〈Case Report〉

Advanced gastrointestinal stromal tumor with intracerebral hemorrhage during sunitinib treatment

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ABSTRACT Herein, a 70-year-old female was initially treated with sunitinib 50 mg/day to treat an imatinib-resistant gastrointestinal stromal tumor. After sunitinib initiation, nausea, hypertension, hepatic dysfunction, anorexia, fatigue, thrombocytopenia, epistaxis, and palmoplantar erythrodysesthesia syndrome developed; the dose was reduced to 25 mg/day.

Subsequently, adverse events improved, and from the fifth course onward, sunitinib 37.5 mg/day was continued. Approximately 11 months after initiating sunitinib therapy, the patient developed disturbance of consciousness, aphasia, and left hemiplegia. Computed tomography of the head revealed intracerebral hemorrhage, and the patient was hospitalized. No brain metastases, cerebral aneurysms, or cerebral arteriovenous malformations were observed. Sunitinib-induced hypertensive cerebral hemorrhage was suspected as the cause of intracerebral hemorrhage. Conservative treatments, such as antihypertensive drugs, were administered without surgical treatment. The symptoms and intracerebral hemorrhage gradually improved, and the patient was discharged from the hospital. Intracerebral hemorrhage with sunitinib is extremely rare, but has a high mortality rate. During sunitinib treatment, controlling blood pressure and thrombocytopenia is important to prevent bleeding.

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Key words：Gastrointestinal stromal tumor, Sunitinib, Angiogenesis inhibitor, Intracerebral hemorrhage

INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) therapy with the monoclonal antibody bevacizumab and tyrosine kinase inhibitors sorafenib and sunitinib has afforded clinical benefits in randomized clinical trials involving patients with diverse solid tumor types[1－4)].

Sunitinib is an effective agent against imatinib-resistant gastrointestinal stromal tumors (GIST) and is inhibits the platelet-derived growth factor

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receptor, Flt-3, Ret, Kit, Raf, colony-stimulating factor 1 receptor, and VEGF receptor (VEGFR). Sunitinib suppresses multiple signals and causes adverse events[4-6]. Common sunitinib-induced adverse events include myelosuppression, fatigue, diarrhea, anorexia, palmar-plantar erythrodysesthesia syndrome, hypertension; intracerebral hemorrhage is markedly rare.

Herein, we report a case of an advanced GIST that developed intracerebral hemorrhage during sunitinib treatment.

CASE REPORT

The patient was a 70-year-old female with no history of hypertension, stroke, cerebral aneurysm, or dementia. During treatment at her previous hospital, the patient underwent partial gastrectomy for gastric GIST at 65 years of age. She underwent resection of the left subdiaphragmatic peritoneal dissemination at 66 years of age. At 67 years of age, peritoneal dissemination reappeared, imatinib was initiated, and her tumor shrank. At 70 years of age, the patient presented with increased peritoneal dissemination and liver metastasis and was referred to our hospital. Sunitinib 50 mg/day was initiated for imatinib-resistant GIST. After initiating sunitinib, treatment was stopped on day 13 owing to nausea, hypertension, liver dysfunction, anorexia, fatigue, platelet count of 48000/μL, and epistaxis. After resuming sunitinib at 37.5 mg/day, palmar-plantar erythrodysesthesia syndrome was exacerbated, and oral administration was interrupted for 14 days. During the third course, when sunitinib was reduced to 25 mg/day and resumed, oral administration was continued for four weeks, and treatment was discontinued for two weeks. From the fifth course onward, 37.5 mg/day of sunitinib was continued, partly because the adverse events were relieved. Subsequently, the patient experienced fatigue and loss of appetite; however, her hypertension was controlled with antihypertensive agents, and symptoms of palmar-plantar erythrodysesthesia syndrome improved with moisturizing agents and steroid ointments. Approximately, 11 months after initiating sunitinib treatment, the patient was brought to the emergency department owing to disturbance of consciousness, aphasia, and left hemiplegia. Computed tomography of the head revealed left frontal subcortical hemorrhage and ventricular perforation, and the patient was admitted to the hospital (Fig. 1A). Blood pressure was controlled at approximately 120 mmHg during oral sunitinib administration, which increased to 182/98 mmHg during cerebral hemorrhage. Laboratory data showed a platelet count of 150000/μL and no bleeding tendency. She was not taking anticoagulants. Magnetic resonance imaging and magnetic resonance angiography revealed the absence of brain metastases, cerebral aneurysms, cerebral arteriovenous malformations, or amyloidosis. Sunitinib-induced hypertensive cerebral hemorrhage was suspected of causing the intracerebral hemorrhage. The estimated blood loss was 45 mL; however, conservative treatment such as antihypertensive drugs, was administered since the brain compression was mild. Consciousness gradually recovered, and a head computed tomography scan one month later showed an improvement in the subcortical hemorrhage (Fig. 1B). Dysarthria and left hemiplegia gradually improved during rehabilitation. Approximately four months after the cerebral hemorrhage, hepatic metastasis and peritoneal dissemination increased because of imatinib withdrawal; therefore, left hepatic lobectomy + radiofrequency ablation and resection of dissemination were performed. Postoperatively, angiogenesis inhibitors were unavailable, and imatinib was resumed. Approximately four years later, multiple liver metastases appeared, and transcatheter arterial embolization (TAE) was performed three times. Subsequently, the tumor gradually grew, and the

