Regorafenib-Induced Hyperammonemic Encephalopathy in Metastatic Colon Cancer

Abstract

Regorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), is used in metastatic colorectal cancer (mCRC) and gastrointestinal stromal tumors (GIST) for salvage-line therapy. From clinical trials, the most commonly reported adverse events of regorafenib are hand-foot skin reactions, fatigue, diarrhea and hypertension. We report two cases of hyperammonemic encephalopathy induced by regorafenib in patients with mCRC. Hyperammonemic encephalopathy is a life-threatening complication in patients with severe liver cirrhosis, and is often observed in liver dysfunction/failure cases. Cases of hyperammonemic encephalopathy have been reported with various multi-targeted TKIs. The underlying mechanism of encephalopathy remains unclear, but in light of similar presentations, it can be reasonably suspected to be a result of a class effect of these TKIs. We suggest checking ammonia levels in patients on regorafenib presenting with altered consciousness, even if they have normal liver function. Discontinuation of regorafenib, as well as ammonia-lowering therapy, is essential to the management of this adverse effect, and recommencement of regorafenib should be discouraged.

Keywords: Regorafenib; Hyperammonemic encephalopathy; Metastatic colorectal cancer

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Abbreviations: TKI: Tyrosine Kinase Inhibitor; Mcrc: Metastatic Colorectal Cancer; GIST: Gastrointestinal Stromal Tumor; FOLFOX: Folinic Acid, Fluorouracil and Oxaliplatin; FOLFIRI: Folinic Acid, Fluorouracil and Irinotecan; PD: Progressive Disease; SD: Stable Disease; CT: Computed Tomography

Introduction

The CORRECT trial has shown that regorafenib is the first small-molecule multikinase inhibitor with survival benefits in metastatic colorectal cancer (mCRC) that has progressed after standard therapies [1]. As a multi-targeted tyrosine kinase inhibitor (TKI), the expected adverse events of regorafenib are similar to those reported with other multi-targeted TKIs imatinib, sunitinib and sorafenib. Hand-foot skin reactions, fatigue, diarrhea and hypertension are the most common grade 3 or higher adverse events according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) [2]. Other, and rarer, adverse events include hepatotoxicity, hemorrhage, myocardial ischemia and infarction, gastrointestinal perforation or fistula formation, reversible posterior leukoencephalopathy syndrome and impaired wound healing [3]. In the CORRECT trial, the occurrence of increased liver transaminases and bilirubin was higher in the regorafenib group than in the placebo group. The difference was mainly attributable to grade 1 and 2 events, but one fatal case compatible with regorafenib-related drug-induced liver injury was reported [1]. Hyperammonemic encephalopathy is a life-threatening complication in patients with severe liver cirrhosis, and is often observed in liver dysfunction/failure cases. Regorafenib-induced hyperammonemic encephalopathy has been reported once in GIST, though it is a less common complication for CRC [4]. We first report two cases of hyperammonemic encephalopathy induced by regorafenib in patients with mCRC.

Case Report

Case 1

A 65-year-old man diagnosed with cancer of the sigmoid colon and liver metastases underwent surgery for sigmoid resection in December 2011, and started standard chemotherapy in a previous institution. The response to treatment was judged to be progressive disease (PD) after FOLFOX, FOLFIRI with bevacizumab or panitumumab, so he was introduced our institution to receive regorafenib for salvage line. His performance status was 0, and he had no fundamental liver disease. Although there was no obvious liver disease, he had several attacks of acute cholangitis due to liver metastases in the previous course of treatment and in treatment at our institution. However, none of the attacks caused the development of hyperammonemic encephalopathy. We started regorafenib in May 2015, and judged the response to be a stable disease (SD) by RECIST after the first course. However, after 7 days of the second course of regorafenib therapy, he was admitted to our hospital with an episode of acute confusion. Physical examination noted blood pressure 118/76 mmHg, pulse 70 per minute, saturation 96% on room air and Glasgow Coma Scale 13 (eye 3, verbal 4, motor 6). He was afebrile on presentation but had leukocytosis of 14.3×10^9 /L and an elevated C-reactive protein (CRP) of 119.5 mg/L. A liver function test noted albumin 25 g/L, alkaline phosphatase (ALP) 1399 IU/L, alanine aminotransferase (ALT) 39 IU/L, aspartate aminotransferase (AST) 127 U/L and total bilirubin 2.2 mg/dL. A computed tomography (CT) scan of the abdomen revealed that the liver metastases of the CRC had grown, and were pressing on bile ducts nearby. As we diagnosed acute cholangitis, we medicated the patient with ciprofloxacin. In addition, a markedly elevated ammonia level of 235 µg/dL was observed, and a CT scan of the brain did not reveal any intracranial findings. Considering that his acute confusion was

due to hyperammonemic encephalopathy, we injected him with branched-chain amino acids, and he had a complete resolution of the confused state within 24 h. After a 10-day hospital admission, he was discharged without any functional disorders. Regorafenib was discontinued after this episode, and he died after 1 month of best supportive care.

