Regorafenib-induced retinal and gastrointestinal hemorrhage in a metastatic colorectal cancer patient with liver dysfunction
A case report

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Abstract

Rationale: Regorafenib is effective for metastatic colorectal cancer but its toxicity such as hemorrhage should be considered. The safety of regorafenib for the patient with the liver disease is not known.

Patient concerns: Seventy-one-year old man of colon cancer had myodesopsia and blood stool after 14 days from the initiation of regorafenib administration with 50% dose reduction due to liver dysfunction.

Diagnoses: Fundus examination revealed hemorrhage of the retinal vein.

Interventions: Regorafenib treatment was discontinued and observational therapy was pursued.

Outcomes: Retinal and gastrointestinal hemorrhage resolved in 1 week.

Lessons: Retinal hemorrhage should be considered as the differential diagnosis of myodesopsia in the patient treated by regorafenib. Safety and pharmacokinetic of continuous regorafenib administration for patients with liver dysfunction remains to be clarified.

Abbreviations: FGFR = fibroblast growth factor receptor, GIST = gastrointestinal stromal tumor, HCC = hepatocellular carcinoma, mCRC = metastatic colorectal cancer, mFOLFOX6 = modified folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin, PDGFR = platelet-derived growth factor receptor, PEIT = percutaneous ethanol injection therapy, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization, VEGFR = vascular endothelial growth factor receptor.

Keywords: colorectal cancer, CYP3A4, gastrointestinal, hemorrhage, liver dysfunction, myodesopsia, regorafenib, retinal, UGT1A9

1. Introduction

Regorafenib is an oral chemotherapeutic agent targeting multiple kinases such as vascular endothelial growth factor receptor (VEGFR) 1-3, the transmembrane tyrosine-protein kinase receptor TIE2, platelet-derived growth factor receptor (PDGFR) β, fibroblast growth factor receptor (FGFR), KIT, RET, RAF-1, and BRAF. The CORRECT trial (a randomized phase III clinical study) demonstrated the efficacy of regorafenib for metastatic colorectal cancer (mCRC) patients with prolonged overall survival.[1] Further, the CONCUR trial, which was conducted in Asian mCRC patients, also showed a survival benefit of regorafenib against placebo.[2] Regorafenib is now utilized not only for mCRC, but also for gastrointestinal stromal tumor (GIST) and hepatocellular carcinoma (HCC).[3,4]

The common adverse effects of regorafenib are fatigue, loss of appetite, hand-foot syndrome, diarrhea, hypertension, and liver injury.[5] Importantly, thromboembolism and hemorrhage have been reported due to targeting of the maintenance signaling of endothelial cells such as VEGFR.[6] Regorafenib is metabolized by liver enzymes including CYP3A4 and UGT1A9.[7] Although regorafenib has been clinically used with caution for patients with liver disease, the precise pharmacokinetics and safety of regorafenib in liver disease patients is largely unknown. The mCRC patient of this present report had chronic hepatitis C and a medical history of treatment for HCC. Despite a large dose reduction of regorafenib, rare adverse events of retinal hemorrhage and gastrointestinal hemorrhage appeared.

2. Case presentation

The present patient is a 71-year old man who has suffered from chronic hepatitis C since transfusion at the age of 25 years due to a traffic accident. He was diagnosed with ulcerative colitis at age 30 years, and has been treated with mesalazine and steroids. In 2008, he developed HCC, which was treated by radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and percutaneous ethanol injection therapy (PEIT). In 2011, the patient was diagnosed with sigmoid colon cancer in association with ulcerative colitis. Laparoscopic total colon resection and lymph node resection were performed. The pathological stage of colon cancer was stage III, T2N1M0. Adjuvant chemotherapy with modified FOLFOX6 (folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin) was administered in 2012, but terminated at the fourth course due to myelosuppression. After 9 months, metastases in the right upper lobe of the lung and abdominal lymph nodes appeared. The combination of mFOLFOX6 plus bevacizumab was started, but the lung metastasis progressed to show Pancoast syndrome with pain in the right shoulder. Radiation of 60 Gy in 30 fractions was then performed for the lung metastasis. In March 2015, given that HCC was detected, TACE and PEIT were performed. In June 2016, metastases of the left fourth rib and the right lung hilum appeared. Rim metastasis was irradiated with 30 Gy. Given that the patient had heterozygous alleles of both *UGT1A1*6* and *28*, the dose of irinotecan was reduced by 50%, and the combination of irinotecan plus bevacizumab was administered following the radiation therapy. After one course of treatment, Common Terminology Criteria for Adverse Events (CTCAE) grade 3 of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation was detected, so the chemotherapy was stopped. The disease also progressed despite panitumumab monotherapy begun in October 2015 and trifluridine-tipiracil treatment begun in January 2016. In March 2016, one nodule of HCC in the left lobe appeared and RFA against this lesion was performed.

