 doi: 10.2176/jns-nmc.2022-0298

NMC Case Report Journal 10, 61-66, 2023

Tyrosine Kinase Inhibitor-associated Cerebral Arterial Occlusive Disease Treated with High-flow Bypass Surgery: A Case Report

Yurie RAI[1] and Takayuki HARA[1]

[1]*Department of Neurosurgery, Toranomon Hospital, Tokyo, Japan*

Abstract

Nilotinib, one of the tyrosine kinase inhibitors, has been used to treat chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Nilotinib-associated cerebral arterial occlusive disease, which is treated with medicine with/without bypass surgery or stenting, has been sporadically reported to occur. The mechanism of the nilotinib-associated cerebral disease has not been clarified and is still controversial. Here we present the case of a 39-year-old woman with Ph+ ALL treated with nilotinib, which led to symptomatic intracranial arterial stenosis. We performed high-flow bypass surgery and observed the arterial stenotic change in the stenotic portion intraoperatively, whose findings strongly supported the theory of atherosclerosis and seemed to be irreversible.

Keywords: tyrosine kinase inhibitor, nilotinib, cerebral artery disease, BCR-ABL, chronic myeloid leukemia

Introduction

Tyrosine kinase inhibitors (TKI) are molecular targeted drugs. The Breakpoint cluster region-Abelson (BCR-ABL) TKI binds to the oncogenic BCR-ABL protein and inhibits its activity to expand hematopoietic stem cells.[1)] One such TKI, nilotinib, has been widely used to treat chronic myeloid leukemia (CML) and has begun to be used to treat Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).[2,3)] Nilotinib is a well-tolerated drug with few side effects.[4)] However, nilotinib-associated cerebral arterial occlusive disease was reported sporadically in 2013. It has been considered an irreversible arterial stenotic event,[5)] the mechanism of which has not been fully identified and remains controversial. Most reports suggest that the stenotic change involves atherosclerosis, whereas a few suggest that it may be a quasi-moyamoya disease.[5,6)] Accordingly, the treatment options have differed among patients and have included antiplatelet medical therapy with percutaneous transluminal angioplasty (PTA), stenting, or direct bypass surgery [superficial temporal artery (STA) to the middle cerebral artery (MCA)].[7,8)]

Here, we present the case of a patient with nilotinib-associated symptomatic cerebral arterial disease who was treated with high-flow bypass surgery (external carotid artery to MCA M2 with a radial artery graft). Notably, we were able to evaluate the occlusive point under direct vision during bypass surgery.

Case Report

A 39-year-old Japanese woman was diagnosed with Ph+ ALL without central nervous system infiltration 6 years prior to her arrival at our hospital, where she received induction therapy and consolidation therapy and achieved a molecular complete response (mCR). After umbilical cord blood transplantation, she experienced central nervous system recurrence and was treated with an intraspinal injection of methotrexate, cytosine arabinoside, and prednisolone and craniospinal irradiation of 40 Gy/10 fractions. Her mCR was maintained under TKI therapy, and she was treated with imatinib and dasatinib, both of which caused gastrointestinal side effects. Next, ponatinib was administered, which led to conjunctival hemorrhage and was

