Subdural Hematoma Associated with Dasatinib and Intrathecal Methotrexate Treatment in Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia

Hiroshi Ureshino, Atsujiro Nishioka, Kensuke Kojima, Haruna Kizuka, Haruhiko Sano, Takero Shindo, Yasushi Kubota, Toshihiko Ando and Shinya Kimura

Abstract

Dasatinib has been associated with an increased risk of bleeding, with the most prominent risk noted in patients with advanced-stage chronic myeloid leukemia and thrombocytopenia. We herein report two cases of Philadelphia chromosome-positive acute lymphoblastic leukemia in which a subdural hematoma developed in association with low-dose (40-50 mg/day) dasatinib treatment and lumbar puncture for intrathecal methotrexate injection. Both patients were in complete remission, with normal platelet counts and coagulation status. We suggest that dasatinib, even at a low dose, may impair platelet aggregation and that lumbar puncture may increase the risk of a subdural hematoma (occasionally bilateral) in patients receiving dasatinib.

Key words: Philadelphia chromosome-positive acute lymphoblastic leukemia, dasatinib, subdural hematoma, intrathecal chemotherapy, platelet aggregation


Introduction

Dasatinib, a potent inhibitor of the BCR-ABL1 and Src family tyrosine kinases (SFKs), has been approved for the treatment of Philadelphia chromosome (Ph; BCR/ABL)-positive chronic myeloid leukemia (CML) (1) and acute lymphoblastic leukemia (Ph+ ALL) (2). Despite a favorable toxicity profile, dasatinib treatment is associated with various toxicities, including myelosuppression (anemia, neutropenia, and thrombocytopenia), digestive disorders (diarrhea, nausea, vomiting, and gastrointestinal hemorrhage), cutaneous eruption, and fluid retention (pleural or pericardial effusion); these occur mainly as a consequence of broad-spectrum kinase inhibition by dasatinib (1-4). Hemorrhaging has been reported in 9-40% of patients receiving dasatinib, which mostly occurs as gastrointestinal bleeding in patients with advanced-stage leukemia and thrombocytopenia. Central nervous system (CNS) bleeding is a rare event in patients receiving dasatinib, and the development of a subdural hematoma (SDH) has been previously reported only in a few patients (2, 5, 6).

CNS relapse remains a major obstacle in the curative treatment of ALL. To prevent CNS relapse, intrathecal methotrexate (IT-MTX) has been widely used as standard intrathecal chemotherapy (7, 8). Spinal hematoma and subarachnoid hemorrhage are well-known complications of lumbar puncture (LP), and the risk of these complications increases in patients with thrombocytopenia or other bleeding disorders and those treated with anticoagulant therapy (9). In contrast, SDH has been described as a rare complication of LP (10, 11). Cerebrospinal fluid leakage and intracranial hypotension have been suggested as factors leading to traction on the bridging subdural veins, with subsequent hemorrhaging and SDH formation (10). This hypothesis is supported by the observation of a close association between LP-associated SDH and severe and prolonged thrombocytopenia in patients with hematological malignancies and/or those undergoing hematopoietic stem cell transplantation, as well as the finding of bilateral SDH lesions in 68% (43/50) of previously reported cases (11).

We herein report the development of SDH in two patients...
Figure 1. The clinical course of case 1 and a CT scan showing a bilateral subdural hematoma (arrows). WBC: white blood cell, PLT: platelet, CCR: complete cytogenetic response, IT-MTX: intrathecal methotrexate, SDH: subdural hematoma

with Ph’ ALL who were treated with dasatinib and IT-MTX.

