Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4824-20
Intern Med 59: 2419-2421, 2020
http://internmed.jp

【 CASE REPORT 】

Dasatinib-induced Reversible Demyelinating Peripheral Neuropathy and Successful Conversion to Nilotinib in Chronic Myelogenous Leukemia

Hiroyasu Inoue[1,2], Hirofumi Taji[3], Kentaro Yamada[1], Chisako Iriyama[3,4], Touko Saito[3], Harumi Kato[3], Masamitsu Yanada[3], Kazuhito Yamamoto[3] and Noriyuki Matsukawa[2]

Abstract:
Dasatinib, a tyrosine kinase inhibitor, is commonly used in the treatment of chronic myelogenous leukemia. A rare side effect is peripheral neuropathy. A 54-year-old woman experienced gradually accelerated dysesthesia and hypoesthesia in her extremities, 2 months following treatment with dasatinib. Nerve conduction studies revealed a prolonged conduction velocity with temporal dispersion, indicating demyelinating peripheral neuropathy. After changing dasatinib to nilotinib, both her clinical symptoms and electrophysiological data gradually improved. We herein report the findings of this case with a review of the pertinent literature.

Key words: dasatinib, demyelinating peripheral neuropathy, chronic myelogenous leukemia, nilotinib, tyrosine kinase inhibitor

(Intern Med 59: 2419-2421, 2020)
(DOI: 10.2169/internalmedicine.4824-20)

Introduction

The presence of the gene sequence BCR-ABL1 on chromosome 22 confirms the diagnosis of chronic myelogenous leukemia (CML). Tyrosine kinase inhibitors (TKIs), which damage cancer cells through the interruption of BCR-ABL1 signaling, are typically used to treat patients with CML. Dasatinib, a second generation TKI, is 300 times more effective than imatinib, a first generation TKI, as shown by an *in vitro* assay (1). Peripheral neuropathy associated with dasatinib usage has rarely been reported; thus, the clinical characteristics of the symptoms involved, and any data on its clinical course, remain unknown. We herein report the case of a 54-year-old woman who showed neurological symptoms 2 months after starting treatment with dasatinib.

Case Report

A 54-year-old Japanese woman was diagnosed with CML based on a genomic analysis that confirmed she was BCR-ABL1 positive. She started treatment with 100 mg dasatinib, and a complete cytogenetic response (CCyR) was clinically achieved.

After 2 months of the initial treatment, she complained of numbness and tingling in bilateral distal extremities. No prior infections existed. Because of a gradual worsening of her symptoms, she was referred to the neurology department 4 months later.

Neurological examinations revealed no abnormal findings in the cranial nerves. Muscle strength was slightly weakened in her distal dominant extremities with decreasing deep tendon reflexes. No pathological reflex was observed. The patient presented with a tingling sensation accompanied by impairment of tactile and vibration sensation in the distal

[1]Department of Neurology, Nagoya City East Medical Center, Japan, [2]Department of Neurology and Neuroscience, Nagoya City University Graduate School of Medical Sciences, Japan, [3]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Japan and [4]Department of Hematology and Oncology, Fujita Health University, Japan
Received: March 9, 2020; Accepted: April 20, 2020; Advance Publication by J-STAGE: June 30, 2020
Correspondence to Dr. Kentaro Yamada, kentaro.yamada@higashi-hosp.jp

Table. **Nerve Conduction Velocity Test at the Initial Examination.**

		Stimulation site	Latency (ms)	Amplitude (Motor: mV, Sensory:μV)	Conduction velocity (m/s)	F wave min latency (ms)	F wave %
Motor	Median (L)	Wrist	9.2	4.5	51.0	39.1	43
	Median (L)	Elbow	13.6	3.9			
	Ulnar (L)	Wrist	4.4	10.4	51.8	33.2	6
	Ulnar (L)	Elbow	9.3	8.7			
	Tibial (R)	Ankle	7.4	3.9	34.1	66.3	100
	Tibial (R)	Knee	17.7	2.2			
Sensory	Median (L)	Wrist	2.6	2.7	48.8		
	Median (L)	Elbow	Not detected	Not detected	Not detected		
	Ulnar (L)	Wrist	6.6	3.8	16.0		
	Ulnar (L)	Elbow	11.7	1.7	48.8		
	Sural (R)	Calf	4.6	2.5	30.7		