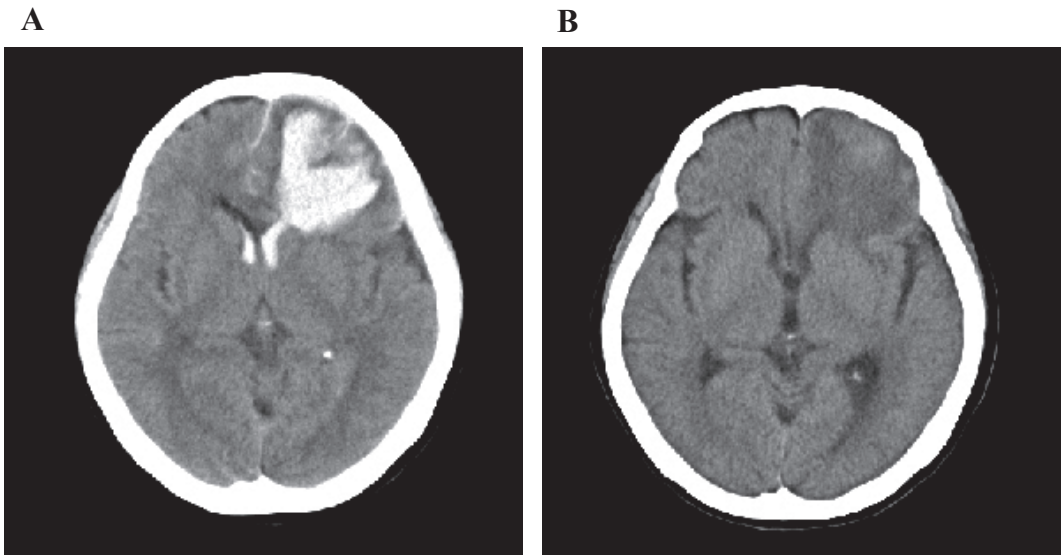

Fig. 1. Head computed tomography
(A) Left frontal subcortical hemorrhage with ventricular perforation, (B) one month later

patient died 6 years and 8 months after the onset of intracerebral hemorrhage.

DISCUSSION

Sunitinib has shown efficacy in randomized, placebo-controlled phase III trials for imatinib-resistant GIST, unresectable or metastatic renal cell carcinoma (RCC), and pancreatic neuroendocrine tumors (PNET), and intracranial hemorrhage has not been reported in phase III trials[7–9]. However, a phase II trial of sunitinib for RCC and advanced non-small cell lung cancer and a phase II trial of sorafenib for hepatocelluar carcinoma (HCC) have reported one case of intracranial hemorrhage each[11–13]. In a phase II trial, intracerebral hemorrhage was associated with brain metastases, and patient with brain metastases were excluded from the subsequent phase III trials.

A search of small-molecule VEGFR inhibitors and intracerebral hemorrhage identified seven reported cases[13–15](Table 1). There were six cases of RCC, one case of HCC, and four cases of sorafenib, two cases of sunitinib, and one case of pazopanib. Three patients had a history of hypertension, and one had a history of stroke and was taking anticoagulants. Cerebral metastasis was observed in five cases, and the number of days from treatment initiation to intracerebral hemorrhage ranged from 2 to 21 days. At the time of intracerebral hemorrhage diagnosis, five out of six patients had elevated blood pressure (≥ 180 mmHg). Regarding the prognosis after intracerebral hemorrhage, five patients died within 3 days. Based on these findings, hypertension, stroke, and brain metastasis were risk factors, and intracerebral hemorrhage developed early after initiating treatment.

Hypertension is one of the most frequent adverse events associated with anti-VEGF therapies. It is speculated that the mechanism of hypertension associated with VEGF inhibition involves reduced nitric oxide (NO) production in the walls of arterioles and other resistance vessels. VEGF increases NO synthesis by upregulating endothelial NO synthase, and VEGF inhibition decreases NO synthesis. As NO is a vasodilator, decreased NO synthesis promotes vasoconstriction,

Table 1. Reports of patients with VEGFR inhibitors-induced intracerebral hemorrhage

