Adverse effects of bevacizumab in metastatic colorectal cancer : a case report and literature review

E. Willems[1], L. Gerne[1], C. George[2], M. D'Hondt[1]

(1) Department of Digestive and Hepatobiliary/Pancreatic Surgery, AZ Groeninge Kortrijk, Belgium ; (2) Department of Gastro-enterology, AZ Groeninge Kortrijk, Belgium

Abstract

Colorectal cancer is one of the most frequently diagnosed malignancies worldwide. One of the most important developments in the management of metastatic colorectal cancer is targeted therapy. Bevacizumab, a monoclonal antibody inhibiting VEGF induced angiogenesis, has been accepted as safe and efficient in the treatment of metastatic colorectal cancer for more than a decade. Addition of bevacizumab to fluorouracil-based chemotherapy is also associated with severe adverse events. We present a case of bevacizumab-induced bowel ischaemia associated with gastro-intestinal haemorrhage. (Acta gastroenterol. belg., **2019**, 82, **322-325**).

Key words : Bevacizumab, metastatic colorectal cancer, bowel ischaemia, gastro-intestinal bleeding.

Introduction

Colorectal cancer is the third most frequently diagnosed cancer and one of the most common causes of oncological deaths worldwide (1). A large part of patients has already developed hepatic metastases at diagnosis (2). A lot of research has been done to develop targeted therapies. Bevacizumab (Avastin®, F. Hoffmann-La Roche Ltd. Switzerland) is a monoclonal antibody inhibiting angiogenesis, an important step in tumour growth(2,3).

The addition of bevacizumab to fluorouracil-based chemotherapy is associated with better efficacy, but also with a higher risk of adverse effects (2,4). Known adverse events of bevacizumab are hypertension, proteinuria, haemorrhage, thrombosis, heart problems, non-healing wounds, fistula formation and gastrointestinal perforation (5,6).

In this report we present a case of of a patient treated with bevacizumab, complicated with bevacizumab-induced bowel ischaemia at first and with haemorrhage later on. We discuss bevacizumab therapy and some of its severe complications.

Case report

A 71-year-old woman presenting with severe abdominal pain and anal blood loss was diagnosed with rectal carcinoma and extensive bilobar liver metastasis. Since she presented with signs of gastro-intestinal obstruction caused by the tumour, a laparoscopic rectal resection (Total Mesorectal Excision-TME) was performed first. Anatomopathological research showed a moderately differentiated adenocarcinoma (pT3 N2b G1 L1 V1 Pn0 R0, RAS wild type, BRAF mutated).

The patient received adjuvant chemotherapy consisting of Folfiri (combination of Irinotecan, Leucovorin and Fluorouracil) and Avastin® (bevacizumab). The first two cycles of chemotherapy were well tolerated. After the third cycle of Folfiri and Avastin®, the patient presented at the emergency department with gastrointestinal complaints.

The complaints consisted of odynophagia, anorexia, nausea, vomiting, diarrhoea and occasional melena. At physical examination, the patient presented with hypotension (70/37 mmHg), dehydration and pressure pain in the right iliac fossa. Laboratory results showed systemic inflammation (CRP 468 mg/l), acute renal insufficiency (creatinine 3.53 mg/dl, GFR 12 ml/min/1.73m²), disturbed liver function tests (bilirubin 3.37 mg/dl, gamma-GT 132 U/l) and pancytopenia (haemoglobin 11.0 g/dl, WBC 1.12X10⁹/l, BP 82X10⁹/l).

She was admitted to the gastro-enterology unit and was given antibacterial and antifungal therapy (Levofloxacine, Ornidazole and Fluconazole) to counter the inflammatory status. A gastroscopy revealed signs of oesophagitis, gastritis and several duodenal ulcers for which proton pump inhibitors were initiated. Computed tomography (CT) of the abdomen performed because of persisting abdominal complaints showed signs of bowel obstruction with dilated small bowel loops without obvious stenosis, and a gastric tube was inserted (Fig. 1). Ultrasound of the abdomen showed dilated bowel loops and free intra-abdominal fluid.