Case Reports

Patient 1

A 77-year-old woman was diagnosed with Ph’ ALL in July 2015 and was treated with prednisolone (20 mg/day) and low-dose dasatinib (40 mg/day). Her circulating lymphoblast counts decreased promptly, followed by a gradual increase in her platelet counts (Fig. 1). She developed minor tracheal bleeding 16 days after the initiation of dasatinib (Fig. 1), which was resolved by discontinuing dasatinib. Her platelet count was 62×10^9/L, and she did not receive transfusions. Dasatinib treatment was restarted, resulting in a complete cytogenetic response within 2 months. The patient received two courses of IT-MTX as a prophylaxis against CNS relapse. She had been well until 12 days after the second course of IT-MTX, when she experienced a headache, gait impairment, and urinary incontinence. A physical examination revealed a disturbance of consciousness, anisocoria, and left hemiplegia. A computed tomography (CT) scan indicated a bilateral SDH with cerebral herniation (Fig. 1, right panel). Her platelet count was 226×10^9/L (Fig. 1, left panel). The results of her coagulation tests were normal, with a prothrombin time-international normalized ratio (PT-INR) of 0.97, activated partial thromboplastin time (APTT) of 28.0 seconds, fibrinogen level of 373 mg/dL, and FDP level of 4.5 μg/mL. Platelet aggregation studies revealed markedly impaired platelet aggregation in response to 1 μM adenosine diphosphate and 0.5 μg/mL collagen (Fig. 3). Dasatinib therapy was thereafter discontinued. Emergency trephination was performed, and subsequently her neurological abnormalities disappeared. Dasatinib therapy was thereafter discontinued.

Patient 2

A 75-year-old woman was diagnosed with Ph’ ALL in September 2015. She was treated with prednisolone (30 mg/day) and low-dose dasatinib (40 mg/day), which yielded favorable hematologic and molecular responses (Fig. 2). One month after the initiation of dasatinib, a real-time polymerase chain reaction analysis could not detect BCR-ABL1 transcripts in her peripheral blood and bone marrow cells. As she did not experience significant side effects from dasatinib treatment, the dose was increased to 50 mg/day. She also received IT-MTX as a prophylaxis against CNS relapse. Nineteen days later, she complained of malaise and appetite loss. Her physical examination findings were unremarkable. A CT scan revealed a left-sided SDH (Fig. 2). Her platelet count was 297×10^9/L. The coagulation tests were normal, with a PT-INR of 0.95, APTT of 34.8 seconds, fibrinogen level of 251 mg/dL, and FDP level of 4.5 μg/mL. Platelet aggregation studies revealed markedly impaired platelet aggregation in response to 1 μM adenosine diphosphate and 0.5 μg/mL collagen (Fig. 3). Dasatinib therapy was thereafter discontinued. The patient underwent observation through serial scans without surgical intervention, as the hematoma was small and did not have a sufficient mass effect to cause a midline shift or neurological signs. Conservative management resulted in a spontaneous, radiologically documented resolution of the SDH. The results of repeated platelet aggregation tests at 72 hours after the last dose of dasatinib were normal, indicating a reversible inhibition of platelet aggregation.

Discussion

Clinical bleeding has been occasionally reported in association with dasatinib treatment. Quintás-Cardama et al. (12) evaluated the incidence and risk factors of clinical bleeding associated with dasatinib therapy for CML. In their series, clinical bleeding occurred in 23% (32/138) of patients receiving dasatinib (grade ≥3 in 7%). The majority of these bleeding episodes were gastrointestinal bleeding (81%); gingival bleeding (11%), vaginal bleeding (5%), and epistaxis (<5%) were much less frequently observed. Severe bleeding episodes (grade ≥3) occurred almost exclusively in patients
receiving ≥140 mg/day dasatinib. Importantly, thrombocytopenia and advanced-phase CML were identified as risk factors for bleeding. Both of our current cases achieved complete remission with low-dose dasatinib and had normal platelet counts at the time of SDH development. They had not received conventional chemotherapeutic agents, anticoagulants or antiplatelet drugs. Interestingly, one of the previously reported cases of SDH during dasatinib treatment also involved a normal platelet count (5). We therefore hypothesized that even at low doses, dasatinib might cause platelet dysfunction and increase the risk of bleeding, a possibility that was confirmed in our second case. Our patients did not have comorbid medical disorders. However, since the incidence of SDH increases with age, we do not exclude the possibility that aging may have contributed to the development. The administration of standard-dose tyrosine kinase inhibitors (TKIs) imatinib, bosutinib, and dasatinib was reported to impair platelet aggregation in 67%, 15%, and 85% of patients, respectively (13). We speculated that dasatinib-induced impairment of platelet aggregation might underlie the pathogenesis of SDH in our cases.