Received October 26, 2022; Accepted January 5, 2023

switched to nilotinib (800 mg). Three and half years after nilotinib treatment began, she experienced repetitive transient weakness of her left extremities, which lasted for approximately 5 min. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed acute and subacute infarctions in the right watershed area (Fig. 1a) with multiple arterial stenoses. She was admitted to the hospital, and dual antiplatelet therapy (100 mg/day aspirin and 75 mg/day clopidogrel) was initiated. Digital subtraction angiography revealed severe stenosis in the M1 portion of the right MCA, A1 of the right anterior cerebral artery (ACA), right posterior cerebral artery, right vertebral artery (VA), and left cervical common carotid artery, without moyamoya vessels (Fig. 1b-g). Fast imaging employing steady-state acquisition (FIESTA) showed a preserved external diameter of the right MCA (Fig. 1h), and vessel wall imaging showed asymmetric wall thickening of the right MCA, with a narrowed internal diameter (Fig. 1i-j). Single-photon emission computerized tomography (SPECT) demonstrated severely low blood perfusion in the right MCA area (Fig. 1k). These images suggest that the cerebral infarction was attributed to right MCA stenosis. Her low-density lipoprotein (LDL) levels were mildly elevated (154 mg/dL), and statin therapy was initiated. Notably, the patient was relatively young and had no risk factors for arterial sclerosis, such as hypertension, diabetes mellitus, smoking habit, or family history of moyamoya disease. Lupus anticoagulants and screening tests for other autoimmune diseases were negative. The MRI performed 4 years prior to this event revealed no arterial stenosis (Fig. 1l). Therefore, nilotinib-associated arterial occlusive disease was suspected, which is considered irreversible.[8] Nilotinib was terminated, and revascularization surgery was planned because the cerebral blood flow did not recover with medical therapy alone. M1 stenosis had a long segment with many perforating branches, which made it difficult to perform PTA or stenting. Her right STA was too thin to supply enough blood to the MCA with STA-MCA bypass. Therefore, a high-flow bypass was performed (Fig. 2a, b). The left radial artery was harvested endoscopically, whose appearance was normal without an atherosclerotic change intraoperatively, and a cervical external carotid artery to the MCA (M2) bypass with an interposition radial artery graft was performed. The main trunk of the MCA (M1 and M2) was observed under direct vision intraoperatively. The external wall of the artery was not narrowed but was maintained with sporadic yellow, shiny, and firm wall thickening, which corresponded to atherosclerosis (Fig. 2c). We chose a normal appearance portion of M2 for arteriotomy. The procedures of arteriotomies and vascular anastomosis proceeded normally successfully without any problems. Postoperative MRA showed a spastic change in the radial artery graft (Fig. 3), probably because the relatively short length of the harvested graft from her short arm forced us to stretch the graft to make the anastomosis. Chronologically, the spasm gradually improved. She developed no neurological deficits nor new cerebral infarction postoperatively and was discharged home. She has maintained good bypass patency without any symptoms for at least 6 months.

Discussion

BCR-ABL TKIs are a class of molecular targeted drugs for leukemia that inhibit BCR-ABL tyrosine kinase activity. Imatinib, a first-generation TKI, was first approved for CML treatment. Many studies have shown the efficacy of imatinib. However, some patients fail to respond to imatinib therapy because of resistance caused by point mutations in the BCR-ABL kinase domain. Nilotinib is a second-generation TKI that was designed to overcome imatinib resistance.[9] Its efficacy is high, but side effects have been reported, such as QT long syndrome and blood cholesterol and glucose level elevations.[10] Nilotinib-associated peripheral arterial occlusive disease was reported for the first time in 2011.[4] Subsequently, cerebral ischemic events with arterial stenosis in a nilotinib user were first reported in 2013,[11] with a total of 14 similar cases, including our patient, reported to date (Table 1). The ages of the reported patients ranged from 39 to 76 years, with our patient being the youngest. Ten of the 14 patients were male, and the location of arterial stenosis was mainly the MCA (8/12 cases). Eight of 12 patients did not have any risk factors for atherosclerosis, which suggests that stenotic changes are associated with nilotinib use. The median period of nilotinib treatment was 5 years (range, 8 months to 7.5 years). Among the 14 patients, PTA alone was performed in one,[8] intracranial stenting in two,[12,13] cervical stenting in one,[14] STA-MCA bypass in two,[6,7] and high-flow bypass in one, which was our patient. Follow-up imaging in the published reports has showed no improvement in arterial stenosis despite the termination of nilotinib use, which suggests that the stenotic change in the arteries is irreversible.[6] Therefore, surgical intervention along with the termination of nilotinib use is considered a reasonable treatment approach.