Because of further deterioration, a diagnostic laparoscopy was performed. Laparoscopic exploration revealed diffuse dilation of the small bowel and an ischaemic segment of approximately 10 cm at the terminal ileum (Fig. 2a). Since the segment still appeared viable, it was not resected. The patient was admitted to the intensive care unit (ICU) and a second look laparoscopy was planned two days later. This laparoscopic exploration

Correspondence to : Edward Willems, President Kennedylaan 4, 8500 Kortrijk, Belgium. Phone: 0032 472 83 65 35.
E-mail : willems.edward@gmail.com

Submission date : 12/09/2017
Acceptance date : 06/10/2017

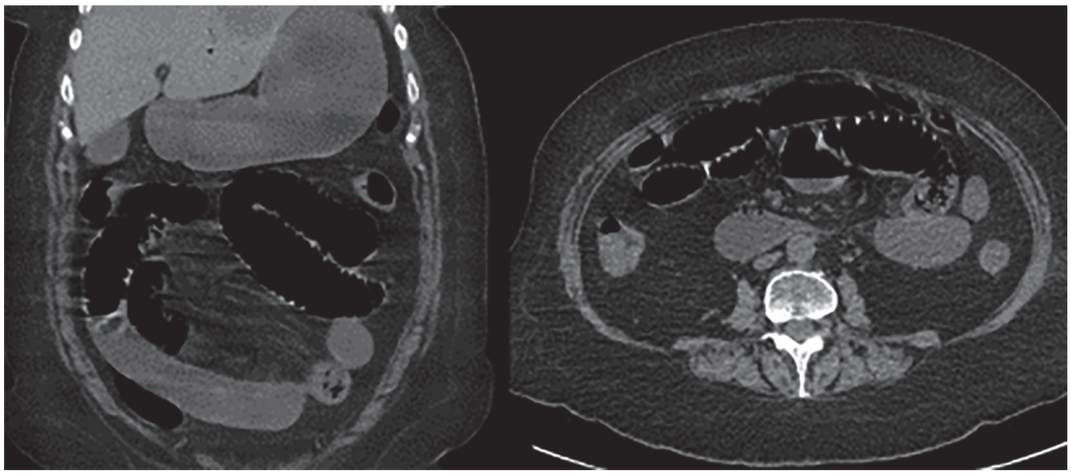

Figure 1. — Preoperative CT-scan (axial and coronal image) showing dilated small bowel loops without obvious stenosis.

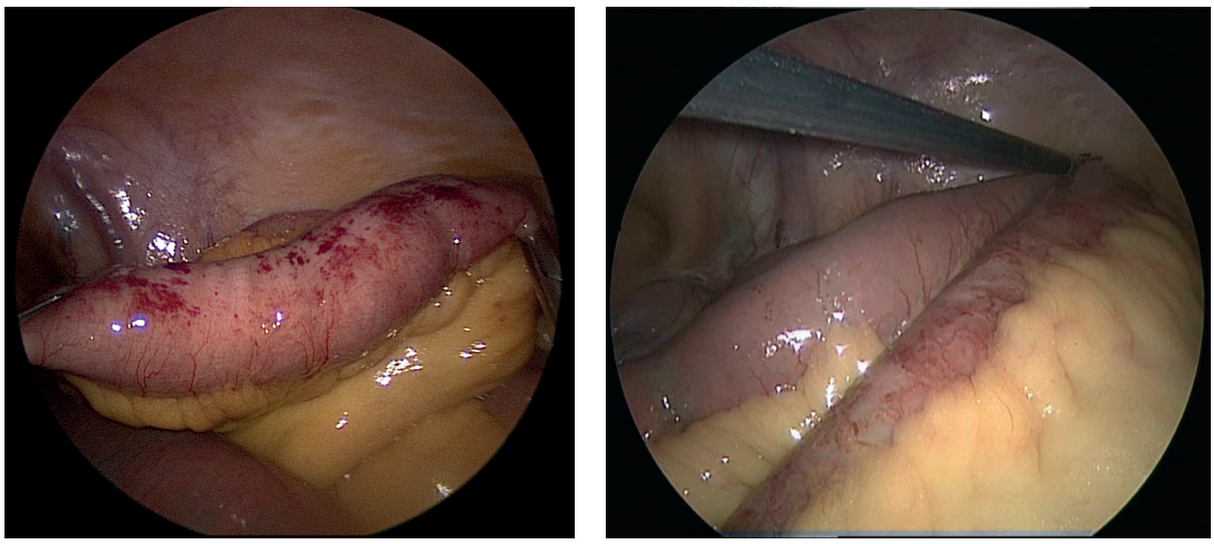

Figure 2 — a) First laparoscopy showing segment of ischemic small bowel, with ischemia most clearly present at the antimesenterial side of the small bowel ; b) Second laparoscopy showing complete reversibility of the small bowel ischemia.

showed complete reversibility of the bowel ischaemia and a bowel resection was not performed (Fig. 2b).

