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CASE REPORT

Multi-Targeted Tyrosine Kinase Inhibitor-Induced Hyperammonemic Encephalopathy: a Report of Two Cases Using Pazopanib, Sunitinib, and Regorafenib

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Introduction

With the development of targeted therapies in the past decades, new side effects in relation to the mechanism of the therapies have surfaced. Several drugs were terminated in the early phases of clinical development due to unanticipated toxicities [1]. Currently in clinical practice, targeted therapies, such as tyrosine kinase inhibitors (TKIs), have become widely used for treatment of several malignancies. Physicians are now increasingly challenged to manage the undesired adverse effects to maximize the clinical benefits of these drugs for their patients. The common adverse effects of multi-targeted TKIs reported in clinical studies include hand-foot syndrome, diarrhea, hypertension, and metabolic and electrolyte imbalance [1]. These common toxicities were reported as a class effect of multi-targeted TKI, such as sorafenib, sunitinib, pazopanib, and regorafenib, due to the class-specific mechanism. However, other uncommon adverse effects are typically underreported before approval of these drugs. Therefore, physicians could potentially be faced with these uncommon toxicities in clinical practice.

Neurological adverse effects are uncommonly reported in multi-targeted TKIs in their pivotal studies. In the CORRECT study, only one patient developed seizure after receiving regorafenib, an effect which was not observed in the GRID study [2, 3]. Similarly, neurological toxicities were rarely observed in the pivotal trials of other TKIs such as sorafenib, sunitinib, and pazopanib.

Drug-induced hyperammonemic encephalopathy is one of the uncommon neurological adverse effects of multi-targeted TKI, which is rarely observed in clinical practice. We have two reported cases of metastatic gastrointestinal stromal tumor (GIST) patients who developed drug-induced hyperammonemic encephalopathy related to pazopanib, sunitinib, and regorafenib.

Case 1

A 51-year-old female patient was diagnosed with metastatic GIST in 2008. She was treated with imatinib and subsequently with sunitinib. She eventually developed disease progression in her liver after 5 years of treatment. Subsequently, the patient underwent right hepatectomy in 2013, followed by observation. After her disease was well-controlled for 2 years, she developed peritoneal metastasis. Regorafenib was started in 2015; however, she was unable to tolerate 80 mg/day due to diarrhea and hand-foot syndrome. After recovery, pazopanib 400 mg daily was initiated. She was brought to the emergency room after two doses of pazopanib with acute alteration of consciousness and behavior changes. Physical examination demonstrated drowsiness, normal blood pressure, otherwise was unremarkable. CT scan of the brain, EEG, and other blood tests were normal. With regard to her clinical history and examination, pazopanib-induced encephalopathy was suspected. However, her ammonia level was not obtained. Despite not checking her ammonia, her symptom resolved within 48 h after pazopanib was discontinued. She received oral lactulose after 3 days of admission and her symptoms completely resolved within a week. She was then discharged home without any residual neurologic symptoms. A month later, sunitinib 12.5 mg daily was started. After one dose of

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sunitinib, she developed fever, seizure, and loss of consciousness. Her blood pressure was normal. She subsequently was intubated. Septic workup, EEG, MRI, and CT brain were unremarkable. Serum ammonia level was 52 mg/dL (normal range < 35 mg/dL). Anticonvulsants and broad-spectrum antibiotic were immediately started. Lumbar puncture was normal pressure and cell analysis. Sunitinib was then discontinued due to another episode of suspected TKI-induced encephalopathy. One day later, she was extubated and her neurologic symptoms normalized. She was then discharged home with best supportive care.

Case 2

A 74-year-old female patient was diagnosed with metastatic small bowel GIST in 2008. She was on imatinib with good clinical response for 7 years, but subsequently developed disease progression. Sunitinib was then initiated and her disease was well-controlled for further few months. Her physician then started regorafenib at dose 120 mg daily. After the 35th day of regorafenib, she was brought to the emergency room with acute onset of confusion. Physical examination showed hypertension (BP = 180/110 mmHg), otherwise unremarkable. CT scan and MRI of the brain were not consistent with posterior reversible encephalopathy syndrome (PRES), otherwise normal. Other blood tests were within normal limit, except elevated ammonia (122 mg/dL). With regard to her clinical history and examination, regorafenib-induced hyperammonemic encephalopathy was suspected. Regorafenib was immediately discontinued. Lactulose and protein intake limitation were initiated. The ammonia level was slightly decreased within the range 88–115 mg/dL after treatment. Unfortunately, the patient deteriorated and passed away 13 days after hospitalization.

Discussion

Ammonia, a compound derived from protein catabolism, is an extremely toxic compound to the central nervous system [4]. Ammonia is normally converted to urea by the liver and eliminated in urine. Imbalance of ammonia regulation leads to hyperammonemia, which may result in encephalopathy. Hyperammonemic encephalopathy usually occurs in patients with hematological malignancies following cytoreductive chemotherapy or bone marrow transplantation. High-dose chemotherapy-induced hyperammonemic encephalopathy such as 5-fluorouracil was occasionally reported with high mortality rates [4, 5]. Drug-induced hyperammonemic encephalopathy is an uncommon neurological adverse effect, which is often diagnosed after exclusion of other common causes of encephalopathy.

