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Bortezomib as a Salvage Therapy for Severe Refractory Thrombotic Thrombocytopenic Purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is considered a medical emergency requiring early identification and administration of prompt therapy to reduce mortality. We hereby report a case of TTP refractory to conventional treatment modalities, later responded to Bortezomib. A 19 year old female presented to the emergency department with altered mental status, thrombocytopenia with a platelet count of 13,000 (13K) microangiopathic hemolytic anemia and normal coagulation studies. Peripheral blood smear revealed numerous schistocytes, normal platelet morphology and nucleated red blood cells. TTP was suspected and daily plasma exchange was initiated along with systemic methyl prednisone. Serum ADAMTS-13 activity and ADAMTS-13 inhibitor later resulted as <3% and 8.7 BEU respectively conforming severe TTP. Platelet counts improved only to 16,000 by Day 5 and so PEX and steroid dose was increased along with Rituximab initiation. No significant improvement was noted with counts of 32,000 on day 13, Bortezomib at dose of 1.3 mg/m^2 was then initiated. Platelet counts improved dramatically to 171,000 by day 20. Repeat ADAMTS-13 activity levels were reported to be 91% on day 23. Subsequently with improving platelet counts and patient's mentation returning to baseline PEX therapy was discontinued on day 42 and patient was discharged to subacute rehabilitation on oral steroid taper.

Keywords: Bortezomib; Refractory; TTP

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a hematological disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia secondary to reduced activity of Von Willebrand factor (vWF) -cleaving protease ADAMTS-13. It is considered as a medical emergency requiring early identification and administration of prompt therapy to prevent mortality. The corner stone therapy for TTP include daily plasma exchange (PEX) aiming at clearing the circulating anti ADAMTS 13 antibodies and repletion of ADAMTS-13 levels. PEX has dramatically improved the survival rates to 80-85% [1]. Immunomodulatory therapy with Rituximab was shown to beneficial as an adjunctive therapy in cases with suboptimal response to PEX [2-7]. Cases of refractory TTP responding to Bortezomib were rarely reported. Adding to the current literature we hereby report a case of TTP refractory to daily plasma exchange, high dose systemic steroids and Rituximab who responded to Bortezomib.

Case Description

A 19 year old female with no significant medical history presented to the emergency department with altered mental status of one day duration. Vitals on presentation were body temperature 101.4F, heart rate of 105 beats/minute, blood pressure of 110/70mm Hg, respiratory rate of 21 per minute and oxygen saturation of 92% on room air. Physical examination revealed a confused young female with conjunctival icterus, skin pallor and petechiae noted on bilateral upper and lower extremities. The rest of the physical examination was unremarkable except for sinus tachycardia.

Laboratory findings on presentation revealed thrombocytopenia with hemolytic anemia. The serum hemoglobin level was 4.5g/dL, hematocrit is 13.5%, MCV 77.0 fL, absolute reticulocyte count 344, platelet count was 13,000/uL and white blood cell (WBC) count 9,700/mm^3. Peripheral blood smear revealed numerous schistocytes, normal platelet morphology and nucleated red blood cells. The serum level of lactate dehydrogenase (LDH) was elevated at 3253U/L, and total bilirubin level was 3.2mg/dL which is predominantly indirect hyper bilirubinemia of 2.7mg/dL. Serum D-dimer was elevated at 28,895ng/mL and fibrinogen level was low at 198mg/dl concerning for disseminated intravascular coagulation (DIC). However, no significant elevation was noted with respect to

prothrombin time (PT) and activated partial thromboplastin times (aPTT) which were 13.7 seconds and 26.7 seconds respectively. The blood urea nitrogen (BUN) and creatinine levels were within the normal limits at 24mg/dL and 1.0mg/dL respectively.

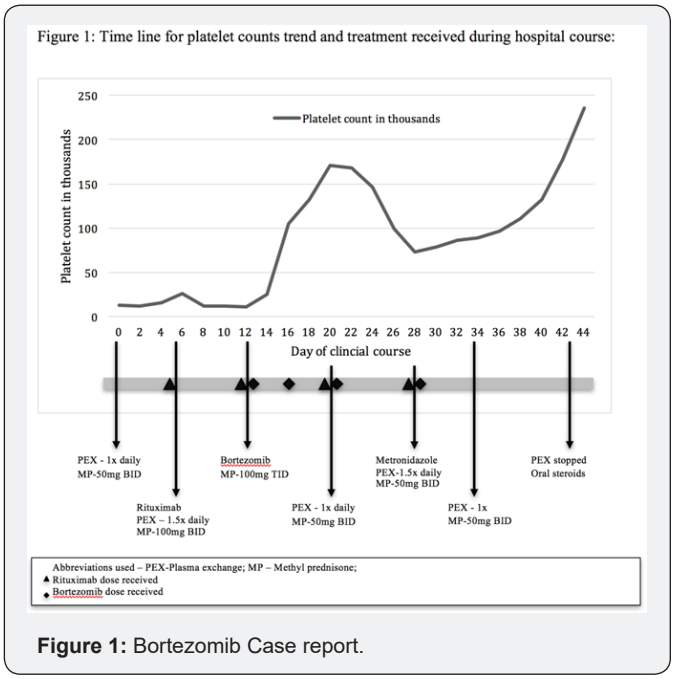

Figure 1: Bortezomib Case report.