Although studies on nilotinib-associated intracranial arterial occlusive disease have been increasingly reported, as well as peripheral, coronary, and pulmonary artery stenosis,[15,16] the mechanism of occlusive disease has not yet been clarified. Nilotinib binds to BCR-ABL and discoidin domain receptor 1 (DDR1).[17] DDR1 is a collagen receptor expressed on smooth muscle cells and macrophages and is implicated in plaque formation in atherosclerosis.[18] Thus, DDR1 inhibition by nilotinib is considered to accelerate plaque formation. Nilotinib also binds to platelet-derived growth factor receptor and KIT receptor kinases, which regulate various vascular and perivascular cells.[17] KIT is essential for the development and survival of mast cells,[19] which contain heparin, histamine, and tissue plasminogen

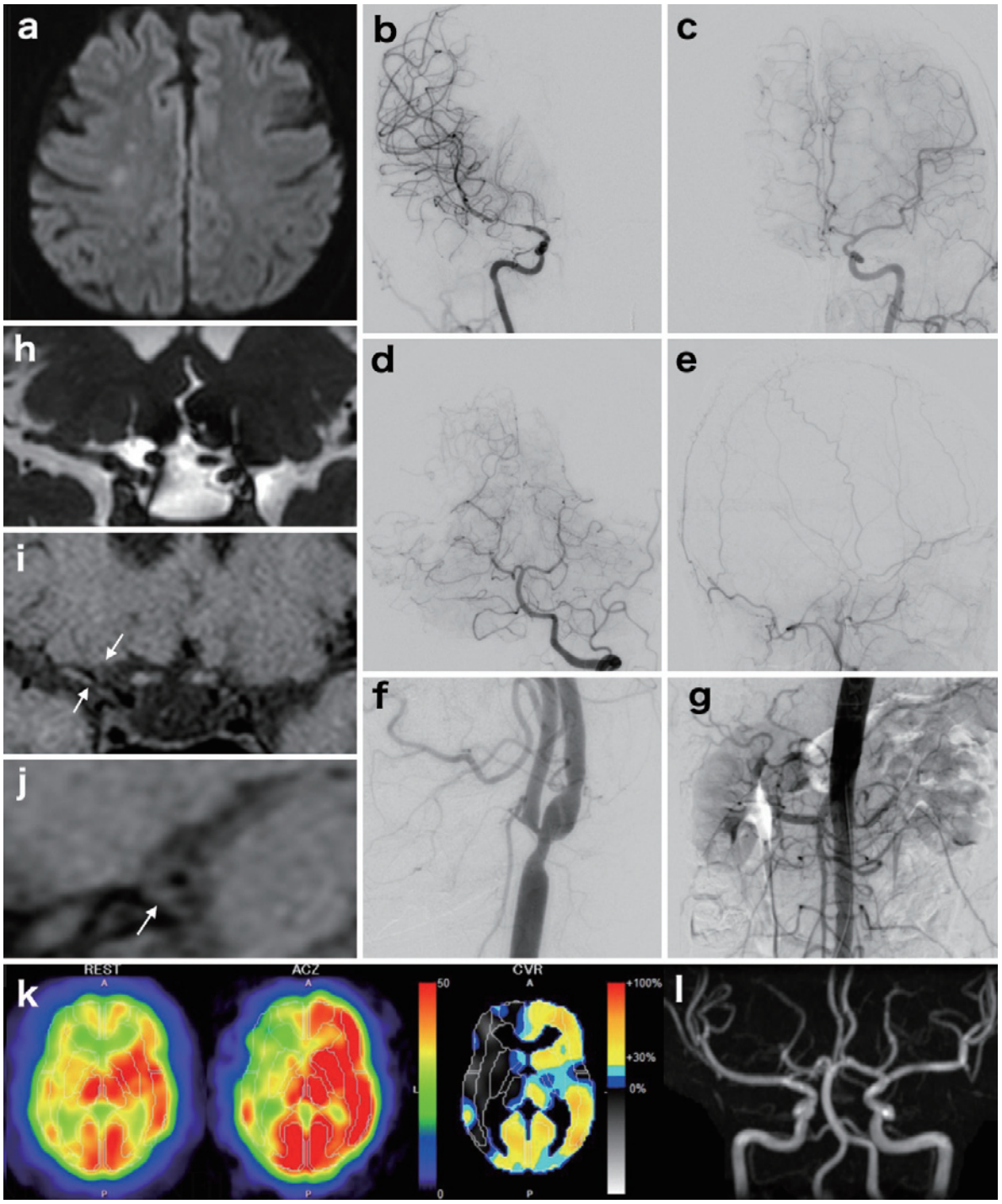

Fig. 1 Preoperative images.

