CASE REPORT doi: 10.2176/nmc.cr.2012-0426

Neurol Med Chir (Tokyo) 54, 664–669, 2014 Online November 20, 2013

Sunitinib Treatment for Multiple Brain Metastases from Jejunal Gastrointestinal Stromal Tumor: Case Report

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare malignant tumors and only a few reported cases of brain metastases can be found. Introduction of a new molecular targeted agent, imatinib mesylate in the last decade has dramatically changed the treatment strategy and prognosis. However, imatinib is usually ineffective for brain metastasis from GISTs. The authors present the case of multiple brain metastases from jejunal GIST. The brain metastasis in the right prefrontal gyrus was detected 20 months after resection of the primary lesion when left hemiparesis began although the patient was on imatinib. Then the patient began taking sunitinib instead of imatinib, and the lesion shrunk and the symptom improved. However, after the dose reduction due to side effects, a new brain metastasis was found and this time, stereotactic radiation was effectively done. Sunitinib is one of the promising receptor tyrosine kinase inhibitors used for metastatic renal cell carcinomas or imatinib-refractory GISTs. Sunitinib is thought to penetrate blood-brain barrier, and recent reports indicate effectiveness to brain metastasis. To the authors' knowledge, this is the first report of brain metastases from jejunal GIST responding to sunitinib therapy.

Key words: gastrointestinal stromal tumor, brain metastasis, sunitinib

Introduction

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal gastrointestinal tumors that account for 6 to 14 annual incidences per million persons.[1–3] The prognosis of the tumor was dismal before the discovery of imatinib mesylate (Glivec®, Novartis Pharma AG, Basel, Switzerland), a novel receptor tyrosine kinase inhibitor, with occasional metastasis to the liver and peritoneum. However, metastasis of the tumor to the brain is extremely rare, with only a few cases hitherto were reported.[4–13] In addition, imatinib is believed to be ineffective for brain metastasis. Here, we present the case of a multiple brain metastases of imatinib-refractory jejunal GIST that was successfully treated with sunitinib malate (Sutent®, Phizer, New York, USA), another receptor tyrosine kinase inhibitor, and provide a literature review regarding this rare disease.

Case Report

A 74-year old, right handed man was referred to the department of surgery, Yamashiro Public Hospital. He was diagnosed as having arrhythmia at the age of 68 (6 years before onset) and was on warfarin. Just before the consultation, routine hematological examination revealed anemia, and abdominal computed tomography (CT) showed a 50-mm jejunal mass. After endoscopic biopsy, single-incision laparoscopic surgery for small bowel resection was performed 2 months after onset. Histological examination showed spindle-shaped cells with round to oval nuclei, and immunohistochemical study revealed the tumor was positive for KIT, CD34, alpha-smooth muscle actin (α-SMA), while negative for desmin and S-100. These findings were consistent with jejunal GIST. The MIB-1 labeling index was 22%. Later he was observed without adjuvant treatment for 18 months until a liver metastasis was detected by scheduled CT check-ups. He began taking imatinib mesylate orally on a continuous daily dosing schedule of 400 mg per day, but soon the dose was decreased to 200 mg because of skin rush. At 23 months after onset, CT revealed enlargement of liver metastasis, and the dose was increased to 300 mg, but in the next month, he complained of left-sided weakness. On examination, he was alert but had minor left hemiparesis and brain magnetic resonance (MR) imaging revealed a ring-shaped enhancing mass (14 × 14 × 15 mm), but negative in diffusion-weighted image with prominent edema in the right precentral gyrus (Fig. 1). Because of the MR imaging findings and preceding liver metastasis,

