Multiple Myeloma Presenting as Autoimmune Hemolytic Anemia: Bortezomib as Potential Therapy for Autoimmune Hemolytic Anemia Refractory to Standard Corticosteroid Therapy

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Received: 15 August 2020; Accepted: 09 September 2020

ABSTRACT
Autoimmune hemolytic anemia (AIHA) presenting concomitantly with multiple myeloma (MM) has been reported in a limited number of cases. Here we report a case of MM initially presenting as AIHA that was subsequently treated with bortezomib (Velcade®, formerly PS-341). Initial treatment of AIHA became refractory to corticosteroids, however subsequent diagnosis and treatment of MM with bortezomib yielded significant clinical responses to both the MM and the relapsed AIHA. Bortezomib is currently approved for treatment of MM and mantle cell lymphoma, but may have potential to treat other hematologic and malignant disorders.

Keywords
Multiple Myeloma, Autoimmune Hemolytic Anemia, Bortezomib, Velcade.

Introduction
Conventional treatment of multiple myeloma (MM) includes chemotherapy, corticosteroids, and hematopoietic cell transplantation in select patients [1-3]. Chemotherapeutic agents include melphalan, thalidomide, lenalidomide, and bortezomib [4-6]. Numerous strategies have been described using these agents often in combination with corticosteroids. Moreover, treatment with thalidomide, bortezomib, and others show promise as single-agent therapy in relapsed MM which is important since many patients eventually relapse [7]. Adjunctive therapies include targeted radiation for pain, prophylactic bisphosphonates for skeletal events, and erythropoietin for anemia [8].

Anemia occurs in approximately 70% of MM patients and is related to displacement of normal bone marrow and inhibition of hematopoiesis by factors produced by expanding tumor cells [9]. Autoimmune hemolytic anemia (AIHA) can also occur in MM, however relatively few cases have been reported [10]. Here we report a case of MM initially presenting as AIHA that was subsequently treated with bortezomib (Velcade®, formerly PS-341). Initial treatment of AIHA became refractory to corticosteroids, however subsequent diagnosis and treatment of MM with bortezomib yielded significant clinical responses to both the MM and the relapsed AIHA. Bortezomib is currently approved for treatment of MM and mantle cell lymphoma, but may have potential to treat other hematologic and malignant disorders.

Case Report
A 65-year-old African American male presented with gradual onset of generalized weakness, shortness of breath, and dizziness. He denied any past medical or surgical history and denied taking any medications or herbal supplements. His family history was significant for hypertension and no known malignancies. On physical exam, he appeared fatigued and jaundiced. He was tachycardic, with palpable pulses in all extremities, increased capillary refill time, conjunctival pallor, and scleral icterus. He was not in respiratory distress and the remainder of the physical exam was unremarkable.

Initial laboratory evaluation revealed a hemoglobin of 4.4 g/dL and a hematocrit of 13.2% with an MCV of 91.1 fl (normal 80-98.8. The white blood count was 38,000/µL with 79% neutrophils, 15% lymphocytes, 5% monocytes, and 1% eosinophils. The platelet count was 446,000/µL. Serum iron was 53 µg/dL (normal,
31-222 µg/dL), total iron binding capacity was 263 µg/dL (normal, 260-445 µg/dL), iron saturation was 80% (normal, 12-50%), and ferritin was not measured. Folic acid was 10.3 ng/mL (normal, 3-16 ng/mL) and cobalamin was 378 pg/mL (normal, 200-1100 pg/mL). Hemolytic anemia was suggested by a serum haptoglobin of 8 mg/dL (normal, 43-212 mg/dL), lactate dehydrogenase of 790 U/L (normal, 100-190 U/L), and an absolute reticulocyte count of 482,000/µL (normal, 10,000-120,000/µL). Moreover, total serum protein was 9.1 g/dL (normal, 6-8.2 g/dL), globulin was 5.0 g/dL (normal, 2-4 g/dL), albumin was 3.6 g/dL (normal, 3.5-5 g/dL), and the erythrocyte sedimentation rate was >150 mm/h (normal, 0-15 mm/h). A positive Coomb’s test with warm autoantibody of anti-Rhesus(e) specificity suggested an autoimmune hemolysis in the absence of any additional physical or laboratory evidence to suggest acquired causes of hemolysis including entrapment, trauma, toxins, or paroxysmal nocturnal hemoglobinuria.