Preoperative images after infarctions (a–k) and for years prior to infarctions (l). a Diffusion-weighted image of the brain MRI showing acute infarctions within the right cerebral hemisphere in watershed distribution. b–g Catheter angiograms showing stenosis of the right MCA M1 (b), ACA A1 (b–c), VA (d), and cervical common carotid artery to the external carotid artery (f). Catheter angiograms of the right external carotid artery in the lateral view showing a very thin STA, which was insufficient for use as a graft in bypass surgery (e). Abdominal aortography showing moderate stenosis of the bilateral renal arteries (g). h FIESTA showing the preserved external diameter of the right MCA M1 (arrow). i–j A coronal slice (i) and a sagittal slice (j) of vessel wall imaging showing asymmetric wall thickening of the right MCA, with a narrowed internal diameter (arrow). k N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) -SPECT showing hypoperfusion of the right hemisphere with rest (left) and acetazolamide (ACZ) stress (middle). Cerebrovascular reserve (CVR) showing a low degree of autoregulatory vasodilation in the right hemisphere (right). l MRA 4 years before infarctions showing no intracranial arterial stenosis.

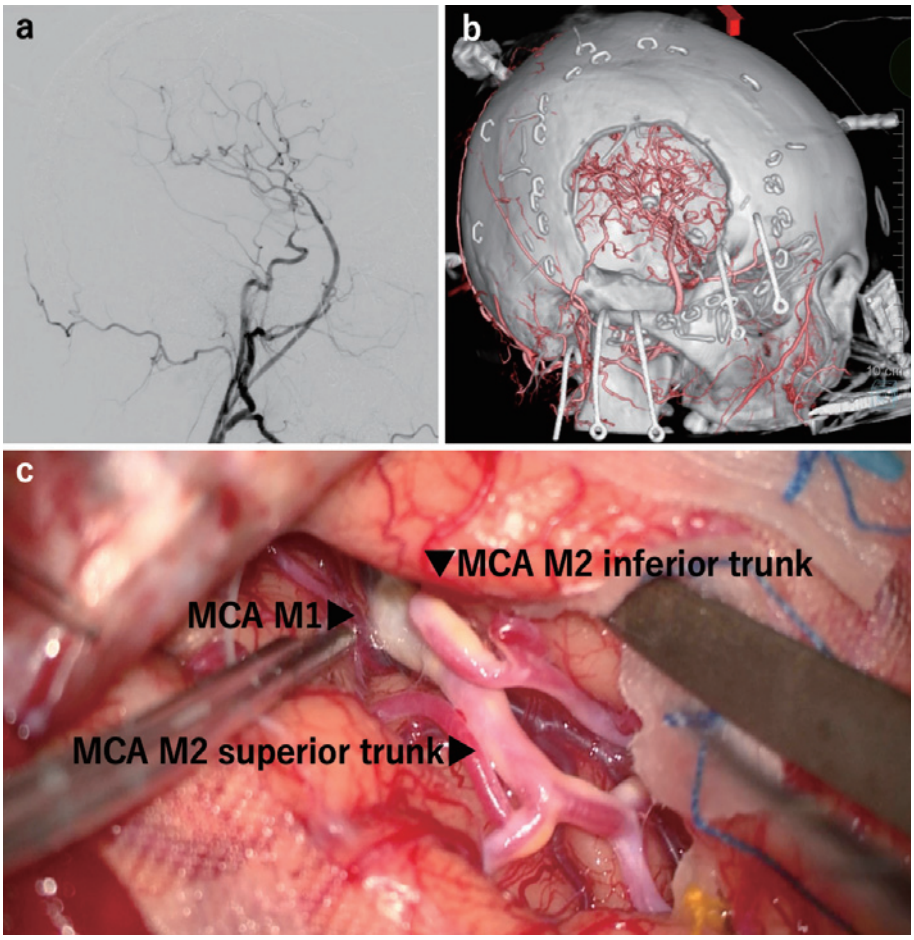

Fig. 2 Intraoperative images.
a, b Intraoperative cerebral angiogram in the lateral view (a) and three-dimensional reconstruction (b) showing good bypass flow through the radial artery graft. c MCA M1–M2–M3 appearance in the Sylvian fissure, whose external artery wall was not narrowed but was maintained, with sporadic yellow, shiny, and firm wall thickening that corresponded to atherosclerosis.

