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Effective treatment of autoimmune thrombocytopenia with rituximab in CLL patient undergoing therapy with acalabrutinib

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Introduction

Chronic lymphocytic leukemia (CLL) is a heterogeneous malignancy characterized by the progressive deposition of monoclonal lymphocytes with specific immunophenotypic features (i.e. CD5+ and CD23+) in the peripheral blood, bone marrow, and lymphoid tissues [1]. Up to 5% of CLL patients experience immune thrombocytopenia (ITP) as a complication [2].

The mainstay of first-line management of ITP is corticosteroid treatment. However, immunosuppressive drugs, vincristine, azathioprine, rituximab monotherapy, RCD (rituximab, cyclophosphamide, dexamethasone), thrombopoietin receptor agonists (TRA) and intravenous immunoglobulin (IVIG) also play a role in treating ITP and underlying CLL [3].

There is a growing body of evidence that small-molecule inhibitors may also be effective in treating CLL-associated autoimmune cytopenias (AIC), particularly Bruton's tyrosine kinase inhibitors (BTKis) such as ibrutinib, zanubrutinib or rilzabrutinib [4, 5]. However, some patients undergoing therapy with BTKi still need additional therapy for ITP [4].

Herein we describe a case where treatment-refractory ITP in CLL, during therapy with the BTKi acalabrutinib, successfully responded to rituximab.

Case report

In June 2021, a 74-year-old woman presented with leukocytosis with lymphocytosis (WBC 46G/l, 76% of lymphocytes) without any other signs or symptoms. The patient was then observed by her family doctor without diagnosis.

In August 2023, the patient was admitted to the Hematology Department due to severe bleeding diathesis affecting the skin and mucosa and active epistaxis. She had been complaining of severe night sweats and loss of weight (10 kg during the last four months). Her medical history included hypertension for five years and no other diseases or autoimmune disorders. On examination, thrombocytopenia (7G/L), mild anemia (8.7 g/dL) and leukocytosis (125G/L) were observed. An indirect Coombs test was negative. Whole body CT scans demonstrated splenomegaly (20 cm) and generalized lymphadenopathy up to 4 cm in diameter. Bone marrow aspirate showed 82% infiltration of mature lymphoid cells and numerous megakaryocytes with inhibited proplatelet formation. Immunophenotyping by flow cytometry from peripheral blood samples revealed the typical immunophenotype of chronic lymphocytic leukemia (CD19+, CD20+, CD23+, CD5+, CD200+, lambda+). Cytogenetic examination by FISH did not reveal any aberrations. Molecular tests showed unmutated *IGHV* gene and no *TP53* gene mutation. The patient was diagnosed with high-risk CLL according to the Rai staging system, with secondary ITP.

Due to epistaxis, the patient first received a platelet transfusion to stop the bleeding and then began a four-day pulse with dexamethasone at a daily dose of 40 mg. Therapy with acalabrutinib was also initiated. Dosing of BTKi was according to the standard administration schedule (i.e. 100 mg twice per day) [6]. After the steroid pulse, platelet counts were still below 10G/l. An infusion of 1g/kg bw intravenous immunoglobulin (IVIg) for two consecutive days was ordered, and the platelet count increased to 57G/l.

After the first three months of therapy with acalabrutinib, the general symptoms eased with a significant reduction in lymph node and spleen size. In addition, white blood

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cell count and hemoglobin level normalized, although mild thrombocytopenia was still observed. During the fourth month of therapy with BTKi, the platelet count decreased, without any other signs or symptoms of progression.

The patient was re-admitted to the Hematology Department due to severe thrombocytopenia (10×10^9/l) with bleeding diathesis affecting the skin and mucosa. Hemoglobin and WBC levels were normal. Abdominal ultrasound did not reveal organomegaly. Bone marrow aspirate showed a reduction of infiltration to 50% of mature lymphoid cells, and numerous megakaryocytes with inhibited proplatelet formation were still apparent. The patient received an infusion of 1g/kg bw IVIg for two consecutive days, and the platelet count increased to 90×10^9/l. Due to the previous good response to acalabrutinib, this therapy was continued. However, steroid-resistant ITP was still present. It was decided to commence therapy with rituximab, an anti-CD20 monoclonal antibody active in autoimmune complications and in CLL. After four doses of rituximab (375mg/m^2, one infusion per week), the platelet count increased above 100×10^9/l. The patient achieved partial remission and continued therapy with acalabrutinib. No further complications were observed during treatment. The current duration of the response to this combination therapy is seven months.

Discussion

In CLL patients with refractory AIC, the optimal therapeutic strategy is to treat the underlying CLL, because control over CLL clone often provides effective control of AIC. Historically, the most common approach was the administration of an anti-CD20 antibody-based chemoimmunotherapy regimen as an RCD drug combination [3]. However, in the era of new, chemo-free therapies based on small molecules, these standards should be reviewed. One promising option for these patients is presented by BTKis [5, 7]. However, some patients need additional approaches to control CLL and its associated AIC. In some cases, the combination of BTKi and steroids can lead to control of AIC [8]. In steroid-refractory patients, a combination of BTKi and an antiCD20 monoclonal antibody, such as rituximab, appears effective. Indeed, the majority of CLL patients with steroid-refractory ITP respond to rituximab monotherapy [9], and ibrutinib in combination with rituximab is highly effective in treating CLL patients with AIC [10]. However, further studies are needed to establish the optimal approach to patients with CLL and AIC.

Article information and declarations

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Authors' contributions
All authors wrote, reviewed and agreed to the final version of the manuscript.

Conflicts of interest
The authors declare no conflict of interest.

Ethics statement
Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

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