Successful treatment with ibrutinib of intractable thrombocytopenia associated with recurrent chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is characterized by lymphocytosis with mild progression, although some CLL patients develop fatal cytopenia. This report describes a 69-year-old Japanese man with CD8+/CD19+ CLL presenting with severe thrombocytopenia. Because he showed extreme resistance to various conventional regimens, we administered a novel agent, ibrutinib. Besides a striking reduction in CLL cells, thrombocytes rapidly recovered within 1 to 2 weeks after treatment. This report suggests that ibrutinib may be clinically useful for such patients. Additionally, as CD8 is rarely expressed in B-CLL cells, it is crucial to accumulate such cases for further evaluations.

Key words: ibrutinib, thrombocytopenia, chronic lymphocytic leukemia, CD8

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the neoplastic proliferation of lymphocytes, with generally slow progression and an asymptomatic history. However, some CLL patients develop severe anemia and thrombocytopenia following repeat disease recurrence, possibly through autoimmune reactions mediated mostly by nonmalignant B cells.1,2 Severe cytopenia is a serious complication in these patients, with a prevalence of 0.13%.3 Thus, appropriate and immediate treatment of CLL itself is required to reduce bleeding complications. In contrast, emergency therapeutic options are limited, usually consisting only of transfusions.

The present report describes a 69-year-old Japanese man with CD8+/CD19+ CLL accompanied by intractable thrombocytopenia (platelet count <3,000/μl), despite transfusions for 25 consecutive days. Because this patient showed extreme resistance to various conventional regimens, we thus administered a novel agent, ibrutinib. Although ibrutinib may provide better outcomes than other salvage treatments,3,4 its effects in CLL-related cytopenia remain largely unknown. We here report a possible benefit of ibrutinib for such patients. Moreover, we also found that CLL cells in this patient were positive for expression of both CD8 and CD19. Given that the significance of CD8 expression in B-CLL patients remains to be determined,3 it is therefore important to report such cases for further investigations.

Case Report

A 69-year-old Japanese man first diagnosed with CLL 14 years earlier was admitted to our hospital for severe thrombocytopenia with CLL progression, characterized by lymphocytosis and lymphadenopathy. This was the sixth such recurrence in this patient’s history.

Formerly, the patient was treated with fludarabine, cyclophosphamide, rituximab, bendamustine, pulsed methylprednisolone, and ofatumumab. During his previous relapse, he exhibited thrombocytopenia that led to severe hematoma at the dorsal pancreas. He underwent interventional radiology to prevent active bleeding and recurrent bleeding complications were in adequately controlled. Within 2 weeks of starting ofatumumab, he showed marked recovery of platelet counts, to around 110,000/μl. Nevertheless, maintenance treatment with ofatumumab became ineffective, with thrombocytopenia (platelet count <10,000/μl) becoming evident 6 months later. At the time of admission, his CLL status was
**Figure 1.** Flow cytometry analysis (A, top, left) of CLL tumor cells and (B, bottom, left) mononuclear cells in the patient in the present report. Two color graphs were generated: (A, top, right) CD19 (Y-axis) and CD8 (X-axis), and (B, bottom, right) with CD25 (Y-axis) and FOXP3 (X-axis).

**Figure 2.** Immunofixation electrophoresis upon admission
Figure 3. The patient’s clinical course, showing the effects of ibrutinib treatment (A, top) on platelet and lymphocyte counts and (B, bottom) on serum phosphate and LDH.
found to be Rai classification IV and Binet classification C, with factors indicating poor prognosis, in that he was CD38 positive and had an elevated level of serum β2-microglobulin. A blood test at admission showed a marked increase in lymphocyte count, 108,000/μl (normal range: 1,200−3,690/μl); anemia, 9.9 g/dl (normal range: 11.5−15.0 g/dl); an increased level of lactate dehydrogenase (LDH), 322 U/l (normal range: 119−229 U/l); a normal uric acid (UA) level, 6.4 mg/dl (normal range: 2.4−7.0 mg/dl); a slightly elevated serum phosphate level, 4.4 mg/dl (normal range: 2.5−4.7 mg/dl) and severe thrombocytopenia, 0.9 × 10^4/μl (normal range: 16.0−39.0 × 10^4/μl). These findings suggested self-destruction of tumor cells due to severe disease progression. Over the next 3 days, he showed further progression of both lymphocytosis (>140,000/μl) and thrombocytopenia (<0.3 × 10^4/μl). Direct and indirect Coombs tests were both negative, and there were no signs of collagen diseases; elevations of anti-nucleated antibody, anti-double strand DNA IgG, anti-Sm/SS-A/SS-B, anti-ENA, and anti-centromere IgG.