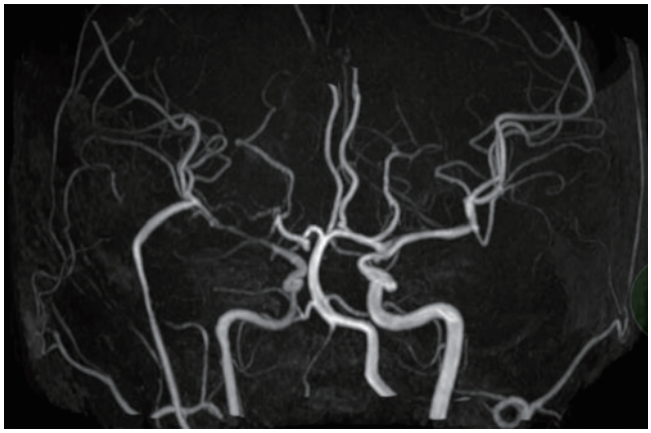

Fig. 3 Postoperative image.
MRA showing good patency of the radial artery and right MCA M2 anastomosis.

activator (tPA). Notably, these factors are produced and released in a KIT-dependent manner,[20] and nilotinib can lead to thrombophilia by inhibiting KIT. Another study showed that nilotinib exerts direct proatherogenic and antiangiogenic effects on vascular endothelial cells *in vitro* and *in vivo*.[4] Moreover, nilotinib elevates blood LDL and glucose levels, which can contribute to atherosclerotic changes and ischemic events. Therefore, nilotinib-associated arterial occlusive disease has been implicated in atherosclerosis.

Conversely, another prior study identified, using vessel wall MRI, diffuse concentric thickening of the stenotic artery, which differed from ordinary simple atherosclerosis and represented a type of quasi-moyamoya disease.[6]

In summary, this is the first report to observe the intracranial artery directly. The arterial appearance during surgery was atherosclerotic, with asymmetrical, sporadic, yellow firm wall thickening. This finding strongly supports the theory of atherosclerotic changes. The appearance of MCA M1-M2-M3 revealed an atherosclerotic change intraoperatively. However, we cannot firmly conclude this finding because we did not confirm the pathology. We also report only one patient, and thus, we can only draw lim-

Table 1 Nilotinib-associated cerebral arterial occlusive disease in previous reports and our case