Thrombotic thrombocytopenic purpura was suspected given the evidence of severe thrombocytopenia with microangiopathic hemolytic anemia and normal coagulation studies. Serum samples for ADAMTS-13 activity and ADAMTS-13 inhibitor later resulted as <3% and 8.7 Bethesda units BEU respectively conforming severe TTP. She was admitted to the intensive care unit and daily plasma exchange was initiated along with intravenous methyl prednisone 50mg twice daily. However no significant improvement was noted with platelet counts improving only to 16,000 by Day 5 (Figure 1). Rituximab at 375mg/m^2 every 7 days was initiated on day 6 as an adjunctive treatment along with increasing PEX therapy to 1.5 times the plasma volume (1.5x) and systemic methyl prednisone dose to 100 mg twice daily. Platelets count improved only to 32,000 by day 13 and neurological status deteriorated with magnetic resonance imaging of brain showing multifocal areas of punctate abnormal diffusion restriction concerning for acute or subacute infraction. Patient was deemed as slow responder and Bortezomib at dose of 1.3mg/m^2 was initiated. She received Bortezomib on days 13 and 16 after which platelet counts dramatically improved to 171,000 by day 20. Given improving platelet count PEX holiday was given on day 22 and resumed on day 23 at a reduced rate of 1x the plasma. Decline in platelet count was noted around day 24 which was likely attributed to multitude of reasons including decreased intensity of therapy and newly diagnosed Clostridium difficile colitis for which metronidazole was initiated.

PEX therapy was resumed to 1.5x on day 25. Patient in total received 4 doses of Bortezomib on days 13, 16, 20 and 28. Repeat ADAMTS-13 activity levels were reported to be 91% on day 25 and 151% on day 31. Platelet counts gradually improved to 23,000 by day 36 and PEX was transitioned to 1x every other day. Subsequently with improving platelet count and patient's mentation returning to baseline PEX therapy was discontinued on day 42 and patient was discharged to subacute rehabilitation on oral steroid taper.

Discussion

TTP is a medical emergency which is almost always fatal without prompt clinical suspicion and treatment initiation. Wide spread hyaline thrombi in capillaries and arterioles now considered pathological hallmark of TTP was first described by Moschcowitz in 1925 [8]. The estimated annual incidence of TTP in the United states was reported to be 1 in 50,000 hospital admissions. Reported prevalence rates from Canada and UK were 2.2 and 3.2 cases per million population respectively [9]. Initial diagnostic suspicion is largely based on the physical examination and laboratory investigations consistent with microvascular thrombi and hemolytic anemia along with the presence of schistocytes in the peripheral smear with no other alternative diagnosis. ADAMTS-13 activity of <10%, drawn before the treatment initiation strongly supports the diagnosis [10]. Plasma exchange (PEX) remains the corner stone therapy for TTP, which works by removing the inhibitor antibodies and replacing ADAMTS13 [11]. PEX should be continued daily until treatment response is seen, defined by a platelet count of 150,000 for 2 days with normal/near normal LDH and stable/improving neurological function is achieved [12]. Steroids were also shown too beneficial in management of TTP likely by suppressing his production of ADAMTS-13 antibodies. PEX along with steroids was shown to improve survivals to 91% [13].

Management of TTP is largely based on clearing inhibitory autoantibodies against ADAMTS-13 by plasmapheresis along with suppression of antibody production using immunomodulatory and immunosuppressive agents. Refractory TTP is defined as failure of platelets to respond after 4 to 7 days of therapy or development of new neurological symptoms. 10 to 40% of TTP cases do not respond of conventional PEX-Corticosteroid therapy [14-17]. Treatment options for refractory TTP include twice daily PEX, pulse dose corticosteroids and Rituximab [6,18-21]. Alternative therapies shown to be beneficial in cases of persistent refractory TTP include splenectomy, Cyclosporine, Cyclophosphamide and Vincristine [22-25].

Bortezomib is first in class of proteasome inhibitors used in treating plasma cell disorders, lymphoid malignancies and antibody-mediated rejection of solid organs [26,27]. The mechanism of action is by blocking 26S proteasome thereby altering the ubiquitin–proteasome pathway of cellular protein homeostasis [28]. Role of Bortezomib in treating refractory TTP was described by Shortt et al in a case of TTP refractory to Cyclophosphamide and Rituximab. They noticed the absence of CD19 B cells and presence of scattered CD 138+ B cells in bone marrow cytometry and postulated that Bortezomib induces

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remission by targeting autoreactive B-cells and plasma cells [29]. Bortezomib was also found to induce apoptosis in immature dendritic cells necessary for CD4 cell activation there by leading to decreased production of inhibitory ADAMTS 13 antibodies from CD4 cells [30,31]. In our case, initiation of Bortezomib led to improved platelet count by more than 50% as reported in previous studies. Though Bortezomib seems promising in the setting refractory TTP, cases of Bortezomib induced TTP were also reported [32,33]. More prospective trails should be done to determine the safety, efficacy and the timing of initiation of Bortezomib in refractory TTP cases.

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