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Intestinal Perforation in a Patient with Colon Cancer during Treatment with Regorafenib: A Case Report and Review of the Literature

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The multikinase inhibitor, regorafenib, is known to exert its antitumor effects by targeting several kinases, inhibiting interstitial intracellular signaling and suppressing tumor cell proliferation. Regorafenib causes gastrointestinal perforation and gastrointestinal fistula as adverse events, and discontinuation is recommended if these adverse events occur during administration. However, there are no prescribed standards for re-administration after discontinuation and for administration in patients with a history of gastrointestinal perforation. Herein, we report a case of gastrointestinal perforation in a patient, with a history of gastrointestinal microperforation, undergoing bevacizumab therapy, within a few days of starting regorafenib; this had a significant effect on the prognosis. The site of gastrointestinal perforation was consistent with previously reported sites around the tumor and at the anastomotic site. Based on a review of literature and our experience with the case presented here, we recommend that administration of regorafenib to patients with a history of gastrointestinal perforation should be avoided to the extent possible. Moreover, in case of prior administration of a drug reported to cause gastrointestinal perforation, such as an anti-VEGFR drug, the risk of gastrointestinal perforation should be considered during the administration of regorafenib. In the event of complaints, such as abdominal pain, gastrointestinal perforation should be considered as a differential diagnosis and appropriate tests and treatments should be initiated at an early stage.

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Introduction

Regorafenib is a multikinase inhibitor that exhibits antitumor effects by inhibiting various kinases, suppressing tumor cell proliferation and angiogenesis, and inhibiting interstitial intracellular signaling to affect the tumor microenvironment (Wilhelm et al. 2011). Adverse effects of this drug that require special attention include hand-foot syndrome, liver function abnormalities, and hypertension, and criteria for dose reduction and discontinuation are set for each grade. Regorafenib is also recommended to be discontinued in the event of occurrence of gastrointestinal perforation and gastrointestinal fistula are also recommended to be discontinued if they are observed during administration of regorafenib, but the criteria have not been set for re-administration of the drug after the appearance of gastrointestinal perforation and in cases with a history of gastrointestinal perforation (https://www.medicines.org.uk/emc/; https://www.fda.gov/). Regorafenib is thought to cause gastrointestinal perforation and gastrointestinal fistula through its antagonistic action against vascular endothelial growth factor receptor (VEGFR) (Chen and Cleck 2009).

Here, we report a case of gastrointestinal perforation during the use of regorafenib in a patient with a previous

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history of gastrointestinal microperforation. We also conducted a review of literature to assess the safety of regorafenib administration in patients with a history of gastrointestinal perforation and gastrointestinal fistula, and in those undergoing re-administration after gastrointestinal fistula.

Case Presentation

The patient was a man in his 60s who visited our emergency outpatient department with abdominal pain and vomiting. He was diagnosed with cecal cancer, multiple liver metastases, and cancerous peritonitis upon close examination. The cancer was regarded as unresectable, however, laparoscopic ileo-transversostomy was performed to avoid intestinal obstruction due to the cancer.

Thereafter, he was referred to the Department of Oncology at our hospital, and one course of capecitabine + oxaliplatin (XELOX), two courses of oxaliplatin + levofolinate + fluorouracil (mFOLFOX6), and eight courses of bevacizumab + mFOLFOX6 were performed on outpatient basis. Six months after the operation, he was hospitalized for a pericecal abscess, which was thought to be due to microperforation of the tumor. The abscess was relieved by administration of antibacterial agents for approximately 2 weeks, and the patient was discharged from the hospital. Chemotherapy was resumed at the outpatient department, and mFOLFOX6 was administered in five courses, levofolinate + irinotecan + fluorouracil (FOLFIRI) in four courses, and mFOLFOX6 in one course. One year after the operation, the patient was hospitalized on suspicion of microperforation near the anastomotic site, but after 7 days of tazobactam/piperacillin hydrate (TAZ/PIPC) (13.5 g/day) administration, his condition improved rapidly and he was discharged. Thirteen months after the operation, the patient visited the hospital with a chief complaint of vomiting, which was thought to be due to chemotherapy, and he was hospitalized after discontinuing the mFOLFOX6 scheduled for the second course. The nausea subsided in about 1 week, and he was discharged from the hospital after one