Received December 7, 2012; Accepted April 28, 2013

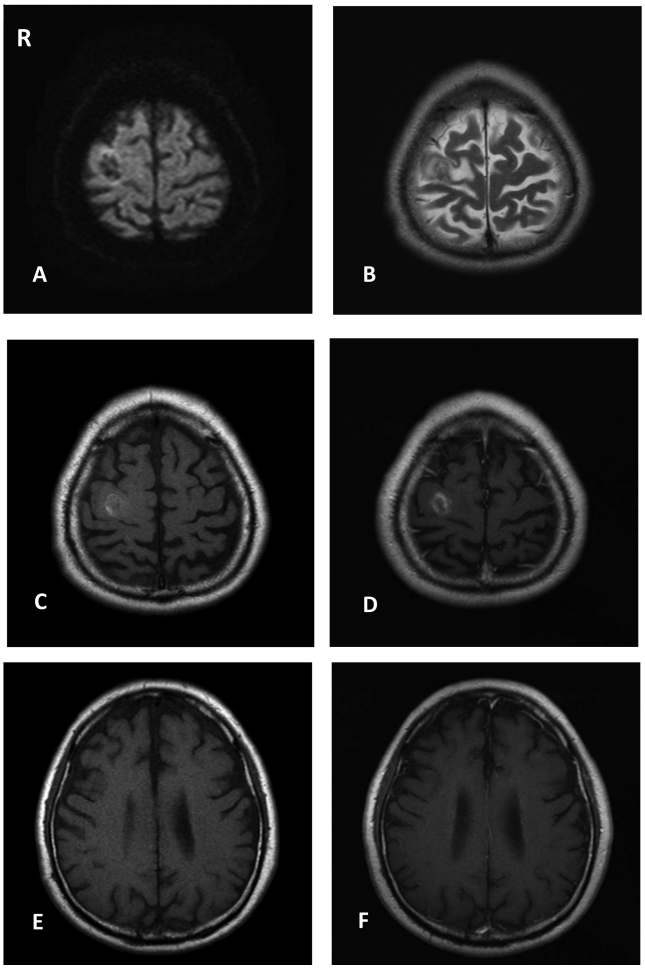

Fig. 1 Axial magnetic resonance (MR) images obtained at 24 months after onset. A: A negative diffusion-weighted image indicating denial of brain abscess. B: T_2-weighted image show marked brain edema around the lesion. C: Nonenhanced T_1-weighted image show isointensity lesion partly surrounded by high-intensity rim, suggesting minor hemorrhage. D: Post-gadolinium T_1-weighted image show ring-shaped enhancement, indicating a hemorrhagic tumor. T_1-weighted images without (E) and with (F) gadolinium injection at the level of lateral ventricles showing non-existence of tumor.

we diagnosed the brain lesion to be metastasis from GIST. He was then switched to sunitinib malate at a dose of 50 mg once daily in repeated 6-week cycles of 4 week on treatment, followed by 2 week off (schedule 4/2). In the first 2 weeks, he complained of general fatigue and the dose was reduced to 37.5 mg per day, but at the same time his symptoms gradually improved. In the next 2 weeks he experienced nasal bleeding and the blood examination showed platelet count of 45,000/mm^3, therefore the dose was again decreased to 25 mg. In the meantime, his symptoms further improved and objectively no motor laterality could be detected. Radiological examination confirmed the remarkable shrinkage of the enhanced

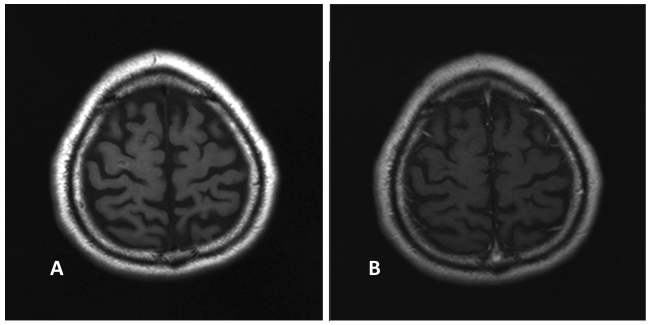

Fig. 2 Axial T_1-weighted magnetic resonance images at 26 months after onset without (A) and with (B) gadolinium injection demonstrating disappearance of the enhancing tumor.

lesion and surrounding edema (Fig. 2). Although he was symptom-free, a follow-up brain MR imaging study at 28 months after onset revealed emergence of a new lesion on the wall of right lateral ventricle with the size of 8 × 6 × 8 mm (Fig. 3), so that sunitinib dose was increased to 37.5 mg. But soon he suffered from pneumonia, and blood examination revealed bone marrow suppression (white blood cell count of 2,720/mm^3, platelet count of 23,000/mm^3), so he stopped taking sunitinib. Four weeks later, treatment resumed at the dose of 25 mg per day and this time he chose gamma knife radiosurgery (GKR) in addition to sunitinib therapy. Subsequently the second lesion disappeared and no other new metastasis was detected by repeated MR images for 9 months from initiation of sunitinib (Fig. 4) and he is doing well, taking 25 mg sunitinib continuously on schedule 4/2 without any symptoms.

