with bevacizumab increased the response rate, progression-free survival and overall survival of patients with mCRC. However, the reports of adverse effects from this drug are also growing. Bevacizumab-induced bowel perforation has been widely discussed because it may lead to lethal outcome. Gastrointestinal perforation event may relate to the mechanism of bevacizumab, which will inhibit angiogenesis by directly against VEGF, leading to thrombosis formation of splanchnic or mesenteric vessels, bowel ischemia and ultimately bowel perforation.[2] It will also affect post-operative wound healing due to the influence of bowel mucosa microcirculation and lead to anastomosis dehiscence, colocutaneous fistula formation or anastomosis site perforation.

A recent systemic review and meta-analysis about the efficacy and safety of bevacizumab plus chemotherapy reviewed 9 trials comprising 3,914 patients.[5] The result showed the combination group (bevacizumab + chemotherapy) had higher response rate, higher progression-free survival and higher overall survival rate. However, the risk of bowel perforation, thromboembolic events and bleeding is also higher in chemotherapy plus bevacizumab group compared to chemotherapy along group. The incidence of gastrointestinal (GI) perforation in patients with mCRC treating

Table 2.

Patient Age/gender	Perforation site	Perforation finding	Operation & bevacizumab interval	Treatment	Outcomes
1 67/F	Anastomotic site	Necrotizing fascitis	5 weeks	T-colostomy, fasciotomy	Return to oral diet intake
2 71/F	Tumor site	Pneumoperitoneum		T-colostomy,	Return to oral diet intake
3 44/F	Tumor site	Pneumoperitoneum		T-colostomy, IA drainage	Return to oral diet intake
4 48/F	Tumor site	Pneumoperitoneum		T-colostomy	Return to oral diet intake
5 41/M	Tumor site	Pneumoperitoneum		Ileostomy	Return to oral diet intake
6 75/M	Tumor site	Pneumoperitoneum		T-colostomy	Return to oral diet intake
7 50/F	Tumor site	Pneumoperitoneum		IA drainage	Expire due to bilateral lung metastasis
8 62/M	Tumor site	Intra-abdominal abscess		Ileostomy, IA drainage	Return to oral diet intake
9 64/M	Anastomotic site	Necrotizing fascitis	5 weeks	T-colostomy, fasciotomy	Return to oral diet intake
10 75/F	Anastomotic site	Pneumoperitoneum	> 6 months	T-colostomy, IA drainage	Return to oral diet intake
11 79/M	Proximal to anastomotic site	Pneumoperitoneum	> 6 months	Ileostomy, IA drainage	Return to oral diet intake
12 73/F	Anastomotic site	Enterocutaneous fistula	6 weeks	Ileostomy	Return to oral diet intake
13 79/F	Anastomotic site	Enterocutaneous fistula	6 weeks	Total parenteral nutrition	Return to oral diet intake

IA: intra-abdomen drainage.

with bevacizumab is about 1-2%. In our case series, the incidence of bowel perforation is a slightly higher than other previous studies. Patient of mCRC usually are immunocompromised with terminal illness. Some GI perforation presentation maybe asymptomatic and difficult to diagnose, which is easily negligent as terminal oncological morbidity. Moreover, intra-abdominal abscess and fistula formation may not be link to GI perforation if the clinicians are not aware of the adverse effect of Bevacizumab. In our institute, we recognized the event of bowel perforation in patients underwent bevacizumab administration immediately with image studies within 24 hours. It may result higher incidence before mortality occurs.

Some predispose factors to GI perforation have been reported including existing tumor, previous radiotherapy, non-steroidal anti-inflammatory drugs or corticosteroids use.[6] Sanjaykuma et al. have reported a meta-analysis about bevacizumab use and the risk of GI perforation.[7] It shows the incidence of bowel perforation was 0.9% and the mortality rate is 21.7% in patients receiving bevacizumab. The study calculated the overall risk of GI perforation is affected by bevacizumab dose and cancer type. High-dose bevacizumab infusion (5 mg/kg) compared with control remained statistically significant with GI perforation, but was not statistically significant for low-dose bevacizumab (2.5 mg/kg) compared with control. In our study, the dose of bevacizumab administration is 5 mg/kg. The most common location of GI perforation was tumor site. It's compatible to previous studies.[2]

Borzomati et al. have reported a cohort of 142 patients treated with bevacizumab, 3 (2.1 %) experienced GI perforation after bevacizumab treatment. 2 of 3 ex-

pired in one week after bowel perforation event despite broad-spectrum antibiotic use and diversion colostomy creation.[1] Uchino et al. recently reported four cases of bevacizumab-related GI perforation.[8] The 4 patients all presented with mild abdominal pain and were detected within 14 days after bevacizumab administration. Three patients were successfully treated with only minimal surgical procedures and 1 patient could be managed with conservative treatment for a perforated duodenal ulcer. In a case series about management of bevacizumab-associated bowel perforation, Badgwell et al. retrospectively reviewed 1442 patients treated with Bevacizumab with perforation rate 1.7% noted.[9] In 24 patients with bowel perforation associated with bevacizumab administration, only 5 patients underwent surgical intervention and the overall 30-day mortality rate was 12.5%. The author concluded that conservative treatment is a viable approach to management in selected patients of bevacizumab-associated bowel perforation.

