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THROMBOTIC THROMBOCYTOPENIC PURPURA REFRACTORY TO PLASMA EXCHANGE AND RITUXIMAB: IS THERE ROOM FOR BORTEZOMIB?

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BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by fever, neurological deficits, thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and renal failure. Acquired TTP occurs due to deficiency of von Willebrand factor (vWF) cleaving protease due to anti-ADAMTS13 autoantibodies. Absence of ADAMTS13 activity leads to accumulation of vWF, which binds to platelets and causes spontaneous microthrombi in high shear environments, causing MAHA and microvascular occlusion. Rapid onset of plasma exchange (PEx) and immunosuppressive therapy constitute the standard of care for acquired TTP. Rituximab has emerged as an option for refractory patients and other second-line therapies include cyclosporine, vincristine and splenectomy with lower remission rates and long-term side effects. Recently, a few cases of bortezomib-induced remission of TTP have emerged.

CASE REPORT

A 45-year-old woman with history of endometrial neoplasia treated two years ago presented with cough, fever, myalgia and hematuria for 4 days. Initial labs demonstrated anemia (hemoglobin 9.1 g/dl), thrombocytopenia (57x10^3) and peripheral blood smear revealed schistocytes. Intravenous methylprednisolone was initiated as well as PEx in suspicion of TTP. This diagnosis was confirmed by an ADAMTS13 activity level of <5% with an inhibitor titer of 4.1. After 7 days there was no improvement and the patient had seizures. Brain scan showed petechial hemorrhage. Rituximab (375 mg/m2) was administered and peripheral CD20+ B-cell lymphocyte decreased from 53% to 2% within 14 days. Despite PEx, rituximab and steroid, platelet count did not increase more than 8 - 11x10^3 and the patient was still in a coma. Bortezomib (1mg/m2), a proteasome inhibitor, was given on days 19 and 22 along with twice PEx and steroids. There was a reduction in plasma cells in the bone marrow from 0.19% to 0.045% after 7 days of first dose of bortezomib. At day 45, her platelets started to increase and remained above 150x10^3. Fluorodeoxyglucose Positron Emission Tomography combined with a Computed Tomography (F18-FDG PET-CT) was negative for active cancer. After one year since admission, platelets did not fall again. Rituximab has been used for maintain therapy every 3 months.

CONCLUSION

The goal of treatment in TTP is to reduce the circulating vWF multimers and ADAMTS13 autoantibodies, often using PEx and immunosuppressive therapy. Rituximab destroys only B-cells. The mechanism of action of bortezomib in TTP is thought to be inhibition of autoantibody generation by inducing apoptosis in both B-cells and plasma cells. In some particular cases, bortezomib has been demonstrated to be effective.