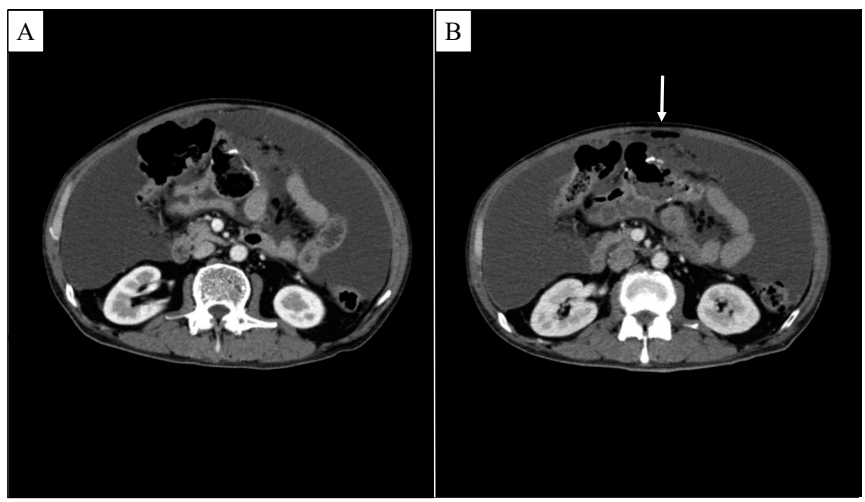

Fig. 1. Computed tomography images of the patient with gastrointestinal perforation. Image taken on the first (A) and second (B) day of hospitalization. Images on the second day of hospitalization show free air near the anastomotic site (shown by an arrow).

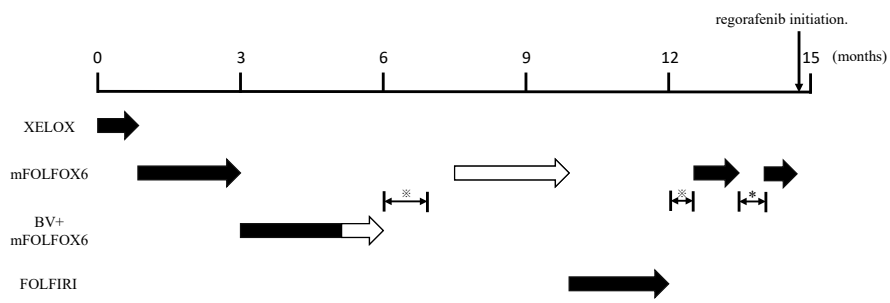

Fig. 2. History of cancer chemotherapy of the patient.
The history of cancer chemotherapy administered to the patient after surgery is shown. The axis shows the postoperative course on a monthly basis; 0 month represents the month of surgery. The white arrows indicate that oxaliplatin was not administered. ※Hospitalized for microperforation of the gastrointestinal tract. *Hospitalized for nausea.
XELOX, Capecitabine + Oxaliplatin; mFOLFOX6, Oxaliplatin + Levofolinate + Fluorouracil; BV + mFOLFOX6, Bevacizumab + Oxaliplatin + Levofolinate + Fluorouracil; FOLFIRI, Levofolinate + Irinotecan + Fluorouracil.

course of mFOLFOX6.