Serum protein electrophoresis revealed a monoclonal band equaling 1.37 g/dL or 66.8% of the total gamma globulin fraction of 2.05 g/dL. Serum immunofixation revealed of 2710 mg/dL of IgG (normal 694-1618 mg/dL), 145 mg/dL of IgA (normal 68-378 mg/dL), and 83 mg/dL of IgM (normal 53-334 mg/dL), with a monoclonal IgG kappa detected. Core biopsy of bone marrow revealed hypercellularity with maturing trilineage hematopoiesis with significant erythroid hyperplasia (Figure 1). Bone marrow analysis for lymphoproliferative disorders by flow cytometry revealed a monoclonal population of plasma cells expressing the human myeloma cell adhesion molecule syndecam-1 (CD138) and IgG-kappa (CD138-positive, IgG-kappa-positive) [11]. The remaining B lymphocytes (1.9% of the total population) and T lymphocytes (9.3% of the population) were polyclonal and otherwise antigenically unremarkable. In situ distribution of these abnormal CD138-positive myeloma cells was demonstrated by immunohistochemistry of bone marrow biopsy sections (Figure 2). Overall, these findings were consistent with a diagnosis of MM.

Figure 1: Core biopsy of bone marrow demonstrating hypercellular marrow with maturing trilineage hematopoiesis and erythroid hyperplasia (100X).

The hemoglobin increased from 4.4 to 9.8 g/dL after transfusion of 4 units of packed RBCs. Treatment for AIHA was initiated with oral prednisone 60 mg daily and tapered over four weeks. Although serum haptoglobin and lactate dehydrogenase improved, the hemoglobin declined from 9.8 to 7.3 g/dL suggesting relapse of the AIHA despite corticosteroid therapy. During the initial treatment of AIHA, a diagnosis of MM was established as described and chemotherapy initiated with bortezomib and dexamethasone. Similar to other clinical trials, four cycles of intravenous bortezomib 1.3 mg/m2 and intravenous dexamethasone 10 mg were administered on days 1, 4, 8, and 11 of a 28-day cycle [12,13]. Remarkably, two weeks after bortezomib therapy, the corticosteroid-refractory AIHA also demonstrated significant improvement with hemoglobin increasing from 7.3 to 12.6 g/dL and serum IgG decreasing from 2710 to 1070 mg/dL.

Figure 2: Core biopsy of bone marrow demonstrating a mild plasmacytosis and in situ expression of the human myeloma cell adhesion molecule syndecam-1 (CD138-positive). These abnormal plasma cells were further characterized by flow cytometry and found to be CD138-positive and IgG kappa-positive consistent with a diagnosis of multiple myeloma. (40X).

Discussion
Approximately 7 in 100,000 people are diagnosed with MM annually in the U.S. [14]. While anemia is common in MM, AIHA is relatively rare. In patients with immune system malignancies, AIHA has been associated with non-Hodgkin's lymphoma and chronic lymphocytic leukemia. A variety of factors may initiate autoantibody production in AIHA including viral infections, autoimmune diseases, hematopoietic and lymphoid neoplasms, prior allogeneic blood transfusion, and hematopoietic cell transplantation. Conventional AIHA treatment is with corticosteroids, however patients may become refractory. While optimal treatment for MM has not been determined, many regimens have been described. Conventional MM treatment includes chemotherapy, corticosteroids, and hematopoietic cell transplantation in select patients. Alternative treatments include thalidomide, lenalidomide, bortezomib, and others.