Figure 4. The patient's CT scan images showing improvements (top) in splenomegaly and (bottom) axillary lymphadenopathy (left, day 3; right, day 49)
SS-B antibody, lupus anticoagulant, anti-CL β2GPI, or CL-IgG. He also manifested a high fever and mucocutaneous hemorrhages. Bone marrow aspiration showed a marked increase in lymphocytes exhibiting CLL markers, including CD5+, CD10-, CD19+, as well as CD20+, CD23+, CD38+, and CD52+ phenotype and skewed kappa chain production. Flow cytometry also showed that these CLL cells were CD8+ B cells (Figure 1A). Immunofixation electrophoresis showed the presence of M protein, IgM kappa type (Figure 2). Computed tomography (CT) at admission showed cervical, mediastinal, hilar, peritoneal, and retroperitoneal lymphadenopathy and splenomegaly. Although we initially administered dexamethasone 16.5 mg/day for 5 days with supportive treatment, including antibiotics, intravenous immunoglobulin, and platelet transfusions; the effects on lymphocytosis and thrombocytopenia were only marginal. For the preparation of the treatment with ibrutinib, a novel agent that inhibits Bruton’s tyrosine kinase (BTK), we administered fludarabine (40 mg/day) for 3 days to reduce absolute lymphocyte numbers. Although fludarabine lowered the total white blood cell count in this patient, it did not affect the relative lymphocyte ratio, which remained at approximately 95%. Thrombocytopenia (<3,000/μl) also persisted despite continuous transfusions. While CD52 was expressed on CLL cells in the present case, the study by Byrd et al.6 reporting that ibrutinib was more effective than alemtuzumab for refractory CLL patients convinced us to use ibrutinib for the present patient.

Administration of ibrutinib (420 mg/day) resulted in the rapid disappearance of oral and urinary hemorrhages within a few days, prior to a recovery of thrombocytes. Platelet numbers also gradually increased, to 11,000/μl at 2 weeks and 25,000/μl at 3 weeks after starting ibrutinib (Figure 3A). Platelet transfusions were less frequent and were deemed unnecessary after day 20. The levels of serum phosphate and LDH had also decreased (Figure 3B). No adverse effects of ibrutinib, such as liver dysfunction, arrhythmia, severe cytoreduction, or infection were observed. The reduction in malignant CLL cells was accompanied by a marked recovery of T lymphocytes, reflecting a correction of lymphohematopoiesis. CT scans also showed marked improvements in systemic lymphadenopathy and splenomegaly (Figure 4). Collectively, these findings indicate that the benefits of ibrutinib included the rapid recovery of CLL mediated autoimmune thrombocytopenia as well as a decrease in CLL clones.

Discussion

CLL generally progress slowly and does not require emergency treatment. This report describes a patient with recurrent CLL who experienced life-threatening thrombocytopenia. Intriguingly, the B-CLL cells in this patient displayed aberrant expressions of CD8. The frequency of CD8+ B cells in CLL patients has been reported to be less than 1%.7 Although CD8+ B cells have been reported associated with poor prognosis,7 this finding was not supported by the results of another study.5 Thus, to date, it is unclear whether the aberrant expression of CD8 is an aggressive disease marker for CLL. Indeed, although our patient showed a trend toward aggressive disease progression, the expression of CD8 on his CLL cells before and after ibrutinib treatment did not differ significantly, suggesting that CD8 was not indicative of disease status or responsiveness to treatment, at least in this patient.

The underlying mechanisms causing CLL related thrombocytopenia have not yet been determined. However, autoimmunity in CLL may be related to previous treatment with purine analogues and alkylating agents.1 Fludarabine therapy may mediate the suppression of regulatory T cells, leading to the production of autoreactive T cells.8,9 Even though the patient had been treated with these agents, his peripheral blood regulatory T cell count did not increase after ibrutinib (Figure 1B).

Several mechanisms of action of ibrutinib in CLL related thrombocytopenia have been proposed. For example, nonmalignant B cells may produce autoantibodies that target the platelet surface antigens, Ib/IX and IIb/IIIa, resulting in platelet destruction through opsonization and platelet-dependent cellular cytotoxicity.8,10 Ibrutinib primarily induces apoptosis of both malignant and nonmalignant B cells by inhibiting B cell receptor signaling. BTK, which is expressed on B cells but not on T cells, plays important roles in B cell survival, adhesion, and migration. BTK inhibition by ibrutinib would likely reduce the surface expression of CXCR4, releasing lymphocytes into the blood stream from the spleen and lymph nodes, and inhibit their homing capacities, thereby enhancing the efficiency of apoptosis.11 Moreover, ibrutinib may inhibit crosstalk between CLL cells and immune effector cells, resulting in a reduction in autoreactive T cells.12 Taken together, these findings suggest that ibrutinib ought to be effective for CLL-related thrombocytopenia. Furthermore, modulation of phagocyte signaling is also promising in patients with immune thrombocytopenic purpura (ITP). The spleen tyrosine kinase (Syk) inhibitor fostamatinib,
which blocks Fc γ receptor signaling in phagocytes, may be effective at ameliorating the destruction of platelets in patients with ITP.13,14 BTK is responsible for the downstream signaling of Syk molecules15 and is likely responsible for macrophage functions.16

These findings suggest that ibrutinib may potentially become feasible even for the treatment of patients with ITP. Although ibrutinib treatment for the patient in the present report resulted in the recovery of thrombocytes, his platelet counts did not reach the normal range, remaining at approximately 50,000/μl. This finding is in agreement with the mechanisms of ibrutinib action. Ibrutinib may not immediately "eradicate" CLL cells but rather decrease them and correct their supporting environment. We, therefore, continued this patient on maintenance treatment with ibrutinib, in addition to careful follow-up.

In conclusion, we encountered a patient with intractable thrombocytopenia associated with severe recurrent CLL who was successfully treated with ibrutinib. Although it remains unclear whether ibrutinib is always warranted for such CLL patients, additional studies are required, and our findings suggest that ibrutinib ought to be considered for the treatment of CLL-associated severe thrombocytopenia. In addition, CLL is less common in Japan than in western countries, and its etiology may show racial and ethnic differences. Therefore, it would be of great importance to evaluate additional Japanese patients treated with ibrutinib.

References