Case 2

A 63-year-old man diagnosed with cancer of the sigmoid colon, involving liver and lung metastases, underwent surgery for sigmoid resection in April 2011, and started on standard chemotherapy in our institution. He had alcohol-related cirrhosis with Child-Pugh Class B, and had several episodes of hyperammonemic encephalopathy because of bacterial infection. The response to treatment was judged to be PD after second line regimens, so we started regorafenib as a third-line treatment in November 2014. His performance status was 1, and his liver function was fair to start regorafenib. However, on the second day of the first cycle of regorafenib therapy, he was admitted to our hospital with an episode of acute confusion. Physical examination noted blood pressure 172/86 mmHg, pulse 88 per minute, saturation 96% on room air and Glasgow Coma Scale 14 (eye 4, verbal 4, motor 6). He was afebrile on presentation but had leukocytosis of 17.3×109 /L and almost normal CRP level of 10.8 mg/L. A liver function test noted albumin 21 g/L, ALP 373 IU/L, ALT 16 IU/L, AST 44 U/L and total bilirubin 1.6 mg/dL. As there was a possibility of infection, he received broad-spectrum intravenous antibiotics with ceftriaxone, but a septic screen including blood culture and urine culture was unremarkable. In addition, a markedly elevated ammonia level of 178 µg/dL was observed, and a CT scan of the brain did not reveal any intracranial findings. As his acute confusion was due to hyperammonemic encephalopathy, the patient received branched-chain amino acids and had a complete resolution of the confused state within 24 h. After a 2-day hospital admission, he was discharged without any functional disorders. Regorafenib was discontinued after this episode, and he died after 6 months of best supportive care.

Discussion

Ammonia, the major nitrogenous product of protein catabolism, is a highly toxic compound, particularly to the brain. Ammonia activates the mitochondrial benzodiazepine receptors and increases the production of neuroactive steroids. The neuroactive steroids activate the γ-aminobutyric acid (GABA) receptors in the cerebral cortex, resulting in neuroinhibition [5]. Hyperammonemia occurs when ammonia is either overproduced or insufficiently eliminated from the blood. The metabolism of ammonia occurs primarily through the urea cycle, where it is a by-product of the conversion of amino acids to α-ketoacids [6].

Hyperammonemic encephalopathy is characterized by an abrupt alteration in mental status with a markedly elevated serum ammonium level, and is a rare, potentially fatal complication of chemotherapy in the absence of obvious liver disease [6]. Hyperammonemic encephalopathy sometimes occurs in patients with hematologic malignancies during the period of neutropenia following cytoreductive therapy or high-dose chemotherapy for bone marrow transplantation, or in patients with solid organ malignancies treated with fluorouracil [7,8]. It is uncommon for patients with hepatic malignant infiltration to develop hyperammonemic encephalopathy, except in primary hepatocellular carcinomas or neuroendocrine tumors with hepatic metastases [9].

Cases of hyperammonemic encephalopathy have been reported with various multi-targeted TKIs. There are four cases of sunitinib-induced hyperammonemic encephalopathy [10-12], one case of sorafenib-induced hyperammonemic encephalopathy [13], and one case of regorafenib-induced hyperammonemic encephalopathy [4] (Table 1). The underlying mechanism of encephalopathy remains unclear, but in light of similar presentations, it can be reasonably suspected to be a result of a class effect of these TKIs [9].

Table1: Summary of previously reported cases of hyperammonemic encephalopathy induced by multi-targeted TKIs.