Discussion

GISTs are mesenchymal tumors of the intestinal tract, that have been described to originate from interstitial cells of Cajal or a stem cell-like subset of KIT-positive spindle cells around the myenteric plexus.[14] GISTs can be found anywhere in the alimentary tract and small intestine as the second most frequent location, accounting for 20–30%. Symptoms are highly dependent on the size and location of the tumor. Symptomatic patients are as low as 47–69% at the diagnosis,[1,2] and most symptoms are non-specific. Besides, in 20–30% of cases, patients present features of metastasis upon first diagnosis.[14] In this case, the patient's symptom directly related to the tumor was only on the left hemiparesis, and even though anemia was due to intra-intestinal hemorrhage by the tumor it did not cause any subjective symptom. Metastases are mostly observed in the liver and peritoneum[14,15] while metastasis to brain is extremely rare and as long as we recognize, only 11 cases including this case were reported in English literatures.[4–13] Before the advent of

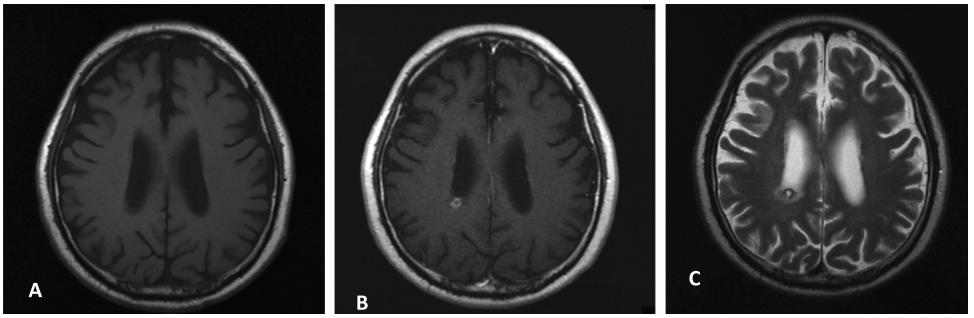

Fig. 3 Axial T_1-weighted magnetic resonance images at 28 months after onset without (A) and with (B) gadolinium injection demonstrating new ring-shaped enhancing lesion on the wall of right lateral ventricle. C: T_2-weighted image show a lesion at the same portion of ring-shaped enhancement surrounded by edema. The relatively wide expansion of edema compared with the lesion suggest metastatic tumor.

imatinib, GISTs were notoriously unresponsive to chemotherapy and radiation therapy, and the prognosis was poor with the overall 5-year survival rate of only 54%.[16] The prognosis of GISTs revolutionary improved as a result of the introduction of imatinib. Imatinib significantly improved recurrence-free survival compared to placebo (98% vs. 83% at 1 year) and suppressed recurrence rate (8% vs. 20% at median follow-up of 19.7 months) in a double-blinded multicenter trial.[15] The current clinical practice guidelines recommend surgical resection for limited disease and adjuvant imatinib therapy as an option for patients with a substantial risk of relapse.[17] However in some patients the tumor is tolerant to or may have acquired resistance to imatinib. In addition, central nervous system could be a sanctuary site for tumor cells since imatinib cannot pass blood-brain barrier (BBB), and does not achieve adequate levels as lower concentration of imatinib in the central nervous system have been detected in both mice[18] and humans.[19] In most of the reported cases of brain metastases from GISTs, imatinib did not exert anti-tumor effect.[4–7,9,11,12] Table 1 displays all English-language published cases of brain metastasis from GISTs (including this case report) found during a thorough literature review. Of note, in 2 cases among the 11 cases (18%), brain metastases were found prior to detection of primary lesion.[11,12] There seems no tendency about the duration from the first operation of GIST to detection of brain metastasis (from 3 weeks to 5 years).

