# Intestinal perforation after regorafenib usage

**Barış Sarıcı[1], Serdar Karakaş[1], Ufuk Uylas[1], Aydın Aktaş[1], Mustafa Dikilitaş[2], Cüneyt Kayaalp[1]**

[1]Department of Surgery, İnönü University School of Medicine, Malatya, Turkey
[2]Department of Medical Oncology, İnönü University School of Medicine, Malatya, Turkey

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Dear Editor,

Angiogenesis is effective in tumor growth and vascular endothelial growth factor, an angiogenesis factor in chemotherapy drugs, is targeted. Bevacizumab (BV) (Altuzan, Roche) sunitinib sorafenib tyrosine kinase inhibitors that target vascular endothelial growth factor pathways. These anti-neoplastic agents have some important side effects, such as gastrointestinal perforation and fistula, on patients.

Regorafenib is an oral anti-neoplastic agent that inhibits multi-kinase activity in tumoral cells, affects the tumoral angiogenetic pattern and is used for especially high-grade colorectal tumors and gastrointestinal stromal tumors (1). Well-known side effects of regorafenib are hand-and-foot syndrome, hypertension, and diarrhea; there are very few reports on intestinal perforations and fistula (1-5). The case of intestinal perforation of an operated high-grade colon tumor, which may have been caused by regorafenib usage, is presented here.

A 60-years-old woman with abdominal pain and hematochezia was referred to our outpatient clinic. Physical examination, laboratory study and a colonoscopy were performed. A tumoral mass at the hepatic flexure with a length of 8 cm and nearly totally obstructed colonic segment was detected. A computerized tomography (CT) of the abdomen detected no metastatic findings in the abdominal organs or lymphadenopathy. Multiple biopsies were performed and an adenocarcinoma was detected based on the reports. Laparoscopic right extended hemicolectomy and ileocolonic anastomosis were performed. No complications regarding surgery and patient discharged on the fifth postoperative day were observed. The pathology of specimens was reported as mucinous adenocarcinoma with no lymph node metastasis but serosal infiltration. The first adjuvant chemotherapy course was initiated 40 days after surgery with capesitabine (Xeloda, Roche)/oxaliplatine (Eloxatin, Sanofi) (Xelox) combination. After three-course of chemotherapy, a thoracal nodule and lymphadenopathy at the portal hilus were detected on the CT scan and three-course of Xelox was readministered. Instead of adjuvant chemotherapy, multiple liver masses with a maximum size of 2 cm were detected on the abdominal CT scan and a core biopsy was performed. The specimens were reevaluated to detect the mutant oncogenes on k-ras and n-ras because the biopsy indicated mucinous adenocarcinoma. Then, a combination of leucovorin (Leucovorin Atafarm, Novartis)/fluorouracil (5-florourasil, Sandoz)/irinotecan (Camptosar, Pfizer) (Folfiri) was administered. After the first course of therapy, because the k-ras and n-ras oncogenes reported as mutant, BV was included in the chemotherapy and four more courses of Folfiri plus BV were administered. Instead of the Folfiri plus BV treatment, control CT revealed multiple liver and peritoneal metastasis and regorafenib therapy was initiated with a dose of 120 mg/day. On the ninth day of therapy, the patient was referred to the emergency department because of abdominal pain and tenderness. CT scan and radiography detected free air in the abdomen and a suspected organ perforation. Emergent surgery launched and a perforation, on the dead ended loop side of the intestine, next to the ileocolonic anastomosis was detected (Figure). Resection to end loop and primer closure was performed with double suturation. The patient was followed up with no serious complication except wound infection.

There are several reports of intestinal perforations caused by other anti-neoplastic agents like BV usage. The mechanisms of intestinal and colonic perforations seem to be decreasing vascular endothelial cell function, particularly on the side of the targeted intra abdominal tumor (6).

The incidence of intestinal perforation is high in the use of BV. The incidence of these perforations is 0.9%-3.1% in

**ORCID IDs of the authors:** B.S. 0000-0001-8237-9701; S.K. 0000-0001-8314-7806; U.U. 0000-0003-4195-5498; A.A. 0000-0003-3407-0210; M.D. 0000-0003-3346-1623; C.K. 0000-0003-4657-2998.

Address for Correspondence: **Barış Sarıcı** E-mail: **kemalbarissarici@mynet.com.tr**
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some series (1,7). However, perforation has been reported in the areas of primary tumor presence, tumor-related narrowing, and anastomotic or peritoneal insemination areas, where circulatory disturbances may occur (6,8). Regorafenib is an anti-neoplastic drug, which is used for especially high-grade and chemoresistant colorectal tumors. The main side effects of regorafenib are hand-and-foot syndrome, hypertension, diarrhea, and rashes (1). The mechanism of the anti-neoplastic effect depends on the decreasing multi-kinase activity in tumor cells. However, this effect also deteriorates the healthy cell functions of cells such as vascular endothelial cells, especially those which belong to tissues near the primary tumor. An ischemia of these organs may cause perforations (1,3).

However, the reports of intestinal perforations and fistula caused by regorafenib usage are rare. So far, nine cases have been reported. Eight of these cases are of colon cancer and one is of a gastrointestinal tumor. Perforation occurred in four and fistula occurred in four cases. In these cases, the time to perforation was given as the shortest five days and the longest 84 days. In these cases, complaints of fever and abdominal pain leading authors to perforation. Three patients were conservatively treated, and five patients were operated. Mortality was reported in three patients (1,3-5).

Also, in a randomized, double-blind, placebo-controlled, three-phase trial (RESORCE) by Bruix et al. (9), which included 753 cases, gastric perforation had been reported. Regorafenib plus supportive care and placebo plus supportive care were compared by Li et al. (10) in 136 Asian patients with previously treated metastatic colorectal cancer and they observed a vaginal fistula, rectal fistula, and colonic perforation (CONCUR trial).

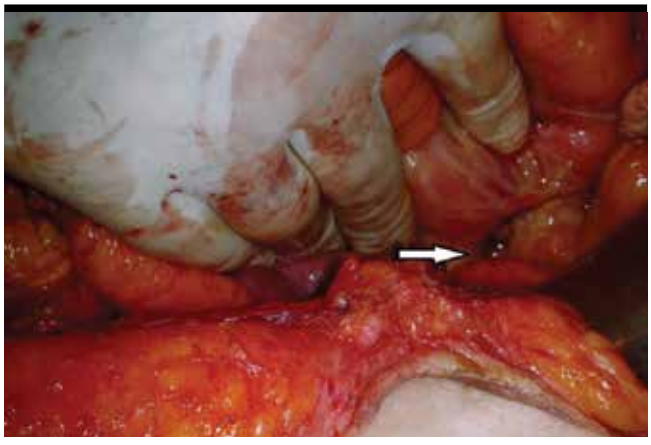

**Figure 1.** Ileal perforation

It was concluded that the perforation in our case was due to regorafenib usage because of occurring on the ninth day of regorafenib therapy, also in which BV and other anti-neoplastic administrations were too earlier. The half-life of bevacisumab is two weeks. The patient did not receive any treatment for 11 days. BV had been received 20 days ago. In the case of an acute abdomen with the usage of regorafenib, organ perforation should be considered. Therefore, we believe that regorafenib caused this perforation.

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