At this point, supportive care was considered because most of the standard chemotherapies for mCRC had already been ineffective, and considerable hepatic failure induced by regorafenib was expected because the patient was experiencing Child A liver dysfunction. Based on the patient's strong desire to continue chemotherapy, we administered regorafenib at a 50% reduced dose in June 2016. Values of albumin (Alb), prothrombin (PT) %, and total bilirubin (T-bil) were 3.2 g/dL, 81%, and 0.7 mg/dL, respectively. The Child–Pugh score was A. Platelets (Plt), AST, ALT, and lactate dehydrogenase (LDH) values were $11.8 \times 10^4/\mu L$, 53 U/L, 22 U/L, and 326 U/L, respectively.

The patient showed grade 1 hoarseness 3 days after the initiation of regorafenib. Values of Plt, T-Bil, AST, ALT, and LDH were $9.8 \times 10^4/\mu L$, 1.0 g/dL, 70 U/L, 30 U/L, and 400 U/L, respectively, after 8 days, indicating slight progression of thrombocytopenia and deterioration. Administration of regorafenib continued. After 14 days, the patient experienced myodesopsia of the right eye. Fundus examination revealed hemorrhage of the retinal vein (Fig. 1A). Since the hemorrhagic area of the retina was relatively small, observational therapy was pursued. The patient also showed a small amount of blood in the stool, indicating gastrointestinal hemorrhage. Because no obvious anemia was detected, an immediate endoscopic examination was not performed. No worsening of the other adverse events was observed, including liver dysfunction. After discontinuation of the regorafenib, these adverse events resolved spontaneously in 1 week (Fig. 1B). The patient was referred to another hospital for palliative care in October 2016 and died of the tumor in November 2016. Retinal hemorrhage was not relapsed. Informed consent was obtained from the patient for the publication of the case details before treatment initiation.

3. Discussion

Regorafenib is an inhibitor for multiple kinases such as VEGFR1-3, TIE2, PDGFRβ, FGFR, *KIT*, *RET*, *RAF-1*, and *BRAF*. It suppresses signaling pathways relating to tumor progression, the tumor microenvironment, and angiogenesis. In colon cancer, the CORRECT trial showed the efficacy of regorafenib against placebo with prolonged overall survival (6.4 months vs 5.0

Figure 1. (A) Fundus examination revealed hemorrhage of the retinal vein (arrow). (B) Retinal hemorrhage spontaneously disappeared in 1 week after the discontinuation of regorafenib treatment.

months, hazard ratio (HR) 0.77).[1] Further, the efficacy of regorafenib was also shown for HCC and GIST.[3,4] These data show clinical efficacy of regorafenib in various tumors.

