American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e928514
DOI: 10.12659/AJCR.928514

Received: 2020.09.12
Accepted: 2021.01.14
Available online: 2021.01.30
Published: 2021.XX.XX

Can Treatment with Venetoclax for Chronic Lymphocytic Leukemia (CLL) Result In Autoimmune Hemolytic Anemia?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared
Source of support: The Moncton Hospital Clinical Trial

Patient: Female, 62-year-old
Final Diagnosis: Autoimmune hemolytic anemia
Symptoms: Anemia
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual clinical course

Background: Chronic lymphocytic leukemia (CLL) is a hematological disease characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Autoimmune hemolytic anemia (AIHA) is an acquired hemolytic anemia in which the destruction of erythrocytes is helped by anti-erythrocyte auto-antibodies. This has a controversial effect on the clinical outcome and survival of patients with CLL. Venetoclax, a second-generation BH3 mimetic compound, is one of the new therapies that has been approved for the treatment of CLL. Venetoclax disrupts the antiapoptotic signaling through BCL2. Common adverse events associated with venetoclax include neutropenia, thrombocytopenia, and diarrhea. This case report describes a patient with CLL who developed AIHA when treated with venetoclax.

Case Report: A patient of 62-year-old woman, who was treated with multiple lines of therapy, presented autoimmune hemolytic anemia after treatment with venetoclax. The anemia was resolved after holding venetoclax and being treated with rituximab. In January 2019, there were reports of 7 patients developing AIHA related to venetoclax therapy in Europe, according to the EudraVigilance database. How venetoclax can cause AIHA is not completely clear. This complication can happen when the erythrocyte antigen is altered by the drug that can produce antibodies. The other described mechanism is the binding of the drug with erythrocytes, which leads to production of an immune response.

Conclusions: Although AIHA can be a complication of CLL, it may be caused by treatment with venetoclax. That may be confirmed after eliminating other causes.

Keywords: Anemia, Hemolytic, Autoimmune • Drug-Related Side Effects and Adverse Reactions • Leukemia, Lymphocytic, Chronic, B-Cell

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/928514

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Background

Chronic lymphocytic leukemia (CLL) is a hematological disease characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen [1,2]. It is the most frequent type of leukemia in Western countries. It is most common among patients older than 65 years of age and it is more prevalent in men. The disease is usually asymptomatic in its early stages [3]. The main features in symptomatic patients are generalized lymphadenopathy, fatigue, and weight loss. With increased bone marrow infiltration, anemia and thrombocytopenia may become apparent [1]. The overall risk of autoimmune hemolytic anemia (AIHA) in patients with CLL is 5-10% (Zent et al, 2010). AIHA is an acquired hemolytic anemia in which the destruction of erythrocytes is helped by anti-erythrocyte auto-antibodies. This has a controversial effect on the clinical outcome and survival of patients with CLL. There have been several advances in recent years in the treatment of CLL; the new treatments mainly target 2 key regulatory mechanisms for CLL cell survival: B-cell receptor signaling and the intrinsic pathway of apoptosis. Venetoclax, a second-generation BH3 mimetic compound that disrupts the antiapoptotic signaling through BCL2, is one of the new therapies that has been approved for the treatment of CLL [4]. Common adverse events associated with venetoclax include neutropenia, thrombocytopenia, and diarrhea [5].

This article describes the case of a patient with CLL who developed autoimmune hemolytic anemia (AIHA) when treated with venetoclax.

Case Report

A female patient, who neither smoked nor drank, was diagnosed with low-grade CLL at the age of 62 years in November 2011, after a routine blood test. Initially, the patient was asymptomatic, and the decision was made to follow up regularly rather than initiating treatment at the time of diagnosis. She experienced clinically significant progression of lymphadenopathy, and in June 2012 it was noted that she had progressive lymphadenopathy with rapid lymphocyte doubling time. The cytogenetic study was positive for trisomy 12, and 13q deletion, but negative for 17p deletion and 11q deletion (in the 5th line). DAT was previously negative. The patient then started systemic chemotherapy with fludarabine, cyclophosphamide, and rituximab at 28-day intervals for a total of 6 courses. The patient tolerated chemotherapy well and there was improvement of the disease. She had to stop treatment after the third cycle, because of neutropenia. After the neutropenia resolved, she continued treatment but with a dose reduction of 20%. Treatment was completed on November 21, 2012. She achieved a complete hematological response to treatment for her CLL on January 16, 2013. The patient did well for the next 2 years, except for low-grade anemia. The anemia at that time was mild, caused by the CLL itself. It was investigated and was not related to autoimmune hemolytic anemia. The Coombs test was negative, total bilirubin, reticulocytes, lactate dehydrogenase, and haptoglobin were all normal. The lactate dehydrogenase increased at the end of 2015 in keeping with progression of her CLL. On May 20, 2015, she was diagnosed with early recurrence of CLL without symptoms. As such, no treatment was suggested. On September 21, 2015, pathological lymphadenopathy in the axilla had increased, indicating progression of CLL. On December 10, 2015, the patient started second-line therapy with bendamustine/rituximab for 6 cycles. The sixth and final cycle of the treatment was cancelled because of neutropenia, which developed on May 4, 2016. On June 3, 2016, the patient's CLL was in remission except that she developed a mild skin rash.

