Successful treatment of severe idiopathic mixed autoimmune hemolytic anemia with bortezomib and intravenous immunoglobulin

Iloabueke Chineke, Suaka Kagbo-Kue, Judith Aniekwena, Myra Rose

ABSTRACT

Introduction: Autoimmune hemolytic anemia (AIHA) is a rare and diverse group of acquired hemolytic anemias which results from increased destruction of red blood cells (RBCs) due to autoantibodies directed against antigens on the RBC surface. Currently, there are no clearly defined evidence-based guidelines on the management of AIHA, and current treatment options are based on small retrospective studies, case reports, as well as expert experiences and recommendations. We report a case of severe idiopathic mixed AIHA that responded to a combination of steroids, intravenous immunoglobulin (IVIG) and bortezomib. Case Report: A 25-year-old African American female presented with jaundice, shortness of breath, and abdominal pain. She had splenomegaly on examination and initial workup was significant for severe anemia (hemoglobin, 3.3 g/dl) and hyperbilirubinemia (total bilirubin, 26.7 mg/dl; direct bilirubin, 21.9 mg/dl). Direct antiglobulin test (DAT) was microscopically positive for anti-IgG and anti-C3d, and cold autoantibodies were identified. An extensive workup for a possible secondary cause of her anemia was non-revealing. She was sequentially treated with prednisone, IVIG, and bortezomib. Marked response was noted as evidenced by improvement in the hemoglobin from a nadir of 3.2 g/dl on admission to 10.1 at discharge. Patient has remained clinically in remission since then. Conclusion: The first line treatment for warm AIHA (w-AIHA) includes glucocorticoids and transfusion of least incompatible RBCs. Steroids are rarely necessary or effective in cold agglutinin AIHA in which case high dose IVIG and plasmapheresis have been used albeit with inconsistent results. Bortezomib is an inhibitor of the 26S proteasome and is approved for the treatment of multiple myeloma. It has been reported to have some activity in rituximab-resistant cold agglutinin disease (CAD) due to its activity against the CD20-negative plasma cell compartment that may be responsible for IgG anti-RBC autoantibody production.

Keywords: Anemia, Autoimmune, Hemolysis, Mixed

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) results from increased RBC destruction caused by autoantibodies reacting against RBC antigens with or without complement activation. The clinical presentation...
depends on the subclass type (warm agglutinin, cold agglutinin, and mixed type); a classification based on the thermal amplitude of the causative autoantibody. Mixed AIHA is an unusual and rarely reported type of AIHA in which the laboratory data satisfy the serologic criteria of both w-AIHA and CAD [1]. The rarity of this form of AIHA presents a therapeutic challenge as the class and characteristics of the causative autoantibody play a role in the patient’s treatment and outcome [2]. Equally imperative to treatment outcomes is the need to determine the etiology of AIHA as over 50% of cases are secondary to a number of infectious, neoplastic, and autoimmune disorders [3], where a resolution of symptoms can be achieved with the treatment of the underlying etiology. Therapeutic options for the treatment of hemolysis associated with mixed AIHA are limited [4], as it is associated with a more severe disease course. Herein, we present the case of a patient in whom resolution of hemolysis and improvement in hemoglobin count was achieved following sequential treatment with steroids, IVIG, and bortezomib.

CASE REPORT

A 25-year-old female visiting from Out-of-State presented to the Emergency Department (ED) with abdominal pain, shortness of breath, vomiting, and subjective fevers. She had previously been investigated for abdominal pain about seven months prior to the current presentation. At that time, she was informed of some problems with her liver and asked to return to the clinic but was lost to follow-up. The patient did not have any other significant past medical history and was not taking any regular medications.

Her vital signs were stable except for sinus tachycardia of 143 beats/min. Physical examination revealed pallor, deep jaundice, and mild splenomegaly. Laboratory findings included anemia (hemoglobin 3.3 g/dl and hematocrit 10.2%), elevated absolute reticulocyte count (205.6), macrocytosis (MCV 107 fL), elevated bilirubin (total bilirubin 26.7 mg/dl and direct bilirubin 21.9 mg/dl), mildly elevated lactate dehydrogenase (LDH) of 193 U/l (ref 91–180), a normal haptoglobin (149 mg/dl) and total bilirubin 5.2 mg/dl (Figure 1), direct bilirubin 2.3 mg/dl. A follow-up call to her Hematologist seven months post discharge confirmed that she has remained in remission and hemoglobin levels have remained stable without any need for further transfusions.