Author	Tumor	Agent	Year	Sex	Previous history	Cerebral metastasis	From drug initiation to ICH (day)	Hypertensive peak at diagnosis of ICH	Survival after ICH (day)
Pouessel D 2008	RCC	Sunitinib	71	Female	None	None	14	190 / 100	3
	RCC	Sunitinib	59	Female	None	+	4	130 / 80	3
	RCC	Sorafenib	71	Male	Cerebral stroke Antiplatelet therapy	+	2	200 / 100	0
	RCC	Sorafenib	62	Male	Hypertension	+	6	185 / 60	3
	RCC	Sorafenib	78	Male	Hypertension	+	5	210 / 100	1
Miller-Patterson C 2017	RCC	Pazopanib	69	Female	Hypertension	None	21	204 / 92	NR
Hata T 2019	HCC	Sorafenib	75	Male	NR	+	4	NR	NR
Present case	GIST	Sunitinib	70	Female	Hypertension with sunitinib	None	11months	182 / 98	6 years 8 months

VEGFR, vascular endothelial growth facter receptor; ICH, intracerebral hemorrhage; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumor; NR, not reported

increased peripheral resistance, and increased blood pressure[16]. The frequency of all grades of hypertension associated with VEGF inhibition is approximately 20-30% with bevacizumab and 15-60% with small-molecule tyrosine kinase inhibitors[17]. In GIST, RCC, and PNET phase III trials of sunitinib, hypertension was 11-26% considering all grades (grade 3 ≤ : 3-10%)[7-9]. Uncontrolled high-grade hypertension is a risk factor for myocardial infarction and cerebrovascular disease; therefore, caution should be exercised. Considering the present case report, dose reduction was undertaken after initiating sunitinib administration, owing to multiple adverse events, and hypertension was well controlled with antihypertensive agents. However, hypertention aggravated to 182 mmHg during intracerebral hemorrhage, suggesting that hypertension was the cause of intracerebral hemorrhage.

A relationship between brain metastases and intracerebral hemorrhage has also been reported. Pouessel *et al*. have reported that 5 of 67 patients with RCC treated with sunitinib and sorafenib developed intracerebral hemorrhage[13](Table 1). Brain metastasis was observed in four of five patients, and brain metastasis was considered a risk factor of ntracerebral hemorrhage. In contrast, three patients with brain metastasis but no intracerebral hemorrhage were reported simultaneously, and these patients were normotensive. Subsequently, the results of an expanded access trial of sunitinib have been reported[18]. Of the 4371 patient with RCC who received sunitinib, 321 (7%) had brain metastases, and only one presented with intracerebral hemorrhage. Sorafenib has been reported to reduce the incidence of brain metastasis[19]. Previously, higher mortality owing to intracerebral hemorrhage has been reported in patients receiving sunitinib or sorafenib, but this may be related to the effects of uncontrolled hypertension rather than bleeding. Sunitinib and sorafenib are not contraindicated for patients with brain metastases.

The mechanism underlying anti-VEGF therapy-induced bleeding remains poorly understood. This mechanism possibly involves decreased endothelial cell regeneration and increased vascular fragility resulting from VEGF blockade[16]. In addition, thrombocytopenia may exacerbate the bleeding risk. The most commonly reported bleeding event with sunitinib in the GIST phase III trial was epistaxis (7%). In the present case report, hypertension, fatigue, and malaise appeared immediately after

initiating sunitinib 50 mg, followed by a platelet counts of 48,000/μL and epistaxis. The blood concentration of sunitinib was expected to be high; therefore, the dose was reduced to 25 mg, and the adverse events resolved. The patient continued to receive sunitinib (37.5 mg) while controlling blood pressure with antihypertensive drugs; however, 11 months after treatment initiation, the patient developed an intracerebral hemorrhage. In previous reports of intracerebral hemorrhage (Table 1), all events occurred within one course, 2-21 days after initiating treatment. In the present case, no cerebral aneurysm was observed 11 months after initiaing treatment, suggesting that hypertension was caused by sunitinib. Five of the seven patinets with reported intracerebral hemorrhage died early.

Deaths due to intracerebral hemorrhage were due to extensive hemorrhage or brain metastases combined with intracerebral hemorrhage. This case had relatively extensive subcortical hemorrhage, but with regular confirmation of neurological symptoms, CT imaging, and strict blood pressure control, the subcortical hemorrhage did not spread and the patient was saved. Subsequently, resection of liver metastases and dissemination, continued imatinib therapy, and TAE were performed, and the patient survived for 6 years and 8 months after intracerebral hemorrhage.

CONCLUSION

We encountered a case of advanced GIST with intracerebral hemorrhage during sunitinib treatment. In clinical trials, the frequency of cerebral hemorrhage due to anti-VEGF/VEGFR therapy is markedly low (< 1%), but remains a serious complication. Additionally, the risk of bleeding may be confounded by hypertension or thrombocytopenia. Managing blood pressure and thrombocytopenia is important during sunitinib treatment.

DISCLOSURE STATEMENT

The authors have no conflict of interest.

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