Author, year	Age/ sex	Disease	Risk factor	Clinical presentation	Symptoms	Arterial stenosis	Period of nilotinib use	Treatment
Coon, 2013[11]	70/F	CML	None	CI	Lt hemiparesis, dysarthria	Bil. MCA, bil. PCA, rt. intracranial ICA, rt ACA A1	7 years	APT
Jager, 2014[21]	69/F	CML	None	CI	Aphasia, paresis, epilepsy	ND	12 months	APT
Alshiekh-nasany, 2016[7]	50/M	CML	None	TIA	Rt. hemiparesis	Bil. MCA	ND	APT, bil. STA-MCA bypass
Ozaki, 2017[12]	74/M	CML	ND	TIA	Transient hemiplegea	Lt. intracranial ICA, BA	2.5 years	APT, stent
Gomez-galvan, 2017[22]	66/M	CML	Hypertension	CI	Vertigo, diplopia, central facial palsy, gait ataxia	VA, and intracranial ND	8 months	APT
	56/M	CML	Hypertension	CI	Dysarthria, hemiparesis, hemiparesthesia	Lt. ICA, rt. ICA, bil. MCA	5 years	APT, stent
	66/M	CML	None	CI	Hemiparesis, hemiparesthesia	ICA, MCA	7 years	APT
Chen, 2018[13]	49/F	CML	Type 2 diabetes mellitus, hyperlipidemia	TIA	Rt. hemiparesis	Lt. intracranial ICA	1 year	APT, stent
Suzuki, 2018[6]	55/M	CML	ND	CI	Transient lt. sided weakness	Rt. ICA, lt. ICA, MCA and ACA	3 years	APT, rt. STA-MCA bypass
Nakaya, 2019[14]	76/M	CML	None	CI	Rt. hemiparesis	Bil. Cervical ICA	7 years	APT, CAS
Uemura, 2020[5]	62/M	CML	None	CI	Dysesthesia	Rt. MCA, lt. ACA, lt. PCA	9 years	APT
	59/M	CML	Hypertension	CI	Hoarseness, dysarthria, lt. hemiparesis	Lt. MCA, BA	7.5 years	APT
Fujiwara, 2021[8]	53/M	CML	None	None	Disparity in blood pressures in both arms	Bil. subclavian artery, lt. VA, bil. cervical ICA	5.5 years	APT, PTA
Our case	39/F	Ph+ALL	None	CI	Rt. hemiparesis	Rt. MCA, rt. ACA A1, VA, lt. cervical ECA	4 years	Med, rt. ECA-RA-MCA bypass

ND, not described; M, male; F, female; CML, chronic myeloid leukemia; CI, cerebral infarction; TIA, transient ischemic attack; rt, right; lt, left; bil, bilateral; MCA, middle cerebral artery; ACA, anterior cerebral artery; VA, vertebral artery; ICA, internal carotid artery; ECA, external carotid artery; APT, antiplatelet medical therapy; CAS, carotid artery stenting; PTA, percutaneous transluminal angioplasty; RA, radial artery

ited conclusions. More cases are needed to understand the pathobiology of this disease.

Conclusion

Nilotinib has been associated with cerebral arterial oc-

clusive disease, which can cause cerebral ischemic events. Occlusive and irreversible changes are implicated in atherosclerosis. Therefore, in addition to the termination of nilotinib use, the correction of hyperlipidemia and hyperglycemia, and antiplatelet therapy, revascularization surgery should be considered to properly treat patients with this condition.

Acknowledgments

We thank Dr. Naoyuki Uchida and Dr. Mitsuhiro Yuasa at the Department of Hematology, Toranomon Hospital, for their hematological treatment and consultation.

Informed Consent

The patient provided written informed consent.

Conflicts of Interest Disclosure

All authors have no conflict of interest, and they have registered online self-reported COI Disclosure Statement Forms through the website for JNS members.