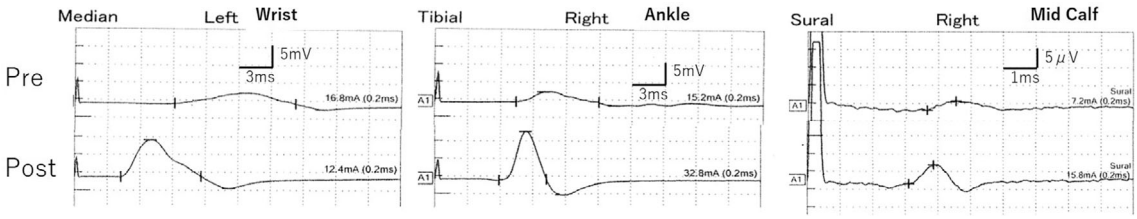

Figure. **Changes based on the nerve conduction study. The amplitude and distal latency improved after switching from dasatinib to nilotinib.**

dominant extremities. No tremors existed. A clinical neurological examination comprehensively suggested sensory-motor peripheral polyneuropathy.

A biochemical examination showed normal findings, including vitamin B12, folic acid, IgG 1,152 mg/dL, IgA 136 mg/dL, and IgM 37 mg/dL. No M protein was found by immunoelectrophoresis. The κ and λ chains were not analyzed. Antibodies associated with autoimmune disease, such as anti-SSA, anti-SSB, anti-P-ANCA, anti-C-ANCA, and various anti-ganglioside antibodies and cryoglobulin, were negative. A cerebrospinal fluid (CSF) examination was not performed due to lack of consent from the patient. Magnetic resonance imaging (MRI) including gadolinium contrast enhanced imaging revealed no abnormal findings in the brachial plexus, lumbosacral plexus, and nerve root. MRI showed no demyelination of the brain or spinal cord. A nerve conduction velocity (NCV) revealed significantly prolonged distal latency and increased duration, indicating demyelinating peripheral neuropathy (DPN) (Table, Figure). Based on this clinical information, the patient was first diagnosed with drug-induced DPN, with dasatinib as the possible causative candidate.

Two weeks after terminating treatment with dasatinib, her symptoms gradually improved without any treatment for polyneuropathy. One month later, 400 mg nilotinib treatment was initiated to treat her CML. After 3 and 5 months of the initiation of nilotinib treatment, major molecular response (MMR) and complete molecular response (CMR) were achieved, respectively. A few months following these responses, the patient's neurological symptoms disappeared, and the results of nerve conduction studies also improved. CMR of CML was maintained.

Discussion

To our knowledge, only one case of DPN associated with the use of dasatinib has been previously reported (2). The patient was treated with immunotherapy, including the administration of intravenous immunoglobulin (IVIg) and steroids, and alterations were made to the drug treatment administered. Therefore, our case is the first report indicating that DPN improved only by changing the drugs used.

The symptoms in this case were a sensory impairment of the glove and stocking type, distal weakness, and a reduction in tendon reflexes. A clinical neurological examination suggested sensory-motor peripheral polyneuropathy. Regarding axonal or demyelinating disorders, NCV satisfied the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) demyelination criteria, including extended distal latency and temporal dispersion. A nerve biopsy was not performed, but it was thought that the patient had demyelinating neuropathy, which showed a relatively quick improvement thereafter. A diagnosis of Guillain-Barré syndrome (GBS) was ruled out because the course was prolonged and all anti-glycolipid antibodies were negative. A CSF examination in the previously reported case was nor-

mal (2) but this examination could not be performed in this case as the patient did not give her consent to undergo a lumbar puncture. Because the patient's symptoms improved only after changing the drug, and she had a monophasic course with no subsequent relapse and no nerve root abnormalities on contrast MRI, and chronic inflammatory demyelinating polyneuropathy (CIDP) was therefore not considered. However, drug-related demyelinating peripheral neuropathy was considered. Although this was a case of reversible demyelinating peripheral neuropathy consistent with the previous report, the course of treatment was different.