A review article of bevacizumab-induced bowel perforation has mentioned about the management of these patient should be based on individual severity, risks of morbidity and bleeding, clinical signs and expectation of outcome.[2] It indicated that the mortality rate is up to 50% in patients with bevacizumab-induced bowel perforation because of the terminal illness characteristics. Another review article mentioned about the management of bowel perforation depends on the overall condition of the patient.[4] In this study, operative intervention even bowel resection was thought to be necessary for these patients. However, it also mention about increased risk of unplanned, urgent surgical procedure due to the long half-life of bevacizumab. Recurrent bowel perforation or anastomosis leakage may occur in this circumstance. In our case series, we found broad-spectrum antibiotic administration with early intervention of stoma creation or intra-abdominal drainage is effective management with low mortality.

In a retrospective case series, Amal et al. indicated that both bevacizumab and self-expanding metal stents (SEMS) are associated with GI perforation.[10] The combination of chemotherapy, Bevacizumab and intra-luminal stents use may associate with high perforation rate. In this case series, up to 50% total complication rates (including bowel perforation, reobstruction and migration) was noted in the SEMS plus chemotherapy and bevacizumab group.

Gordon et al. have reviewed bevacizumab and its adverse effect on wound healing.[11] The article indicated that post-operative re-initiation of bevacizumab in surgical patients should be delayed for at least 4 weeks to prevent an increased risk of wound healing complications. Moreover, elective operation should be delayed 6-8 weeks after the last bevacizumab administration. According to our investigation in this case series, perforation at the anastomosis site would happened on patients who had bevacizumab infusion 5 to 7 weeks after surgery. Thus, postoperative initiation of bevacizumab 6 weeks or longer may prevent an increased risk of wound healing complications.

Conclusion

Colon perforation is a rare but fatal complication which mortality rate has been reported up to 40%, especially among patients administrated with chemotherapy. From our current investigation, most bowel perforation episodes occurred in 1-3 cycles as the neoadjuvant setting or as the first-line setting. Postoperative initiation of bevacizumab 6 weeks or longer may prevent an increased risk of wound healing complications. Regarding the treatment strategy, empiric antibiotic treatment with early intervention of stoma creation, or add the intra-abdominal drainage may be effective and successful to reduce mortality and morbidity rate.

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原　著

以 Bevacizumab 及 FORFIRI 治療轉移性大腸直腸癌導致之腸穿孔重大併發症

謝依蒨[1]　蘇偉智[1]　張琮琨[1]　馬政仁[1]　蔡祥麟[1,2]
葉永松[1,3,4,5]　黃敬文[1,2,6]　王照元[1,2,3,6]

[1]高雄醫學大學附設醫院　大腸直腸外科
[2]高雄醫學大學醫學院　醫學系　外科學
[3]高雄醫學大學醫學院　臨床醫學研究所
[4]高雄醫學大學附設醫院　外傷及重症外科
[5]高雄市立小港醫院　急診醫學科
[6]高雄醫學大學醫學院　醫學研究所

目的　Bevacizumab 是一種血管內皮增生因子的單株抗體，經常用於治療轉移性大腸直腸癌的病人，其所造成之腸穿孔副作用發生率 0.3~2.4%，雖罕見卻致命。本研究對其發生率、處理方式及相關預後做進一步討論。

方法　以單一醫學中心，從 2013 年 4 月至 2017 年 8 月，總共收錄了 213 位接受 bevacizumab + FORFIRI 治療之轉移性大腸直腸癌病人。回顧性的記錄其腸穿孔發生之臨床特徵、處理方式和預後。

結果　經過統計，共有 13 位病人 (6.1%) 發生腸穿孔之併發症，其中 8 位 (61.5%) 以氣腹表現，2 位 (15.3%) 以壞死性筋膜炎表現，2 位 (15.3%) 臨床表徵為腸皮廔管，1 位 (7.6%) 以腹內膿瘍呈現。經過廣效性抗生素和即時手術處理，包含腸造口或腹內膿瘍引流以及清創手術，其中 12 位病人預後良好，只有一位病人因末期癌症肺部轉移死亡。統計結果顯示並無因 bevacizumab 治療產生之併發症所造成之死亡案例。

結論　針對轉移性大腸直腸癌病人以 bevacizumab 治療所造成之腸穿孔併發症。臨床醫師須特別注意腸穿孔相關之臨床表徵，以廣效性抗生素及保守性手術治療可有效處理此併發症及避免致命之結果。

關鍵詞　腸穿孔、Bevacizumab、FOLFIRI、轉移性大腸直腸癌。