Considering the rarity of CNS bleeding in patients treated with dasatinib, additional factor(s) might be actively involved in the pathogenesis of dasatinib-related SDH. We consider that LP might have been a critical triggering factor related to SDH formation in both cases. LP is associated with SDH formation through lumbar cerebrospinal leakage, intracranial hypotension, downward brain displacement, and bleeding into the inner dural layers of the cerebral convexities (10, 11). Importantly, patients with prolonged periods of profound thrombocytopenia were found to have a high risk of LP-associated SDH (11). Our patients did not show clinical signs or symptoms suggestive of an increased bleeding tendency. However, one case exhibited impaired platelet aggregation rather than thrombocytopenia, which might inhibit hemostasis. The period between LP and the clinical onset of SDH was relatively long in our cases: 12 days in case 1, and 19 days in case 2. Such a prolonged latency period is common with LP-associated SDH, and in some cases, an initial CT scan indicated normal findings at the time of the

Figure 2. The clinical course of case 2 and a CT scan showing a left-sided subdural hematoma (arrows). WBC: white blood cell, PLT: platelet, CMR: complete molecular response, IT-MTX: intrathecal methotrexate, SDH: subdural hematoma

Figure 3. Platelet aggregation in a normal subject (control) and patient no. 2 during therapy with dasatinib. Aggregation was recorded as an increase in light transmission. Dasatinib treatment was associated with a decreased response to low concentrations of adenosine diphosphate (ADP) (1 μM) and collagen (0.5 μg/mL).
symptomatic onset of LP-associated SDH (14, 15). This latency suggests that longitudinal changes in the platelet count and/or function after LP are as important as those at the time of LP. Given the small number of reported cases, it is unclear whether an intrathecal injection of methotrexate increases the risk of SDH relative to diagnostic LP. However, to date, there are no known drug interactions between MTX and dasatinib (16).

Some researchers have reported that dasatinib induces platelet dysfunction through inhibition of SFKs (17). Dasatinib is a potent inhibitor of BCR-ABL1 and SFKs, and SFKs play a central role in platelet activation downstream of collagen receptor glycoprotein VI and IgG Fc receptor RIIA (FcγRIIA/CD32). Inhibition of SFKs by dasatinib has been shown to rapidly and reversibly affect platelet activation and induce hemostatic defects (17). To a lesser extent, platelet dysfunction has also been described in the context of other TKIs, including imatinib, bosutinib, and ponatinib (13, 18, 19). As nilotinib is not known to affect the platelet function, it appears that the different spectra and levels of inhibition of off-target signaling pathways induced by individual TKIs might play a role in TKI-associated platelet aggregation abnormalities. As of January 2016, only dasatinib and imatinib have been approved for the treatment of Ph’ ALL. As both TKIs can affect platelet aggregation and intrathecal chemotherapy plays an important role in the treatment of ALL, monitoring of the neurological symptoms and signs after intrathecal chemotherapy is advisable for Ph’ ALL patients receiving dasatinib or imatinib. We also believe that dasatinib may be temporarily stopped a few days before LP in patients at high risk of bleeding, since the platelet inhibitory effect would disappear within 24-48 hours after oral administration (17). It has been reported that dasatinib is rapidly absorbed following oral administration, with peak concentrations between 0.5-3 hours and a short plasma half-life (3-4 hours) (20). Indeed, in our second case, the results of repeated platelet aggregation tests returned to normal at 72 hours after the last dose of dasatinib. It remains unclear, however, if temporary withdrawal of dasatinib sufficiently reduces the risk of bleeding complications of LP in Ph’ ALL.

Author’s disclosure of potential Conflicts of Interest (COI).
Shinya Kimura: Honoraria, Bristol-Myers Squibb and Novartis Pharmaceuticals; Research funding, Bristol-Myers Squibb and Novartis Pharmaceuticals.

References


© 2016 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html

2706