Sunitinib is one of the promising molecular targeted, orally active, small-molecule multiple receptor tyrosine kinase inhibitor that selectively blocks vascular endothelial growth factor receptors (VEGFRs) types 1 through 3, platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), KIT, Fms-like tyrosine kinase-3 (FLT3), and colony-stimulating factor-1 receptor. Sunitinib exhibits potent antiangiogenic and antitumor activity. Sunitinib is approved for the treatment of advanced renal cell carcinoma (RCC), imatinib-refractory GIST, and advanced pancreatic neuroendocrine tumors, with starting dose of 50 mg once daily on schedule 4/2. Dose reductions to 37.5 mg per day and then to 25 mg per day are permitted on the basis of individual patient tolerability. For patients with imatinib-refractory GIST, sunitinib prolonged time

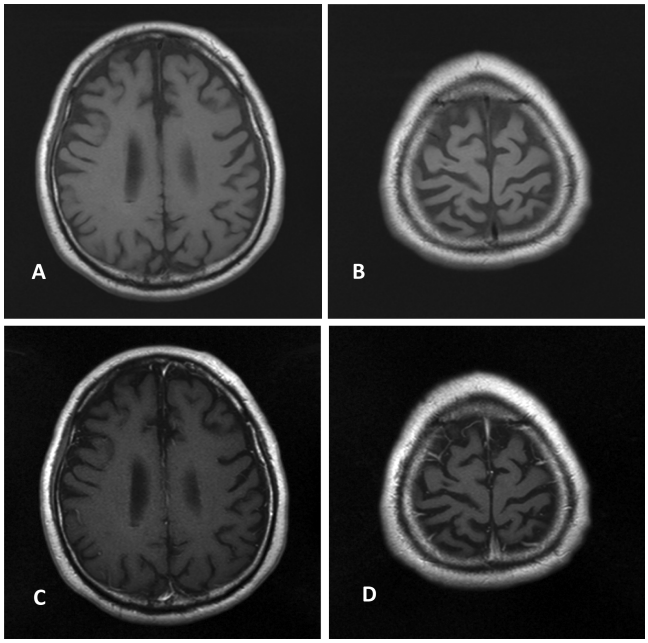

Fig. 4 Axial T_1-weighted images at 34 months after onset without (A, B) and with (C, D) gadolinium injection showing no evidence of remaining tumors.

to tumor progression of 6.3 months for patients treated with sunitinib compared to 1.5 months for patients dosed with placebo.[20] Unlike imatinib, accumulating evidences show sunitinib's ability to penetrate BBB. In mice, concentration of sunitinib were higher in brain (7-fold) than in plasma, and in monkeys, brain concentration of sunitinib and its metabolite SU12662 were similar to the concentrations in plasma,[21] and another report show 8.4-fold greater concentrations of sunitinib in mice brain tumor than plasma 12 hours after single injection.[22] Sunitinib is currently under clinical trials for primary (malignant gliomas,[23,24] meningiomas[25]) and metastatic[26,27] brain tumors. Suppressive effect of sunitinib for brain metastasis from RCC is already reported in some case reports,[28–30] and another clinical study shows 12% of objective response rate among 321 patients.[31] These results support the BBB penetration

Table 1 Reported cases of brain metastasis from gastrointestinal stromal tumors (GISTs)

Author (Year)	Age (yrs) /Sex	Primary tumor		Systemic metastasis	Treatment before detection of brain metastasis	Brain metastasis			Imatinib dose (mg/day)	Outcome
		Site	Size (cm)			Location	Time from Op	Treatment		
Brooks et al. (2002)[4]	75/M	Mesentery	N/D	Liver	No	Both hemispheres	14 mo	imatinib	800	CR
Hughes et al. (2004)[7]	47/M	Jejunum	7.5	Liver	Doxorubicin + decarbazine → imatinib	Left parasagittal	41 mo	Craniotomy	400 → 600 → 800	PD
Kaku et al. (2006)[10]	68/F	Perisacrum	N/D	N/D	No	Right parietal	2 yrs	Craniotomy	N/D	SD
Puri et al. (2006)[12]	42/M	Mesentery	8 x 6	N/D	*	Right parietal	N/A	craniotomy + XRT → carboplatin → ifosfamide + epirubicin → imatinib		PD
Gerin et al. (2007)[5]	45/M	Small bowel	N/D	N/D	Imatinib	Pontomedullary junction, cerebellum, leptomeningeal	5 yrs	imatinib	800	PD
Hamada et al. (2010)[6]	54/F	Esophagus	11 x 7	Liver	Imatinib	Left frontal	73 mo	Craniotomy + SRS		SD
Janku et al. (2010)[9]	56/F	Colon	3.4	Lung, liver	Imatinib	multiple	3 wk	Imatinib	600	PD
Wong and Chu (2011)[13]	26/M	Duodenum	6 x 5.4	Liver	Imatinib → sunitinib → radiofrequency ablation	Left frontotemporal	6 yrs	Craniotomy + WBRT		
Naoe et al. (2011)[11]	77/M	Jejunum	3	N/D	*	Right cerebral peduncle, left occipital lobe	N/A	Craniotomy	400 → 0	PD
Jagannathan et al. (2012)[8]	15/M	Stomach	2.8	Liver	Imatinib → sunitinib → sorafenib → nilotinib	Right frontoparietal	12 yrs	Craniotomy		SD
Present case	74/M	Jejunum	5	Liver	Imatinib	Right prefrontal gyrus	20 mo	Sunitinib + SRS		CR