We have reported two cases of multi-targeted TKI-induced hyperammonemic encephalopathy from different TKIs including, pazopanib, sunitinib, and regorafenib (Table 1).

Table 1 Summary of previously case reports of multi-targeted TKI induced hyperammonemic encephalopathy

Case	Sex/age	Diagnosis	Drug (mg/day)	Time to symptom	Ammonia level[a] (xUNL)	Management	Time to recovery (day)	Rechallenge
Case no. 1	F/51	Metastatic GIST	Pazopanib (400)	2 days	–	Lactulose	2	No
			Sunitinib (12.5)	1 day	1.48×[a]	Antibiotic, anticonvulsant	2	No
Case no. 2	F/74	Metastatic GIST	Regorafenib (120)	35 days	3.48×	Lactulose	Death	No
Lee et al. [6]	M/58	Metastatic GIST	Sunitinib (50)	17 days	4.67×	Lactulose	1	No
	F/68	Metastatic GIST	Sunitinib (50)	10 days	8.64×	Lactulose	1	Yes (same dose) with recurrence
Shea et al. [7]	M/61	Metastatic PNET	Sunitinib (12.5)	14 days	4.45×	Lactulose	1	No
Kezban et al. [8]	F/66	Metastatic RCC	Sunitinib (50)	14 days	2.86×	Lactulose	7	No
Brandi et al. [9]	M/77	Metastatic HCC	Sorafenib (800)	5 days	< UNL	Lactulose	< 7	No
	M/75	Metastatic HCC	Sorafenib (800)	10 days	2.62×	No treatment[b]	< 14	Yes (half dose) with recurrence
Kuo JC et al. [10]	M/61	Metastatic GIST	Regorafenib (160)	13 months	–	Antibiotic	3	Yes (same dose) with recurrence
Kitamato et al. [11]	M/65	Metastatic CRC	Regorafenib	35 days	5.22×	BCAA	1	No
	M/63	Metastatic CRC	Regorafenib	2 days	3.95×	BCAA	1	No

BCAA, branched-chain amino acid; *UNL*, upper limit normal; *GIST*, gastrointestinal stromal tumor; *PNET*, pancreatic neuroendocrine tumor; *RCC*, renal cell carcinoma; *CRC*, colorectal cancer

[a] Ammonia level when the symptoms had already improved

[b] Hold sorafenib only

Case no. 1 had recurrence of encephalopathy after switching to the different TKI, which may support potential evidence of a class effect of this toxicity. Although serum ammonia level was not obtained at the first event, the other causes of encephalopathy including PRES were excluded. The patient's condition resolved 1 day after the discontinuation of pazopanib. During the second admission on sunitinib, slight elevation of serum ammonia was demonstrated at 2 days after recovery, which may not have represented the peak level of ammonia. In this particular case, it is possible that her liver reserve was limited after multiple treatments and liver resection. Thus, hyperammonemic encephalopathy could be more likely to develop with smaller doses of TKIs due to reduced hepatic capacity to metabolize ammonia.

To our knowledge, nine cases were previously reported in the literature from various multi-targeted TKIs including sorafenib, sunitinib, and regorafenib [6–11]. These cases are summarized in the Table 1. Three patients were rechallenged with the same drugs, with recurrences of hyperammonemic encephalopathy [6, 9, 10]. Duration to the onset of encephalopathy varied from 1 day to 13 months after starting TKIs. Most of the patients usually recover within the first few days after discontinuation of these drugs. Interestingly, most multi-targeted TKI-induced hyperammonemic encephalopathy cases were reported in Asian patients. Four of 11 cases were reported in the consisted of patients from non-Asian ethnicity [8–10].

The mechanism of hyperammonemia associated with small molecule multi-targeted TKIs is not well-understood. The reports of small molecule multi-targeted TKIs-induced hyperammonemic encephalopathy (Table 1) appear to share the common targets, especially vascular endothelial growth factor receptor (VEGFR), and platelet derived growth factor receptor (PDGFR). The anti-angiogenetic effect of the VEGFR TKIs could inhibit the new vascular formation in many organs including brain. This may interfere vascular-cerebral permeability or "blood-brain barrier." Thus, higher amount of ammonia may cross the blood-brain barrier into the central nervous system than usual.

Since multi-targeted TKI-induced hyperammonemic encephalopathy is rarely reported, no standard treatment is available. Therefore, the clinical knowledge and judgment of the clinician are crucial in management of such cases. Suspected TKIs should be discontinued immediately. Physicians may consider treating these patients with a similar approach to hepatic encephalopathy to reduce ammonia absorption and production [12]. Oral and/or transrectal lactulose, branch-chain amino acids are recommended, but the benefit gained is uncertain.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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