She was transfused several units during her hospital course. The hematology service was consulted and a diagnosis of mixed type autoimmune hemolytic anemia was made. Thus, the patient was given a loading dose of intravenous methylprednisolone 125 mg once, followed by oral prednisone 100 mg daily. Simultaneously, she was started on intravenous immune globulin 100 g daily for two doses in order to slow the hemolytic process. Apart from a sustained decline in her bilirubin levels, the patient’s hemoglobin and clinical status did not improve substantially and she continued to require almost daily blood transfusions. Based on anecdotal isolated reports of the efficacy of bortezomib in autoimmune hemolytic anemia, our patient was started on bortezomib 2.7 mg every 72 hours and got a total of four doses. Following the first two courses of bortezomib, the patient showed a remarkable clinical improvement. Her hemoglobin levels started trending up and she no longer required blood transfusions. Markers of acute hemolysis like lactate dehydrogenase, bilirubin levels, and reticulocyte count also dropped progressively. Subsequently, the prednisone was gradually tapered. At discharge, her hemoglobin was 10.1 mg/dl (Figure 1), total bilirubin 5.2 mg/dl (Figure 2), and direct bilirubin 2.3 mg/dl. A follow-up call to her Hematologist seven months post discharge confirmed that she has remained in remission and hemoglobin levels have remained stable without any need for further transfusions.
can be sustained by long-lived plasma cells which are responsible for hemolysis in CAD [8]. Moreover, rituximab, which targets CD20 B lymphocytes, bortezomib targets proteasome signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. In contrast to rituximab, which targets CD20 B lymphocytes, bortezomib targets differentiated plasma cells that typically do not express CD20 but may be responsible for secretion of the abnormal IgM responsible for hemolysis in CAD [8]. Moreover, chronic inflammatory processes in autoimmune diseases can be sustained by long-lived plasma cells which continuously secrete pathogenic antibodies. Proteasome inhibitors that target plasma cells like bortezomib could effectively weaken this antibody-producing category of cells. In view of its effect on malignant B cells and plasma cells, bortezomib has been used to treat other plasma cell disorders, with case reports of successful treatment of immune hemolytic anemia related to cryoglobulinemia, systemic lupus erythematosus, and myasthenia gravis [9]. Danchaivijitr et al. reported that a combination of bortezomib and low-dose cyclophosphamide was successfully used to treat a patient with transfusion-dependent and steroid/rituximab-refractory AIHA [7].

The combined use of prednisone, IVIG, and bortezomib in our patient leading to her successful therapeutic outcome may make it difficult to discern which components of the combination therapy were responsible for the improvement in the hemolytic process. However, it is noteworthy that the observed sustained improvement in her hemoglobin level was noticed only after the introduction of bortezomib. That is not to discount the significance of the sustained decline in the bilirubin levels following the commencement of the steroids and IVIG. Although steroids suppress antibody production and down regulate Fc-receptor-mediated red cell destruction in the spleen, reports indicate that their effect is not immediate and often takes 2–4 weeks to manifest [10]. The effectiveness of high dose intravenous immunoglobulin has been more pronounced in children with AIHA secondary to infections rather than adults with idiopathic disease [11]. Similarly, however, to the reported cases where IVIG was reported effective in AIHA, our patient had a low pre-treatment hemoglobin (3.3 g/dl) and splenomegaly.

The diagnosis of mixed AIHA is based on the detection of autoantibodies by monospecific direct DAT showing a pattern of IgG, complement C3d, and presence of cold agglutinins [5] which are mostly of the IgM class. It is a rare diagnosis, comprising <5% of reported cases of AIHA. Based on our patient’s clinical presentation, laboratory analysis and absence of an obvious secondary etiology after an extensive workup, she meets the criteria for idiopathic or primary mixed autoimmune hemolytic anemia.

The standard therapeutic approaches to the treatment of autoimmune hemolytic anemia include corticosteroids, splenectomy, immunosuppressive agents, and monoclonal antibodies [3], the most reported of which is rituximab. Rituximab is a potent anti-CD20 monoclonal antibody that destroys B lymphocytes via complement activation and has been used in the management of patients with CAD with severe hemolysis that has not responded to conventional therapy. However, the effect of treatment with rituximab is unpredictable and is usually not abrupt [2]. Khandelwal et al. hypothesized that autoimmune cytopenias become refractory because current therapies do not target autoreactive plasma cells, and outcomes can be improved with plasma cell agents [6] such as bortezomib.

Bortezomib is an inhibitor of the 26S proteasome, a large protease complex that degrades ubiquitinated proteins and is approved for the treatment of multiple myeloma and mantle cell lymphoma in the United States [7].