Bortezomib is a prototypic proteasome inhibitor demonstrated to have anti-tumor activity in both solid and hematologic malignancies and is approved for treatment of MM and mantle cell lymphoma. Bortezomib represents a significant advancement in MM therapy, including use as a single-agent therapy, and complete clinical responses have been achieved in patients with refractory or advancing disease. Bortezomib reversibly inhibits the 26S proteasome complex that functions to degrade proteins tagged with ubiquitin for elimination. Ubiquitinated proteins are typically misfolded, oxidized, or otherwise damaged proteins that no longer contribute to maintaining intracellular homeostasis. The ubiquitinin-
proteasome pathway plays an essential regulatory role in variety of intracellular processes including the cell cycle, transcriptional activation, and cell signaling [15]. Bortezomib inhibits this pathway, thus preventing degradation of intracellular proteins and disrupting multiple intracellular signaling cascades. In tumor cells, such disruption inhibits cell growth and promotes apoptosis.

Bortezomib may have potential to treat other hematological and malignant disorders. Bortezomib has several myeloma-specific mechanisms, including one involving the nuclear factor kappa B (NF-κB) complex [16]. NF-κB is a central regulatory protein that controls a variety of key inflammatory and immune response signalling pathways, and its dysregulation is associated with induction of cancer and other inflammatory disorders. NF-κB activity is tightly regulated in vivo and is usually found in the cytoplasm associated with its inhibitory protein I-κB. Dissociation of I-κB from NF-κB is required for its nuclear translocation and subsequent induction of gene transcription. Bortezomib suppress I-κB breakdown in myeloma cells, thereby prolonging stability of the NF-κB/I-κB complex, preventing NF-κB nuclear translocation, thereby suppressing transcription of key regulators of multiple downstream pathways important in myeloma cell signaling [17]. Bortezomib also decreases myeloma cell adhesion to stoma cells in the bone marrow microenvironment which suppresses prosurvival cytokine-mediated signaling by interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α), which further increases sensitivity to apoptosis [18,19]. Other myeloma-associated effects of bortezomib include inhibition of angiogenesis, DNA repair, and osteoclast activity.20 In general, tumor cells appear to be more sensitive to proteasome inhibition than normal cells, likely due to dysregulation of several key cell cycle checkpoints during tumorgenesis. These checkpoints ensure fidelity of cell division and verify that processes at each phase of the cell cycle have been accurately completed before cell cycle progression. Moreover, normal cells are more likely than tumor cells to recover after bortezomib treatment since inhibition is transient and reversible.

Bortezomib has been evaluated in a number of clinical trials to determine its efficacy in treating MM alone or in combination with other therapeutic agents including dexamethasone, prednisone, melphalan, cyclophosphamide, and thalidomide [12,13,21,22]. The two-drug combination of bortezomib and melphalan demonstrated significant activity in patients with relapsed or refractory myeloma and is currently under investigation in previously untreated patients [13]. The three-drug combination of bortezomib, dexamethasone, and cyclophosphamide also demonstrated significant activity in patients with relapsed myeloma [12]. The four-drug combination of bortezomib, melphalan, prednisone, and thalidomide also demonstrated significant activity in patients with relapsed or refractory myeloma [22]. The three-drug combination of bortezomib, melphalan, and prednisone also demonstrated significant activity in previously untreated patients [21]. Bortezomib also demonstrated significant activity in myeloma due to deleterious molecular genetic defects associated with poor prognosis with conventional therapies [23-25]. Finally, new potential uses for bortezomib continue to be reported in a wide range of disorders in which lymphocytes are thought to contribute to pathogenesis including graft vs host disease [26,27].

**Conclusion**

AIHA presenting concomitantly MM has been reported in a limited number of cases. Here we report a case in which initial treatment of AIHA with corticosteroids became refractory and relapsed. Subsequent diagnosis and treatment of MM with bortezomib yielded significant clinical responses to both the MM and the relapsed AIHA. To our knowledge, this is the first case of AIHA apparently treated successfully with bortezomib. Therefore, further investigation of bortezomib as a potential treatment for AIHA refractory to corticosteroid therapy may be warranted.

**References**