Subsequently, after one course of mFOLFOX6 at the outpatient department and then it was judged to be a progressive disease. Therefore, his regimen was switched to regorafenib 120 mg/day from 14 months after the operation, and the outpatient treatment was continued. However, on the 7th day after the start of regorafenib, he complained of severe pain around the navel from the epigastric region and was urgently examined. Although computed tomography (CT) showed no free air, a large amount of ascites, nor severe inflammation, he was hospitalized under the diagnosis of bacterial peritonitis (Fig. 1A). After admission, TAZ/PIPC (13.5 mg/day) was started on the first day. Because high fever was observed on the second day, CT was performed again, which showed free air (Fig. 1B). The perforation of the anastomotic site and diffuse peritonitis were strongly suggested. In addition, abdominal puncture was performed to confirm the property of ascites, which was not turbid. So, considering the stage of the disease, a conservative treatment without operation was continued. A nasogastric tube and an abdominal drainage tube were inserted. The fever decreased slightly, and the inflammatory reaction on blood sampling also tended to improve. Based on the results of the bacterial culture, a small amount of *Escherichia coli* was detected in the ascites, and de-escalation was subsequently performed to ceftriaxone sodium hydrate (CTRX) (2 g/day) on the 7th day. Since the discharge from the nasogastric tube decreased, the tube was removed on the 8th day. Thereafter, the patient was followed up until the 12th day of illness, but abdominal puncture was performed again due to the persistence of a high fever of 38°C or higher and prolonged inflammatory reaction on blood sampling. So CTRX was discontinued, and the antibiotics were switched to meropenem hydrate (3 g/day).

After the change of antibacterial drug, temporary improvement of fever was observed, but since the fever exceeded 38°C again from the 14th day of illness, micafungin sodium (50 mg/day) was added and the antibiotics drug was changed to doripenem hydrate (1.5 g/day). When dexamethasone (3.3 mg/day) was administered on the 28th day of illness, the fever and general condition improved, as evidenced, for example, by an increased appetite. He was discharged on the 32nd day at his and family's request and was referred to a visiting doctor at home. After discharge from the hospital, he was able to eat a small amount of food for approximately 2 weeks, but it gradually became difficult, and he died 30 days after discharge. The course of anti-cancer drug treatment is shown in Fig. 2.

In reporting this case, we have complied with the guidelines on patient privacy protection (Surgery-related Academic Society Council) in medical papers, including case reports and presentations at academic meetings, and obtained approval from the ethical review committee of Tohoku Medical and Pharmaceutical University Hospital (Approval number: 2020-4-055).

Discussion

In this case, gastrointestinal perforation occurred within a few days of regorafenib administration, although it

Table 1. Reported gastrointestinal perforation or intestinal perforation induced by regorafenib.

Age	Sex	Primary tumor	Focus	Previous treatment	Symptoms	Days of regorafenib treatment (Days)	Treatment	Patient outcome	References
65	Female	Cecum	Cecum	FOLFOX/BV, FOLFIRI/BV	Pain	32	Surgery	Improved	Ogata et al. 2017
62	Male	Rectum	Rectum	Surgery, FOLFOX/BV, FOLFIRI/BV	Fever, pain	51	Surgery	Improved	Doi et al. 2017
59	Male	Rectum	Rectum	Surgery, radiation, FOLFOX, FOLFIRI/BV	Fever, pain	20	Surgery	Improved	Doi et al. 2017
44	Male	Rectum	Rectum	FOLFOX/BV, FOLFIRI/aflibercept,TAS-102/BV	Fever, pain	84	Surgery	Improved	Doi et al. 2017
52	Female	Transverse colon	Transverse colon	FOLFOX/BV, FOLFIRI/BV	Fever	5	Antibiotics	Improved	Doi et al. 2017
78	Female	Ascending colon	Jejunum	Surgery, FOLFOX/BV, FOLFIRI/BV	Pain	10	Surgery	Improved	Doi et al. 2017
72	Female	Colon	Enterocutaneous fistula	FOLFIRI/cetuximab	Pain	19	Opioids	Died	Adenis et al. 2013
66	Male	Stomach (GIST)	Ileum	imatinib, sunitinib	Pain	58	Not implemented	Died	Adenis et al. 2013
60	Female	Colon	Ileocolonic anastomosis	Surgery, XELOX, FOLFIRI/BV,	Pain	9	Surgery	Improved	Sarıcı et al. 2018

GIST, gastrointestinal stromal tumor; FOLFOX, Oxaliplatin + Levofolinate + Fluorouracil; BV, Bevacizumab; FOLFIRI, Levofolinate + Irinotecan + Fluorouracil; TAS-102, Trifluridine/Tipiracil Hydrochloride; XELOX, Capecitabine + Oxaliplatin.

had been more than 6 months since the improvement of microperforation of the gastrointestinal tract, which is considered to be related to previous bevacizumab administration. Although a conservative treatment was adopted considering the disease stage, gastrointestinal perforation may have significantly affected the prognosis of the patient.