At an examination on January 16, 2018, the patient showed multiple lymphadenopathies in the chest and the axilla, which varied between 2 and 4 cm, indicating clear progression of CLL and requiring a third line of treatment. The patient was also diagnosed with severe thrombocytopenia and severe anemia. Ibrutinib was started on February 6, 2018. Her lymphocyte levels doubled in less than 6 months. Between May and August 2018, during her treatment with ibrutinib, she developed neutropenia with a rash in different areas and fatigue. After the treatment was put on hold, the patient's lymphocyte levels increased rapidly, and she experienced rapid enlargement of peripheral lymphadenopathy.

Given her condition, the patient was enrolled in a clinical study (DEVOTE), with treatment with venetoclax, on October 12, 2018. She received the ramping dose of 20 mg for the first week, 50 mg the second week, 100 mg the third week, 200 mg the fourth week, and 400 mg thereafter. On December 14, 2018, the patient had grade 2 neutrophil toxicity and grade 3 neutropenia without fever or infection. This neutropenia was treated with filgrastim, a colony-stimulating factor.

After her 17th cycle of venetoclax, she faced a few challenges. She was admitted to the hospital on May 26, 2020, with severe anemia that required transfusion with 2 units of packed red blood cells after her hemoglobin level was found to be 4.8 mg/dL. Her blood work done the same day showed reticulocytes 274×10^{9}/L, haptoglobin was less than 0.1, total bilirubin 86 µmole/L, indirect bilirubin 73 µmole/L, LDH 697 U/L (for a higher normal level of 220), and direct antiglobin test positive with IgG specific 2+, suggesting autoimmune hemolytic anemia. She received dexamethasone 40 mg daily for 4 days along with pantoprazole, which resulted in some improvement, but she was requiring a transfusion every other day. The venetoclax

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and filgrastim were both stopped. She received supplementation with potassium to optimize her potassium level to address the hypokalemia. The response to dexamethasone was suboptimal, since the hemoglobin went up mildly from 6.3 to 8.9, then back down to 6.9 mg/dL. Therefore, the patient was started on rituximab on June 5, 2020 and tolerated it well. Her Coombs test result was positive. She was then less transfusion-dependent, and hemoglobin started to improve progressively after 4 cycles of weekly rituximab.

The rituximab dose was 375 mg/m^2 on cycle 1 to 3 of FCR, then 500 mg/m^2 on cycles 4 to 6, and it was 375 mg/m^2 on cycle 1 of BR and 500 mg/m^2 on following cycles. It was 375 mg/m^2 on the weekly cycle for the AIHA.

Discussion

AIHA is rarely associated with venetoclax treatment. In January 2019, there were reports of 7 patients developing AIHA related to venetoclax therapy in Europe, according to the EudraVigilance database [2]. In the clinical guidance of the Pan-Canadian Oncology Drug Review's report on venetoclax for CLL on April 4, 2019, AIHA was not reported as an adverse event [6].

A case report from Spain reported AIHA as one of the more serious toxicities associated with venetoclax [2]. In a case report from China, a 50-year-old patient who was treated for mantle cell lymphoma with a combination of venetoclax plus ibrutinib, with rapid titration of venetoclax, experienced a hemolytic crisis. This adverse event was attributed to the high-dose combination of venetoclax and ibrutinib, and the rapid titration of venetoclax was also thought to play a role [7]. In a study of 350 patients treated with venetoclax 400 mg daily, AIHA was reported in 17 patients (5%), but only 2 patients discontinued treatment because of AIHA [4].

How venetoclax can cause AIHA is not completely clear. This complication can happen when the erythrocyte antigen is altered by the drug, which can produce antibodies. The other described mechanism is the binding of the drug with erythrocytes, which leads to production of an immune response.

On the other hand, venetoclax is sometimes used to treat AIHA as a complication of CLL, which occurs in 10-15% of patients with CLL. In the present case, the patient did not develop AIHA spontaneously as a complication of CLL, because she developed AIHA only after she had undergone 17 cycles of treatment with venetoclax, with no sign of progression of the CLL, and there was no other reason for AIHA. After treatment was paused, the patient achieved good improvement of her hemoglobin level. This case adds to the evidence that AIHA that can be an adverse event of venetoclax therapy.

Conclusions

AIHA can not only be a complication of the CLL for which venetoclax treatment is needed, it can also be an adverse event associated with venetoclax therapy itself. In patients with CLL who develop AIHA, it is important for clinicians to determine the reason for the AIHA. AIHA is another rare adverse event that should be considered among the possible adverse effects of venetoclax therapy, and investigation needs to be done case by case to determine whether CLL itself or other drugs used to treat CLL are the cause of the development of AIHA.

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