Case Report	Age/sex	Diagnosis	Drug	Serum Ammonia (µmol/L)	Management	Time to Recovery
Lee et al. [10]	58/Male	GIST with liver metastases	Sunitinib	150	Lactulose	24 h
Lee et al. [10]	68/Female	GIST, no known hepatic compro-mise	Sunitinib	278	Lactulose	24 h
Shea et al. [11]	61/Male	Pancreatic NET with liver metas-tasis	Sunitinib	147	Lactulose	24 h
Kezban et al.	66/Female	RCC with liver metastasis	Sunitinib	146	Lactulose	168 h
Brandi et al. [14]	75/Male	HCC with hepatic cirrhosis	Sorafenib	657	Lactulose	24 h
Kuo et al. [4]	61/Male	GIST with liver metastases	Regorafenib	105	None	72 h

NET: Neuroendocrine Tumor; RCC: Renal Cell Carcinoma; HCC: Hepatocellular Carcinoma

Regarding our patients, Case 1, who was without underlying liver disease and cirrhosis, probably developed hyperammonemia with regorafenib owing to liver metastases limiting normal hepatic reserve without overt liver failure. Moreover, the accompanying acute cholangitis might have exaggerated the symptoms. It is interesting that he did not develop hyperammonemic encephalopathy with his previous course of regorafenib. We think the reason for this observation was the gradual growth of metastases in the liver impairing the capacity of the liver to clear up the ammonia via the urea cycle; the same observation was discussed in Shea's report [11]. In Case 2, underlying alcohol-related cirrhosis impaired the liver capacity, and his blood ammonia level was potentially high. Regorafenib might play a role in expressing encephalopathy, but the exact mechanisms are uncertain. Brandi et al. suspected that sorafenib may have direct neuronal action, which could trigger the onset of metabolic encephalopathy [14]. Up to now, three reported cases of sunitinib-induced hyperammonemia occurred in Asian patients. This might point to an ethnic difference with genetic polymorphism in pharmacokinetic or pharmacodynamic pathways predisposing Asian patients to this complication [10]. The relationship between regorafenib and the development of hyperammonemic encephalopathy is not well known, and its mechanism is unclear. Further studies addressing this issue are warranted.

It may be useful to combine regorafenib with ammonia-lowering therapy before hyperammonemic encephalopathy occurs. Ammonia is mainly produced from dietary nitrogenous components, by bacterial metabolism in the colon and from glutamine in the small intestine by glutaminase activity [15]. The ammonia from the gastrointestinal tract eventually enters the portal circulation and is converted in the liver to urea via the urea cycle, and subsequently excreted by the kidneys [16]. Dietary protein restriction is generally not recommended, and lactulose (beta-galactosidofructose) is commonly used to treat acute and chronic hyperammonemic encephalopathies. Lactulose treatment is based on the absence of a specific disaccharidase on the microvillus membrane of enterocytes in the human small bowel, thereby permitting the entry of disaccharides into the colon. The lactulose is then catabolized by the bacterial flora to short-chain fatty acids (e.g. lactic and acetic acids), which lower the colonic pH to approximately 5. This reduced pH in turn favors the formation of non-absorbable NH_4^+ from NH_3, trapping NH_4^+ in the colon and thus reducing plasma ammonia concentrations. Other proposed mechanisms of lactulose action include modification of the colonic flora including a shift from urease-containing bacteria to lactobacilli, and a four-fold increase in fecal nitrogen excretion as a result of increased stool volume, and potentially reduced formation of toxic short-chain fatty acids e.g. propionate or butyrate [17-20]. Non-absorbable antibiotics are also effective for treating hepatic encephalopathy, with rifaximin being the most frequently used. However, antibiotics affect the gut flora, and may be significantly more expensive than non-absorbable disaccharides, making them most suitable for patients who cannot tolerate or do not respond sufficiently to disaccharides. Sharma et al. performed an open-label randomized controlled trial in India and demonstrated that lactulose was also effective in preventing recurrent episodes of hyperammonemic encephalopathy [21].

Conclusion

We report the first two cases of probable regorafenib-induced hyperammonemic encephalopathy in patients with mCRC. Impaired liver function may have been contributory in both cases, but the role of regorafenib is not to be discounted. As a salvage-line treatment, regorafenib is likely to become more widely used in metastatic CRC and GIST, and the possibility of inducing hyperammonemic encephalopathy in the setting of pre-existing liver function derangement needs to be considered. The absence of regorafenib-induced hyperammonemia during an initial course does not rule out the possibility of future complications arising from growing liver metastases. We suggest checking the ammonia levels in patients on regorafenib presenting with altered consciousness, even if they have normal liver function. Discontinuation of regorafenib, as well as ammonia-lowering therapy, is essential for managing this adverse effect, and recommencement of regorafenib should be discouraged.

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