Successful Control of Dasatinib-related Chylothorax by the Japanese Herbal Medicine “Goreisan”

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Abstract:
Dasatinib-related chylothorax is a rare adverse event, and the mechanism underlying its occurrence is still not fully understood. We herein report the case of a 73-year-old woman with chronic myeloid leukemia (CML) who developed dasatinib-related chylothorax refractory to conventional treatments, except for steroids. To the best of our knowledge, this is the first case of dasatinib-related chylothorax which was successfully controlled by combining diuretics with the Japanese herbal medicine “Goreisan.” “Goreisan” is known to inhibit aquaporin channels and regulate the water flow. Our findings showed that “Goreisan” is an effective treatment option for uncontrollable dasatinib-related chylothorax.

Key words: dasatinib, chylothorax, chronic myeloid leukemia, Goreisan, aquaporin

Introduction
Dasatinib is a tyrosine kinase inhibitor (TKI) that blocks the initiation of the BCR-ABL1 pathway and the activity of Src kinases. It is used for the treatment of chronic myeloid leukemia (CML), including newly diagnosed, resistant or intolerant to prior CML therapy, or Philadelphia chromosome-positive acute lymphoblastic leukemia cases (1). Previous studies have shown that up to 10% of patients treated with dasatinib develop pleural effusion (1) and often chylothorax due to some unknown mechanism (2-4). Although the pleural effusion induced by dasatinib quickly resolves after drug discontinuation, symptomatic treatment with diuretics and corticosteroids, or therapeutic thoracentesis, dasatinib-related chylothorax is often refractory. “Goreisan” is a Japanese herbal formulation (Kampo). Its mechanism of action involves the inhibition of the aquaporin (AQP) channels and the regulation of the water flow (5). It is usually used to treat edematous diseases including brain edema (6), chronic subdural hematoma (7), and lymphedema (8). We herein present the first case of refractory dasatinib-related chylothorax that was successfully controlled with “Goreisan” combined with diuretics.

Case report
A 73-year-old woman developed asymptomatic leukocytosis after regular health examinations and was diagnosed with CML. Treatment with dasatinib (70 mg/day) was initiated, and an optimal response of CML was achieved 1 year later until the expression level of mRNA in BCR-ABL was 0.0091% on the international scale. After 1 year of treatment with dasatinib, she developed dyspnea on exertion. Upon arrival at our hospital, her body temperature, blood pressure, heart rate, and respiratory rate were 37.2 °C, 151/82 mmHg, 81 bpm, and 16 breaths/min, respectively. No other significant changes in her vital signs during physical examinations were noticed, except for a reduction in right breath sounds, compared to the left sounds. She had undergone open-heart surgery for an atrial septal defect 25 years ago, which had not

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caused any issues until this visit (Fig. 1A). Her chest X-ray revealed the presence of right pleural effusion (Fig. 1B). Thoracentesis yielded a milky pleural fluid with a total protein level, lactate dehydrogenase activity, cholesterol level, and triglyceride level of 4.3 g/dL, 125 U/L, 5.9 mg/dL, and 273 mg/dL, respectively. The pleural effusion was lymphocyte-dominant exudative in nature (Fig. 2). Further tests were positive, such as the ethyl ether test and a qualitative analysis of chylomicron (Fig. 2). However, other examinations showed negative results, such as pleural fluid cytology, which was negative for malignancy; a pleural fluid culture, which showed no bacterial growth; enhanced computed-tomography, which showed no evidence of thrombosis or malignancy; echocardiography, which suggested no evidence of heart failure; and lymphangiography which showed no extravasation from the thoracic duct. Based on this profile, the patient was diagnosed with dasatinib-related chylothorax. Despite discontinuing dasatinib and switching to bosutinib (300 mg/day), there was no improvement in her symptoms. Her chest X-ray findings gradually became exacerbated, and the chylothorax volume fluctuated slightly. To control the chylothorax, furosemide (50 mg/day) was initiated 4 months after the discontinuation of dasatinib, and therapeutic thoracentesis was performed every other month. However, her chest X-ray showed that the pleural effusion had gradually increased with worsening dyspnea and pedal edema (Fig. 1C). Additionally, the use of systemic corticosteroids was avoided in this patient because of the possible adverse effects associated with long-term administration. For 5 months after the discontinuation of dasatinib, the expression level of BCR-ABL mRNA was within the range of 0.0121-0.0264%, and imatinib administration (400 mg/day) was initiated as an alternative treatment for CML. Then, 14 months after diagnosis of chylothorax “Goreisan” (7.5 g/day) was added to the treatment with a diuretic for controlling the sustained chylothorax and pedal edema. One month after initiation of “Goreisan” treatment, the radiological findings demonstrated a dramatically improved clinical profile. Furthermore, the pleural effusion observed on chest X-rays continued to improve for up to 16 months (Fig. 1D). The patient continued treatment with imatinib and maintained an optimal response (the expression level of BCR-ABL mRNA was 0.0052% on the international scale).