* There was no treatment before detection of brain metastasis because brain metastasis was found prior to recognition of primary lesion. F: female, M: male, mo: months, N/A: not available, N/D: not described, SRS: stereotactic radiosurgery, WBRT: whole brain radiotherapy, wk: weeks, XRT: irradiation, yrs: years.

of sunitinib for brain tumors. In most reported cases of brain metastasis from GISTs, MR imaging findings show isointense in T_1-weighted image,[6,10,32] ring-enhancement after gadolinium injection,[6,32] and hypointense in T_2-weighted image.[8,10,32] In one case the brain metastasis was hemorrhagic.[8] The definitive diagnosis of metastatic brain tumor should be done by histological examination of tumor sample, but in this case, because the lesion, corresponding to the typical findings of metastasis from GISTs mentioned above, emerged after the exacerbation of liver metastasis, we decided it to be brain metastasis. Indeed, the emergence of second lesion that responded to GKR corroborated our diagnosis. In this case, the first metastatic tumor diminished by 50 mg per day of sunitinib. The second metastasis emerged when the dose was decreased (and temporally stopped) due to side effects, therefore we think 25 mg may not be sufficient for initial dose when a brain metastasis is found. Additionally, we guess that effective suppression by sunitinib on the primary lesion and liver metastases contribute to the control of brain metastases.

Besides the general adverse events, such as the classic hand-foot syndrome, stomatitis, and other dermatologic toxicities, one must pay some attention while using sunitinib, especially for patients with brain tumors. One is intracerebral hemorrhage (ICH). Currently, sunitinib application for patients with brain metastasis is, in Japan, requires careful administration by the ministry of health, labor, and welfare owing to the risk of ICH. Indeed, there is one report mentioning high incidence of ICH in patients with brain metastasis from RCC treated with sunitinib,[32] however, in that report ICH occurred preferably in patients with hypertension so that adequate control of blood pressure seems to be able to prevent ICH. Moreover, in other reports there were very few[33] or no[20,26,34] episodes of ICH reported. Another is pseudoresponse which is believed to come about after treatment with antiangiogenic therapies. Antiangiogenic agents can produce marked decrease in contrast enhancement as early as 1 to 2 days after initiation of therapy. These apparent responses to antiangiogenic therapy may be partly a result of normalization of abnormally permeable tumor vessels and not always necessarily indicative of a true antitumor effect.[35] Because sunitinib have inhibition effect for VEGFR, like bevacizumab, it may induce psdudoresponse. As a result, radiologic responses in studies with antiangiogenic agents should be interpreted with caution.[35] In this case the patient did not experience any ICH, and the response persisted more than 4 weeks, indicating sunitinib certainly and safely controlled brain metastases.

Conclusion

We have reported the first case of brain metastases from jejunal GIST responding to sunitinib therapy. Sunitinib proved a relatively safe and effective treatment modality. Although some considerations exist, sunitinib treatment for metastatic brain tumors would be a treatment of choice when it is not amenable to general anesthesia, lesions are located in eloquent areas, or the patient has uncontrolled primary lesion.

Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or findings specified in this article. Among the authors, all of who are members of The Japan Neurological Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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