A day later the patient developed massive anal blood loss. Gastroscopy revealed a bleeding from a duodenal ulcer which was clipped endoscopically. Bleeding from gastrointestinal ulcers has been mentioned as a side effect of bevacizumab therapy.

Following these two severe complications, the question rose whether the patient should continue bevacizumab therapy. In consultation with both the patient and her family, treatment with bevacizumab was stopped and a palliative regimen was started. The patient died six weeks later.

Discussion

Colorectal cancer is the third most frequently diagnosed cancer worldwide. Due to continuing growth and ageing of the population, an increase in diagnoses is expected in future decades. It is the fourth most common cause of oncological death in men, and the third in women worldwide (1). A substantial part of patients with colorectal cancer has already developed hepatic metastasis at diagnosis, another substantial part develops liver or lung metastasis later on in the disease (2).

Because of the great burden of colorectal cancer, a lot of research has been done to develop targeted therapies. The formation of new blood vessels has been identified as an important step in the process of tumour growth and metastasis, and is therefore a good target for therapy. Vascular endothelial growth factor (VEGF) plays a key role in neovascularisation, by binding to its receptors it sets in action a pathway of angiogenesis (3). Bevacizumab is a monoclonal antibody inhibiting VEGF signalling. By forming a complex with VEGF it inhibits binding of VEGF to its receptors and subsequent angiogenesis (2).

First-line systemic treatment of metastatic colorectal cancer consists of intravenous fluorouracil-based chemotherapy. In fit patients with RAS wild type and BRAF mutated colorectal cancer, recent guidelines suggest combination of fluorouracil-based chemotherapy with bevacizumab (7). Bevacizumab was approved in 2004 by the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer (5). After 2004, bevacizumab has also been approved as a potential treatment of various other cancers: advanced non-small cell lung cancer, ovarian cancer, glioblastoma multiforme, renal cell carcinoma and breast cancer (8,9).

The addition of bevacizumab is associated with better efficacy: increased overall survival, progression-free survival and improved overall response rate, but also with higher risk of adverse events (2,4). Known adverse effects of bevacizumab are hypertension, proteinuria, haemorrhage, thrombosis, heart problems, non-healing wounds, fistula formation and gastrointestinal perforation (5,6). As VEGF plays an important role in several physiological processes, these adverse effects could be explained by the inhibitory effect of bevacizumab on VEGF (4).

Bowel ischaemia

Bowel ischaemia has not yet been described as an adverse event of bevacizumab therapy. Bowel perforation on the other hand is a known and rare adverse effect of bevacizumab. Compared to controls, bevacizumab triples the risk of gastrointestinal perforation. Perforation can lead to severe peritonitis and can be fatal (8). The FDA issued a warning after some cases of bowel perforation were seen in a trial of patients with ovarian cancer treated with bevacizumab (3).

Several mechanisms are given as a possible explanation for bevacizumab-induced bowel perforation. Inhibition of VEGF, leading to thrombosis or vasoconstriction of the splanchnic or mesenteric vessels, is one possible explanation. This way, bowel ischaemia can be explained as an adverse event of bevacizumab therapy, possibly leading to secondary bowel perforation (3,5).

If bowel ischaemia occurs, the treatment of choice is not yet clear. Management should be based on clinical presentation and severity. Since the risk of anastomotic failure is presumed to be high in patients receiving bevacizumab, a partial enterectomy should be avoided if possible. In this case, we were confronted with bowel ischaemia that appeared reversible. A resection was avoided at first and a second laparoscopic evaluation confirmed these findings. We think that a conservative attitude towards bevacizumab-induced gastrointestinal ischaemia with a low threshold to re-evaluations, might prevent a number of complications following unnecessary bowel resections.

Haemorrhage

Addition of bevacizumab to chemotherapy significantly increases the risk of haemorrhage (10). These haemorrhages are often life-threatening and fatal (11). The mechanism of bevacizumab-induced haemorrhages is not yet fully understood. The inhibitory effect of bevacizumab on VEGF could offer a possible explanation (11). By inhibiting VEGF, bevacizumab may have an inhibitory effect on endothelial survival and proliferation. At sites of damage or peptic ulcers, where VEGF is important for the proliferation of endothelial cells, inhibition of VEGF could lead to haemorrhages (10). In this case, the haemorrhage occurred at a duodenal ulcer.