Gastrointestinal perforation during anticancer chemotherapy is known to occur due to severe atrophy of the mucosa or intestinal wall, or as a result of the therapeutic effect of anticancer drugs (Ogata et al. 2017). Gastrointestinal perforation during the use of molecular-targeted drugs has been shown to increase the risk of fistula formation due to local tissue effects, such as hypoxia due to anti-VEGFR action and delayed wound healing (Chen and Cleck 2009). In particular, bevacizumab was reported to cause gastrointestinal perforation in 0.93% of patients (Hatake et al. 2016). However, in another study on the efficacy and safety of bevacizumab, the incidence of gastrointestinal perforation was reported to be 11.4% (Cannistra et al. 2007). It has been suggested to occur more likely in areas with cardiovascular disorders, anastomotic sites, and peritoneal dissemination sites (Cannistra et al. 2007; Sliesoraitis and Tawfik 2011).

The PubMed database (MeSH terms: regorafenib and perforation and gastrointestinal or intestinal) contains reports on nine cases of gastrointestinal perforation associated with regorafenib administration (Adenis et al. 2013; Ogata et al. 2017; Doi et al. 2017; Sarici et al. 2018) (Table 1). In five of the nine cases, the site of perforation coincided with the primary site, and in one case it was the anastomotic site of gastrointestinal bypass surgery. In this case, as well, perforation at the anastomotic site was strongly suspected on CT, which is consistent with previous reports (Cannistra et al. 2007; Sliesoraitis and Tawfik 2011) that tumor necrosis results in an area of disruption as a result of treatment with anti-VEGFR drugs, leading to gastrointestinal perforation around the tumor and at the anastomotic site. In addition, the period from the start of regorafenib to the occurrence of gastrointestinal perforation varied from 5 to 84 days, and no consistent characteristics were found. In cases where the primary tumor was colorectal cancer, bevacizumab had been previously administered for all cases except in one wherein cetuximab was administered. Imatinib, a drug that has been reported for gastrointestinal perforation during administration (El Jurdi et al. 2016), was also administered to one patient with GIST of the stomach as the primary tumor. Moreover, it was reported that two out of nine patients died after the occurrence of gastrointestinal perforation, and six patients required surgery even in the case of improvement. Therefore, a history of treatment with drugs linked to gastrointestinal perforations, such as those with an anti-VEGFR action, increases the risk of gastrointestinal perforation during regorafenib administration. In addition, it has been reported that gastrointestinal perforation related to bevacizumab administration occurs 51-178 days after the start of administration (Cannistra et al. 2007). However, gastrointestinal perforation during the administration of regorafenib in this case occurred 7 days after the start of regorafenib and 261 days after the final administration of bevacizumab, which far exceeds the half-life of 20 days for bevacizumab. Therefore, in cases with a previous history of bevacizumab treatment, regardless of the period, it is necessary to be mindful of the risk of gastrointestinal perforation due to regorafenib.

As mentioned above, there are currently no clear criteria for the administration of regorafenib to patients with a history of gastrointestinal perforation or for resuming the administration after improvement of gastrointestinal perforation. The frequency of gastrointestinal perforation associated with regorafenib administration is reported to be about 0.6% (https://www.fda.gov/); however, if it does occur, it may significantly affect the prognosis of patients, and even death has been reported in some cases. Therefore, the risk of gastrointestinal perforation during administration of regorafenib should be considered in patients with a history of being previously treated with drugs associated with gastrointestinal perforations, such as anti-VEGFR drugs. In addition, this also applies to those with no clinical history of gastrointestinal perforation. Moreover, for such patients complaining of abdominal pain, appropriate tests and treatment should be initiated at the earliest, considering the possibility of gastrointestinal perforation. In addition, considering the previously reported cases, it is desirable to avoid administration of regorafenib to patients with a history of gastrointestinal perforation to the extent possible.

Conflict of Interest

The authors declare no conflict of interest.

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