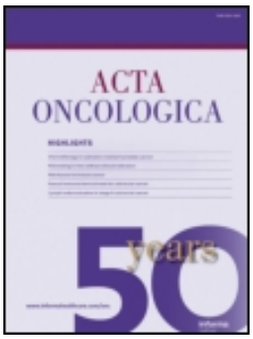

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Regorafenib use as a possible cause of intestinal perforation

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To the Editor,

Regorafenib (Stivarga, Bayer®) is a novel anti-angiogenic agent and a tumour cell mitosis inhibitor. The recommended dose of regorafenib is 160 mg daily, to be orally administered three-weeks on/one-week off. Two trials conducted in metastatic colorectal cancer patients [1] and in advanced gastro-intestinal stromal tumour (GIST) patients [2], both having exhausted all available standard treatments have demonstrated the clinical benefit of regorafenib over placebo. Regorafenib has now been approved by both the FDA and the EMEA for treatment of these two cancers sites.

Here, we report two cases of intestinal perforation (IP) probably related to regorafenib use. A 72-year-old woman was diagnosed with colon cancer and peritoneal carcinomatosis. The primary was removed frontline. As she was refractory to fluorouracil, oxaliplatin, irinotecan, and cetuximab, she received regorafenib. At baseline, she presented with good performance status, without any signs of bowel obstruction but exhibited mild intermittent pain in

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the lower abdomen. Three days after the start of regorafenib, her general practitioner had prescribed opioids because of the worsening of abdominal pain. At day 7, pain intensity decreased but she presented with abdominal tenderness. She was admitted at day 9 for an entero-cutaneous fistula located on the top of an abdominal mass. The decision was made to definitely discontinue regorafenib. The patient died of disease progression 4 months later, with the persistence of this fistula.

The second case concerns a 66-year-old GIST patient who was treated by gastrectomy seven years ago. The disease relapsed three years later as multiple peritoneal masses. As he was found to be refractory to approved medications (imatinib and sunitinib), he received regorafenib treatment. Upon admission for severe abdominal pain, the patient was in good performance status, and had no sign of IP since the start of regorafenib, 58 days earlier. At entry, physical examination revealed signs of peritonitis, and computed tomography (CT) scan showed an IP located within a huge ileal and necrotic mass. The general condition of this patient worsened with the occurrence of septic shock. He died 24 hours after his admission to the emergency room.

Although, it is known that IP may occur during the natural course of any peritoneal metastases, we suspect our two cases to be related to regorafenib use because of the temporal relationship between regorafenib exposure and the outcome of these IP. The occurrence of IP in patients receiving other anti-angiogenic agents [3,4] is known but remains infrequent. In a recent meta-analysis of published randomised trials, the incidence of IP was 0.9% among patients receiving bevacizumab [4]. There is no doubt that any kind of intestinal obstruction (peritoneal metastases or tumour mass invading the bowel wall) is the main condition that predisposes to IP in patients treated with angiogenesis-targeting agents [3,5]. However, physicians have to be aware of the risk of IP in their patients being treated with regorafenib. We suggest they closely monitor the signs suggesting the premises of this toxicity, especially in patients with massive peritoneal relapse.

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