In this case, the symptoms improved by simply changing the drug. In the previous report (2), IVIg was administered along with the discontinuation of dasatinib because the symptoms had worsened relatively suddenly. Although they improved quickly, the same symptoms worsened again when dasatinib was resumed. The patient's symptoms improved after discontinuing dasatinib again, administering IVIg and prednisolone, and switching to nilotinib; no relapse occurred. In contrast, in this case, IVIg and prednisolone were not used, and the symptoms improved only by the discontinuation of dasatinib. Both cases improved relatively quickly, suggesting the possibility of a reversible pathology. Discontinuing dasatinib early in the onset may be a factor that could facilitate symptom reversal. In both cases, early detection and response to symptoms were important. In particular, our case showed that symptoms can improve by only discontinuing dasatinib. However, the discontinuation of dasatinib could exacerbate CML. In our case, after the discontinuation of dasatinib, nilotinib was administered, which has a different, off-target inhibition spectrum of tyrosine kinases. Dasatinib has a strong Src inhibitory effect, whereas nilotinib has no such inhibitory effect (3). After nilotinib administration, no deterioration of the neurological symptoms was observed. Experimental data indicate that Src is necessary for Schwann cell motility, morphology, and myelination via allopregnanolone, a neuroactive steroid. The inhibition of Src results in Schwann cell damage (4). This finding suggests that the off-target inhibitory effect of Src kinase may be involved in peripheral neuropathy.

In addition, Src inhibition by dasatinib inhibits tumor necrosis factor (TNF) α secretion (5). A decreased TNFα secretion increases and prolongs the myelin-specific T cell responses and induces immune-mediated neuropathy (6). In fact, TNFα inhibitors can cause demyelinating peripheral neuropathy (7). Therefore, demyelinating peripheral neuropathy could be caused by Src inhibition. The detailed mechanism is currently unknown, and a report suggests that nilotinib caused demyelination of the central and peripheral nerves (8). Further evaluation of similar cases is therefore necessary in the future.

In conclusion, although little attention has been paid to TKI-related DPN, clinicians must be aware of this adverse effect in future cases.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors would like to thank Dr. Susumu Kusunoki, Department of Neurology, Kindai University Faculty of Medicine, for measuring the anti-ganglioside antibodies.

Hiroyasu Inoue and Hirofumi Taji contributed equally to this work.

References

1. Kennedy JA, Hobbs G. Tyrosine kinase inhibitors in the treatment of chronic-phase CML: strategies for frontline decision-making. Curr Hematol Malig Rep **13**: 202-211, 2018.
2. Ishida T, Akagawa N, Miyata T. Dasatinib-associated reversible demyelinating peripheral polyneuropathy in a case of chronic myeloid leukemia. Int J Hematol **107**: 373-377, 2018.
3. Pasvolsky O, Leader A, Iakobishvili Z, et al. Tyrosine kinase inhibitor associated vascular toxicity in chronic myeloid leukemia. Cardio-Oncology **1**: 5, 2015.
4. Melfi S, Montt Guevara MM, Bonalume V, et al. Src and phospho-FAK kinases are activated by allopregnanolone promoting Schwann cell motility, morphology and myelination. J Neurochem **141**: 165-178, 2017.
5. Fraser CK, Lousberg EL, Kumar R, et al. Dasatinib inhibits the secretion of TNF-alpha following TLR stimulation *in vitro* and *in vivo*. Exp Hematol **37**: 1435-1444, 2009.
6. RP Lisak. Cytokines and chemokines in inflammatory demyelinating neuropathies. Clin Exp Neuroimmunol **1**: 153-164, 2010.
7. Stübgen JP. Tumor necrosis factor-alpha antagonists and neuropathy. Muscle Nerve **37**: 281-292, 2008.
8. Judge C, Moheb N, Melinosky C. Nilotinib-associated demyelinating disease. Neurology **92** (Suppl): P2.2-093, 2019.