The risk of haemorrhages may depend on the type of tumour. Colorectal cancer, non-small-cell lung cancer and renal cell carcinoma are associated with higher risk of haemorrhaging. In patients with metastatic colorectal cancer, the most common site of bleeding is the gastrointestinal tract. The location of the primary tumour may have an influence on the risk of bleeding. Some data suggest that a higher risk of bleeding is associated with primary tumours of the rectum than with primary tumours of the colon (10,12). The risk of haemorrhages seems to be dose dependent, with high doses giving a higher risk than low doses (10,11). Most haemorrhages occurred within the first 5-6 months of bevacizumab treatment, therefore clinicians should be highly vigilant in this period (10,11). Age, race, sex and concomitant anticoagulant therapy might also influence the risk of bleeding (12).

Due to the low incidence of these adverse events and the high efficacy of the therapy, combination therapy with bevacizumab is still considered a standard treatment for metastatic colorectal cancer (2,4). Because of the severity of the adverse effects and the increasing use of bevacizumab, it is important for all clinicians to recognise the adverse effects and treat them correctly. Effective selection of patients and monitoring during treatment can reduce the incidence of severe complications (2). When severe complications occur, patients should not continue their treatment with bevacizumab (8).

Conclusion

Combination chemotherapy with bevacizumab is highly effective, but is associated with a higher risk of adverse events. Because of the low incidence of severe adverse events, it is still considered a standard first-line treatment of BRAF mutated metastatic colorectal cancer. When administered bevacizumab, patients should be monitored closely and the threshold for investigations should be low if complications are suspected. In case of bevacizumab-induced bowel ischaemia, we advocate for a high threshold for bowel resection and suggest a relook laparoscopy if the bowel ischaemia appears reversible. Patients suffering from gastrointestinal perforation, haemorrhage or other adverse events should stop bevacizumab treatment permanently.

References

1. FAVORITI P., CARBONE G., GRECO M., PIROZZI F., PIROZZI R.E.M., CORCIONE F. Worldwide burden of colorectal cancer : a review. *Updates Surg.,* 2016, **68(1)** : 7-11.

2. QU C.-Y., ZHENG Y., ZHOU M., ZHANG Y., SHEN F., CAO J., *et al.* Value of bevacizumab in treatment of colorectal cancer: A meta-analysis. *World J Gastroenterol*, [Internet]. 2015, **21(16)** : 5072-80. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4408482&tool=pmcentrez&rend ertype=abstract
3. HAPANI S., CHU D., WU S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. *Lancet Oncol*., [Internet]. 2009, **10(6)** : 559-68. Available from: http://dx.doi.org/10.1016/S1470-2045(09)70112-3
4. CHEN K., GONG Y., ZHANG Q., SHEN Y., ZHOU T. Efficacy and safety of addition of bevacizumab to FOLFIRI or irinotecan/bolus 5-FU/LV (IFL) in patients with metastatic colorectal cancer : A meta-analysis. *Medicine* (Baltimore) [Internet], 2016, **95(46)** : e5221-e5221. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=27861344&site=ehost-live
5. SLIESORAITIS S., TAWFIK B. Bevacizumab-induced bowel perforation. *J Am Osteopath Assoc.*, 2011, **111** : 437-41.
6. HUANG H., ZHENG Y., ZHU J., ZHANG J., CHEN H., CHEN X. An updated meta-analysis of fatal adverse events caused by bevacizumab therapy in cancer patients. *PLoS One*, 2014, **9(3)**.
7. VAN CUTSEM E., CERVANTES A., ADAM R., SOBRERO A., VAN KRIEKEN J.H., ADERKA D., *et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.*, [Internet]. 2016 : 235. Available from: http://annonc.oxfordjournals.org/lookup/doi/10.1093/annonc/mdw235.
8. QI W.X., SHEN Z., TANG L.N., YAO Y. Bevacizumab increases the risk of gastrointestinal perforation in cancer patients: A meta-analysis with a focus on different subgroups. *Eur J Clin Pharmacol*., 2014, **70(8)** : 893-906.
9. RANPURA, HAPANI V. Treatment-Related Mortality With Bevacizumab. *Clin Rev*., 2013, **305(5)** : 487-94.
10. HAPANI S., SHER A., CHU D., WU S. Increased risk of serious hemorrhage with bevacizumab in cancer patients : A meta-analysis. *Oncology*, 2010, **79(1-2)** : 27-38.
11. ZHU X., TIAN X., YU C., HONG J., FANG J., CHEN H. Increased risk of hemorrhage in metastatic colorectal cancer patients treated with bevacizumab. 30-3.
12. HANG X.F., XU W.S., WANG J.X., WANG L., XIN H.G., ZHANG R.Q., *et al.* Risk of high-grade bleeding in patients with cancer treated with bevacizumab: A meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol*., 2011, **67(6)** : 613-23.