References

1) O'Hare T, Deininger MWN, Eide CA, Clackson T, Druker BJ: Targeting the BCR-ABL signaling pathway in therapy-resistant philadelphia chromosome-positive leukemia. *Clin Cancer Res* 17: 212-221, 2011
2) Shimoni A, Volchek Y, Koren-Michowitz M, et al.: Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia: Nilotinib After SCT in CML or Ph + ALL. *Cancer* 121: 863-871, 2015
3) Giebel S, Czyz A, Ottmann O, et al.: Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A position statement of the Acute Leukemia Working Party of the: TKIs After AlloHSCT in Ph+ ALL. *Cancer* 122: 2941-2951, 2016
4) Aichberger KJ, Herndlhofer S, Schernthaner GH, et al.: Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol* 86: 533-539, 2011
5) Uemura M, Kanazawa M, Yamagishi T, et al.: Role of RNF213 p.4810K variant in the development of intracranial arterial disease in patients treated with nilotinib. *J Neurol Sci* 408: 116577, 2020
6) Suzuki K, Yamamoto J, Kakeda S, et al.: Vessel wall magnetic resonance imaging findings and surgical treatment in nilotinib-associated cerebrovascular disease: A case report. *Mol Clin Oncol* 2018. doi: 10.3892/mco.2018.1780
7) Alshiekh-Nasany R, Zidan A, Martinez C: Extensive intracranial arterial stenoses in conjunction with the use of tyrosine kinase inhibitor Nilotinib. *Clin Case Rep* 4: 1184-1186, 2016
8) Fujiwara S, Fukumoto S, Miyazaki Y, et al.: A case of multiple arterial stenoses due to long-term nilotinib exposure. *Jpn J Neurosurg* 30: 804-810, 2021
9) Blay JY, von Mehren M: Nilotinib: A novel, selective tyrosine kinase inhibitor. *Semin Oncol* 38: S3-S9, 2011
10) Hochhaus A, Saglio G, Hughes TP, et al.: Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia* 30: 1044-1054, 2016
11) Coon EA, Zalewski NL, Hoffman EM, Tefferi A, Flemming KD: Nilotinib treatment-associated cerebrovascular disease and stroke. *Am. J. Hematol* 88: 534-535, 2013
12) Ozaki T, Nakamura H, Izutsu N, Masaie H, Ishikawa J, Kinoshita M: Intracranial stenting for nilotinib treatment-associated cerebrovascular stenosis in chronic myeloid leukemia. *Interv Neuroradiol* 23: 527-530, 2017
13) Chen CJ, Sorace BJ, Shakeri A, et al.: Republished: Tyrosine kinase inhibitor induced rapidly progressive vasculopathy after intracranial stent placement. *J Neuro Interventional Surg* 10: e28, 2018
14) Nakaya A, Ebitani M, Monzen T, et al.: A case of recurrent cerebral infarction during treatment with oral tyrosine kinase inhibitors for chronic myelogenous leukemia. *Rinsho Shinkeigaku* 59: 418-424, 2019
15) Medeiros BC, Possick J, Fradley M: Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: strategies for monitoring, detecting, and managing. *Blood Rev* 32: 289-299, 2018
16) Morris NT, Taylor MB, Hacobian M, et al.: Isolated pulmonary vasculitis associated with nilotinib use: a case report. *Leuk Res Rep* 14: 100214, 2020
17) Manley PW, Drueckes P, Fendrich G, et al.: Extended kinase profile and properties of the protein kinase inhibitor nilotinib. *Biochim Biophys Acta BBA - Proteins Proteomics* 1804: 445-453, 2010
18) Franco C, Ahmad PJ, Hou G, Wong E, Bendeck MP: Increased cell and matrix accumulation during atherogenesis in mice with vessel wall-specific deletion of discoidin domain receptor 1. *Circ Res* 106: 1775-1783, 2010
19) Kitamura Y, Tsujimura T, Jippo T, Hasugai T, Kanakura Y: Regulation of development, survival and neoplastic growth of mast cells through the c-kit receptor. *Int Arch Allergy Immunol* 107: 54-56, 1995
20) Valent P, Baghestanian M, Bankl HC, et al.: New aspects in thrombosis research: possible role of mast cells as profibrinolytic and antithrombotic cells. *Thromb Haemost* 87: 786-790, 2002
21) Jager NGL, Stuurman FE, Baars JW, Opdam FL: Cerebrovascular events during nilotinib treatment. *Neth J Med* 72: 2, 2014
22) Gómez-Galván JB, Borrego S, Tovar N, Llull L: Nilotinib as a risk factor for ischaemic stroke: a series of three cases. *Neurol Engl Ed* 32: 411-413, 2017

Corresponding author: Takayuki Hara, MD, PhD
Department of Neurosurgery, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan.
e-mail: thara@toranomon.gr.jp