LETTER TO THE EDITOR

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

Soğuk Agglutinin Hastalığı Tedavisinde Obinutuzumab: Bir Olgu Sunumu

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To the 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 performance status was scored at 3. The Hb level was 47 g/L (normal: 110-150 g/L), lactate dehydrogenase was 634 U/L (normal: 0-250 U/L), indirect bilirubin was 38 μmol/L, absolute reticulocyte (Ret) count was 199.5×10^9/L (normal: $24\text{-}84 \times 10^9$/L), Ret percentage was 7.69% (normal: 0.8%-2.0%), and haptoglobin was not detectable. The increased serum immunoglobulin (Ig) M level of 25.6 g/L (normal: 0.4-2.3 g/L) with normal levels of IgA and IgG was noteworthy. Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, and antiphospholipid antibodies were negative. A direct antiglobulin test was strongly positive for C3d and negative for IgG. The cold agglutinin (CA) titer was 1:256 at 4 °C. Monoclonal IgMκ was detected at a total level of 13.49 g/L. Additionally, the serum-free light chain κ/λ ratio was 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 indicated no abnormalities. Clinically and radiologically, no enlarged lymph nodes or other signs of malignancy were detected. Tests for *Mycoplasma pneumoniae*, *Cytomegalovirus* DNA, and Epstein-Barr virus DNA were negative. During the course of the disease, the patient received no other special treatment besides intermittent red blood cell transfusions.

A diagnosis of autoimmune hemolytic anemia associated with CA was made, but further identification of primary cold agglutinin disease (CAD) or cold agglutinin syndrome (CAS) was needed due to the detection of monoclonal IgMκ. CAD is a clonal low-grade B-cell lymphoproliferative disorder characterized by red blood cell agglutination and hemolysis induced by CA 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]. In this case, the patient's clinical presentation aligned with CAD without signs of Waldenström macroglobulinemia [3]. Moreover, other causes of CAS such as *Mycoplasma* infection and autoimmune diseases were excluded. A bone marrow smear showed an absence of lymphoplasmacytic cells and flow cytometry of the bone marrow did not reveal any abnormalities. Upon subsequent reevaluation, the MYD88-L265P test was negative.

From January 22, 2023, to February 19, 2023, with a total of four weekly infusions of 1 g of obinutuzumab, her laboratory parameters showed improvements: the Hb level increased from 39 g/L to 103 g/L and both indirect bilirubin and Ret levels returned to the normal ranges (Figure 1). On May 8, 2024, in the 16th month of follow-up after the initial treatment, these results were confirmed, showing a stable Hb level of 99 g/L and normal bilirubin levels.

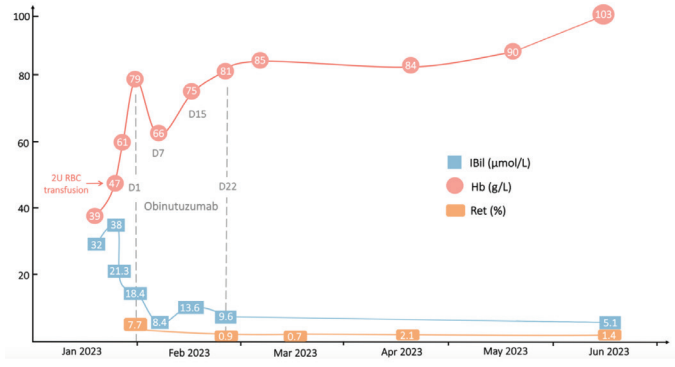

Figure 1. Trends of indirect bilirubin (IBil), hemoglobin (Hb), and reticulocytes (Ret) after obinutuzumab treatment.

RBC: Red blood cell; D: day.

There is no standardized first-line therapy for CAD apart from keeping warm. Obinutuzumab is a type II glycoengineered humanized anti-CD20 monoclonal antibody [4], offering advantages in terms of its efficacy profile over rituximab, which is a chimeric murine/human monoclonal antibody. Despite the lack of an underlying malignancy, CAD is recognized as a distinct low-grade lymphoid neoplasm due to clonal proliferation of cells from a lymphoproliferative disorder, similar to some indolent lymphomas [5]. Clinical trials in indolent lymphomas, such as treatment-naive chronic lymphocytic leukemia and untreated symptomatic follicular lymphoma, showed that obinutuzumab was superior to rituximab in improving the progression-free survival rate [6,7,8]. It could be speculated that obinutuzumab may generate a better treatment response than rituximab in CAD.

Prior cases showed the efficacy of obinutuzumab in secondary CAS [9,10], while the present case is the first case of primary CAD treated successfully with obinutuzumab to our knowledge. In summary, obinutuzumab shows promise in the treatment of CAD that might warrant further investigation.

Keywords: Cold agglutinin disease, Obinutuzumab, Treatment

Anahtar Sözcükler: Soğuk agglutinin hastalığı, Obinutuzumab, Tedavi

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication.

Authorship Contributions

Surgical and Medical Practices: K.S.; Concept: L.Z., K.S.; Design: L.Z.; Data Collection or Processing: L.Z.; Analysis or Interpretation: S.L.; Literature Search: S.L.; Writing: S.L., L.Z.

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