The adverse events caused by multikinase inhibitors are different from those of classical cytotoxic agents. For example, hypertension, hand-foot syndrome, skin eruption, hoarseness, venous or arterial thromboembolism, hemorrhage, and hypothyroidism have been observed.[5] In the present case, retinal hemorrhage and gastrointestinal hemorrhage were observed. The precise location of the gastrointestinal hemorrhage was not clear because endoscopy was not performed. The major causes of retinal hemorrhage are diabetic retinopathy and vessel occlusion, trauma, and drugs. The patient did not have diabetes mellitus, hypertension, or a history of trauma. Given that fundus angiography was not performed, a diagnosis of vessel occlusion such as branch retinal vein occlusion (BRVO) was difficult to define. Whereas VEGF plays a role in preventing platelet aggregation, thrombosis, and proliferation of the smooth muscle cells of the vascular tunica media,[8,9] it is rare that a therapeutic antibody specific for VEGF such as bevacizumab would only cause drug-induced retinal hemorrhage or vessel occlusion. Because not only VEGFR, but also FGFR and TIE2, which are targets of regorafenib, are important for the maintenance or injury response of vascular endothelial cells,[10–12] drug-induced retinal hemorrhage or vessel occlusion might have been caused in the present patient by the inhibition of multiple targets. In cases of severe retinal hemorrhage, surgery is performed to remove the blood. Carbazochrome sodium sulfonate hydrate and kallidinogenase are administered for minor retinal hemorrhage.[13] The retinal hemorrhage in the present patient was sufficiently minor to require only observation after withdrawing the regorafenib. In cases of vascular leakage, intravitreal injection of anti-VEGF antibody is considered.[14] Given that the hemorrhage in this case was caused by regorafenib suppressing VEGFR kinase, administration of anti-VEGF antibody was not thought to be applicable.

Retinal hemorrhage should be considered when blurred vision or visual disturbance is experienced by a patient undergoing treatment with a multikinase inhibitor such as regorafenib. Further, rapid evaluation is important to determine the cause of the symptoms and possible effects of the specific treatment.

In the present patient, the period until the appearance of retinal and gastrointestinal hemorrhage after the start of regorafenib was very short, suggesting that rapid excessive elevation of the regorafenib level or its active metabolite concentration might have been related to these events. Two reasons are suggested. One is the impairment of liver function, and the other is the genotype of *UGT* based on the history of irinotecan-related toxicities. Regorafenib is mainly metabolized in the liver by CYP3A4 and UGT1A9.[7] CYP3A4 converts regorafenib to the N-oxide form, M-2 and N-amine oxide forms, and M-5, which perform activities similar to that of regorafenib. This indicates that liver function is important for the metabolism of regorafenib. However, the pharmacokinetics and safety of regorafenib treatment in patients with liver dysfunction has not been fully elucidated.

Sorafenib is a multikinase inhibitor sharing a similar structure with regorafenib and is metabolized by CYP3A4 and UGT1A9 in the liver. In the subset analysis of the GIDEON trial,[14] which demonstrated the efficacy of sorafenib for HCC, drug-related serious adverse events were observed in 16.2% of the Child score A population, and in 32.8% of the Child score B population. These results suggest that regorafenib may cause more adverse events as liver function worsens. Although the Child score was A

in the present case, the patient had chronic hepatitis C and a history of multiple treatments for HCC by RFA, TACE, and PEIT, suggesting that use of solely the Child score may not sufficiently predict the safety of regorafenib in a given patient. In fact, drug-related serious adverse events were observed in 16.2% of the Child score A patients, as previously shown. The genotype of *UGT1A1* in the present case was heterozygous for both *6 and *28. Adverse events caused by irinotecan are affected by the *UGT1A1* genotype.[15] However, the effects of the *UGT1A1* genotype on regorafenib are not fully known. Only *UGT1A9*22, which is a gene polymorphism in the promoter region, is suggested to relate to the incidence of drug-induced liver injury (DILI) by regorafenib.[16] Further, although the *UGT1A1* genotype did not appear in the present case, patients with DILI also have been seen to have a history of grade 3 or worse neutropenia,[16] suggesting that severe adverse events caused by irinotecan are perhaps related to genotypes such as *UGT1A1*. Therefore, clinicians should be alert to the possibility of toxicities caused by regorafenib. In the present patients, grade 3 AST/ALT elevation due to irinotecan was observed. Taken together, impaired liver function and genotypes relating to drug metabolism such as UGT1A1 might be associated with retinal and gastrointestinal hemorrhage.

4. Conclusion

The present case showed retinal and gastrointestinal hemorrhage despite the half dose of regorafenib administration due to liver disease. In the future, safety management and dosage adjustment of regorafenib in liver dysfunction patients, as well as the association of drug metabolism with genotype, are expected to be established.

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