By blocking the targeted proteolysis usually performed by the proteasome, bortezomib disrupts various cell signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. In contrast to rituximab, which targets CD20 B lymphocytes, bortezomib targets differentiated plasma cells that typically do not express CD20 but may be responsible for secretion of the abnormal IgM responsible for hemolysis in CAD [8]. Moreover, chronic inflammatory processes in autoimmune diseases can be sustained by long-lived plasma cells which

DISCUSSION

Diagnosis of mixed AIHA is based on the detection of autoantibodies by monospecific direct DAT showing a pattern of IgG, complement C3d, and presence of cold agglutinins [5] which are mostly of the IgM class. It is a rare diagnosis, comprising <5% of reported cases of AIHA. Based on our patient’s clinical presentation, laboratory analysis and absence of an obvious secondary etiology after an extensive workup, she meets the criteria for idiopathic or primary mixed autoimmune hemolytic anemia.

The standard therapeutic approaches to the treatment of autoimmune hemolytic anemia include corticosteroids, splenectomy, immunosuppressive agents, and monoclonal antibodies [3], the most reported of which is rituximab. Rituximab is a potent anti-CD20 monoclonal antibody that destroys B lymphocytes via complement activation and has been used in the management of patients with CAD with severe hemolysis that has not responded to conventional therapy. However, the effect of treatment with rituximab is unpredictable and is usually not abrupt [2]. Khandelwal et al. hypothesized that autoimmune cytopenias become refractory because current therapies do not target autoreactive plasma cells, and outcomes can be improved with plasma cell agents [6] such as bortezomib.

Bortezomib is an inhibitor of the 26S proteasome, a large protease complex that degrades ubiquitinated proteins and is approved for the treatment of multiple myeloma and mantle cell lymphoma in the United States [7].

By blocking the targeted proteolysis usually performed by the proteasome, bortezomib disrupts various cell signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. In contrast to rituximab, which targets CD20 B lymphocytes, bortezomib targets differentiated plasma cells that typically do not express CD20 but may be responsible for secretion of the abnormal IgM responsible for hemolysis in CAD [8]. Moreover, chronic inflammatory processes in autoimmune diseases can be sustained by long-lived plasma cells which continuously secrete pathogenic antibodies. Proteasome inhibitors that target plasma cells like bortezomib could effectively weaken this antibody-producing category of cells. In view of its effect on malignant B cells and plasma cells, bortezomib has been used to treat other plasma cell disorders, with case reports of successful treatment of immune hemolytic anemia related to cryoglobulinemia, systemic lupus erythematosus, and myasthenia gravis [9]. Danchaivijitr et al. reported that a combination of bortezomib and low-dose cyclophosphamide was successfully used to treat a patient with transfusion-dependent and steroid/rituximab-refractory AIHA [7].

The combined use of prednisone, IVIG, and bortezomib in our patient leading to her successful therapeutic outcome may make it difficult to discern which components of the combination therapy were responsible for the improvement in the hemolytic process. However, it is noteworthy that the observed sustained improvement in her hemoglobin level was noticed only after the introduction of bortezomib. That is not to discount the significance of the sustained decline in the bilirubin levels following the commencement of the steroids and IVIG. Although steroids suppress antibody production and down regulate Fc-receptor-mediated red cell destruction in the spleen, reports indicate that their effect is not immediate and often takes 2–4 weeks to manifest [10]. The effectiveness of high dose intravenous immunoglobulin has been more pronounced in children with AIHA secondary to infections rather than adults with idiopathic disease [11]. Similarly, however, to the reported cases where IVIG was reported effective in AIHA, our patient had a low pre-treatment hemoglobin (3.3 g/dl) and splenomegaly.

The diagnosis of hemolytic anemia could be argued against in this case given the elevated direct bilirubin as well as normal haptoglobin levels. However, direct bilirubin level is not a criterion in the diagnosis of hemolytic anemia, rather indirect bilirubin is and was highly elevated in this case. The presence of a coexisting liver abnormality leading to direct hyperbilirubinemia could not be entirely ruled out without a liver biopsy. Haptoglobin, on the other hand, is an acute phase reactant and just like procalcitonin, it could have been elevated from an acute inflammatory process, thereby blunting the low values that are typical of a hemolytic anemia.

CONCLUSION

Despite the availability of multiple therapeutic modalities, autoimmune hemolytic anemias especially the mixed type can be refractory to such interventions. Based on our experience with our patient and other reported cases, further research is imperative to explore the potential therapeutic effects of bortezomib in nonmalignant disorders, including autoimmune hemolytic anemias.
REFERENCES


*********

Author Contributions
Iloabueke Chineke – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Suaka Kagbo-Kue – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Judith Aniekwena – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Myra Rose – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None.

Consent Statement
Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

Copyright
© 2019 Iloabueke Chineke et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.
Submit your manuscripts at
www.edoriumjournals.com