Discussion

Although dasatinib-induced pleural effusion has been frequently reported in patients receiving treatment with TKIs for CML (26 of 258; 10.1%) (1), dasatinib-related chylothorax is a rare complication. To the best of our knowledge, only eight cases of this adverse event have previously been reported (Table) (2-4), and no article reporting chylothorax associated with other TKIs (imatinib, nilotinib, or bosutinib) is available. Although the main causes of chylothorax have been identified to include trauma, thoracic surgery, tuberculosis, amyloidosis, and malignant neoplasm (9), the pathophysiology of dasatinib-related chylothorax has not yet been fully characterized. One possible mechanism of the development of this complication could be that dasatinib inhibits tyrosine kinase platelet-derived growth factor receptor beta (PDGFR-β), which regulates angiogenesis, lymphangiogenesis, and vascular smooth muscle cell proliferation, resulting in the leakage of lymph fluid into the pleural space (10-12). Although our patient had a clinical history of open-heart surgery for an atrial septal defect 27 years previ-
time, lymphangiography showed no extravasation, which suggested that the chylothorax was not related to past surgical interventions. To control chylothorax, there are effective symptomatic treatments such as drug discontinuation or a reduction of the dasatinib dosage, diuretics and corticosteroids, and thoracentesis. Nevertheless, in the present case, we observed a worsening of the chylothorax symptoms despite the termination of dasatinib, administration of furosemide, and repeated thoracentesis.

“Goreisan” successfully reduced the pleural effusion in our patient. There are 13 types of AQP5, and several are expressed in the lung, including AQP1, 3, 4, and 5 in the microvascular endothelia, large airways, large- and small-airway epithelia, and type I alveolar epithelial cells, respectively (5). In clinical practice, “Goreisan” has been reported to be effective in treating edematous diseases (6-8). Thus, “Goreisan” might have suppressed these AQP5s and thereby reduce the chylothorax in this patient.

There are certain limitations associated with this report. First, the administration of diuretics was not discontinued in this case, and it is not clear whether “Goreisan” worked alone or synergistically with diuretics. Second, the mechanism underlying the dasatinib-related chylothorax and AQP5 expression in the lungs was not fully elucidated. Furthermore, the factors distinguishing the phenotype interacting with “Goreisan” to reduce dasatinib-related chylothorax are unknown. In addition, the contribution of the active ingredients of “Goreisan” that are responsible for its therapeutic effect are unknown. Although some ingredients of “Goreisan” (Alisma rhizome, Atractylodes lancea rhizome, and Polygonus sclerotium) are known to be effective for treating edematous diseases, further studies are necessary to confirm it.

In conclusion, “Goreisan” showed great efficacy in the treatment of uncontrollable dasatinib-related chylothorax. Thus, “Goreisan” could be an effective treatment option for uncontrollable pleural effusion.

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

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### Table. Summary of Dasatinib-related Chylothorax Cases.

| Age | Sex | Continued/discontinued dasatinib | Alternative therapy | Treatment of chylothorax | Result | References |
|-----|-----|----------------------------------|--------------------|-------------------------|--------|------------|
| 73  | F   | discontinued                    | bosutinib, imatinib | diuretics, "Goreisan," therapeutic thoracentesis | improved | present case |
| 40  | F   | discontinued                    | nilotinib          | diuretics, corticosteroid | improved | (2)        |
| 71  | F   | continued                       | dose reduction     | diuretics, corticosteroid, therapeutic thoracentesis | improved | (3)        |
| 69  | M   | discontinued                    | bosutinib          | therapeutic thoracentesis | improved | (4)        |
| 47  | M   | continued                       | N/A                | diuretics, therapeutic thoracentesis | improved | (13)       |
| 46  | M   | discontinued                    | N/A                | diuretics, corticosteroids, therapeutic thoracentesis | improved | (13)       |
| 49  | M   | discontinued                    | N/A                | ligation of thoracic duct, fasting, parental nutrition support | observation only | improved (13) |
| 90  | M   | discontinued                    | hydroxy carbamide  |                          |        |            |

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