

LETTERS TO THE EDITOR

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Obinutuzumab for the Treatment of Cold Agglutinin Disease: A Case Report

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Dear Editor

A woman in her early 80s was admitted to our hospital in January 2023 due to a 4-year history of hemoglobinuria. She presented with dizziness and fatigue, with a hemoglobin (Hb) level consistently around 40 g/L over the past 4 years. Her symptoms worsened in winter and improved in summer, with recurrent difficulties in blood compatibility. Upon admission, her Eastern Cooperative Oncology Group (ECOG) performance status was scored at 3. The Hb level was 47g/L (normal 110-150g/L), lactate dehydrogenase (LDH) was 634 U/L (normal 0-250U/L), indirect bilirubin was 38 μ mol/L, absolute reticulocyte (Ret) count was $199.5 \times 10^9/L$ ($24-84 \times 10^9/L$), Ret percentage was 7.69% (0.8-2.0%) and haptoglobin was not detectable. It was notable for an increased serum immunoglobulin (Ig) M level of 25.6g/L (normal 0.4-2.3g/L) with normal levels of IgA and IgG. Tests for antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and antiphospholipid antibodies (aPLs) were negative. Direct antiglobulin test (DAT) was strongly positive for C3d and negative for immunoglobulin G (IgG). Her cold agglutinin (CA) titer was 1:256 at 4 °C. Monoclonal IgM κ with a total level of 13.49g/L was detected. Additionally, the serum-free light chain (sFLC) κ/λ ratio was detected to be 67.1. There was no evidence of clonal plasma cells or clonal B cells in the bone marrow biopsy. The bone marrow smear and flow cytometry analysis indicate no abnormality. Clinically and radiologically, no enlarged lymph nodes or other signs of malignancy were detected. Tests for Mycoplasma pneumoniae, CMV-DNA, and EBV-DNA were negative. During the course of disease, the patient received no other special treatment except for intermittent red blood cell transfusion. A diagnosis of autoimmune hemolytic anemias (AIHAs) associated with CA was made, but further identification of primary cold agglutinin disease (CAD) or cold agglutinin syndrome (CAS) was needed due to a detection of monoclonal IgM κ . CAD is a clonal and low-grade B-cell lymphoproliferative disorder characterized by red blood cell agglutination and hemolysis induced by

CAS in the absence of underlying diseases[1]. CAS is a secondary CA-mediated hemolytic anemia, that arises as a complication of diseases such as lymphoma, other malignancies, autoimmune diseases or specific infections[2]. For this case, her clinical presentation aligned with CAD without signs of WM. [3]. Moreover, other causes for CAS, such as mycoplasma infection and autoimmune diseases were excluded. The bone marrow smear showed an absence of lymphoplasmacytic cells, and the flow cytometry of the bone marrow did not reveal any abnormality. Upon subsequent reevaluation, the MYD88-L265P test was negative.

From January 22, 2023, to February 19, 2023, through a total of four weekly infusions of 1g obinutuzumab, her laboratory parameters showed improvements: Hb level raised from 39g/L to 103g/L, and both indirect bilirubin and ret levels returned to normalcy (Figure 1). Sixteen-month follow-up after initial treatment confirmed these results, showing a stable Hb level of 99 g/L and normal bilirubin levels (May 8th, 2024).

There was no standardized first-line therapy for CAD apart from keeping warm. Obinutuzumab is a type II, glycoengineered, humanized anti-CD20 monoclonal antibody[4], offers advantages concerning efficacy profile over rituximab which is a chimeric murine/human monoclonal antibody. Despite the lack of an underlying malignancy, CAD was recognized as a distinct low-grade lymphoid neoplasm due to a clonal proliferation of cells from a lymphoproliferative disorder, similar to some indolent lymphomas[5]. Clinical trials in indolent lymphomas, such as treatment-naïve chronic lymphocytic leukemia and untreated symptomatic follicular lymphoma, have shown that obinutuzumab was superior to rituximab in improving progression-free survival rate[6-8]. It could be speculated that obinutuzumab may have a better treatment response than rituximab in CAD.

Prior cases showed the efficacy of obinutuzumab in secondary CAS[9, 10], while this is the first case of primary CAD treated successfully with obinutuzumab according to our limited knowledge. In summary, obinutuzumab shows a promising role in CAD which might be worth of further investigation.

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Conflicts of interest

None.

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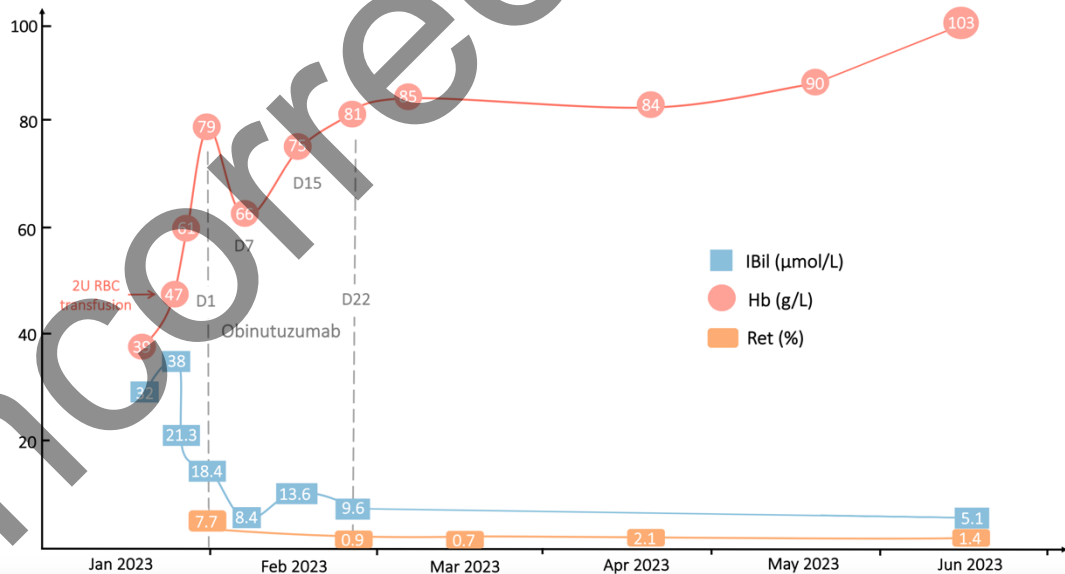


Figure 1. The trend of IBil, Hb, and Ret after obinutuzumab treatment. Abbreviation: IBil, indirect bilirubin; Hb, hemoglobin; Ret, reticulocyte