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Bortezomib for refractory immune-mediated thrombocytopenia purpura (ITP)

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Abstract

The treatment of refractory immune-mediated thrombocytopenia (ITP) can be challenging. This case report describes treatment of refractory ITP with bortezomib, a proteasome inhibitor. This strategy has been successful in relapsing thrombotic thrombocytopenic purpura, but is a novel therapeutic approach for ITP. Further research use of proteasome inhibition in refractory ITP may be warranted.

Keywords

Immune-mediated thrombocytopenia; ITP; bortezomib

Clinical Features

Immune-mediated thrombocytopenia (ITP) is a diagnosis of exclusion based on history, physical exam and laboratory analysis¹. The initial management of ITP includes corticosteroids and immunoglobulin (IVIg) therapy¹. Second line therapies include splenectomy, rituximab, other immunosuppressants, as well as thrombopoietin (TPO) receptor agonists¹. We report the case of a sixty-three year old African American female with refractory ITP successfully treated with the proteasome inhibitor bortezomib.

Our patient was previously treated for ITP over four years with only brief periods of severe (<10,000) thrombocytopenia. She was on weekly romiplostim when she was diagnosed with a catheter-associated brachiocephalic venous thromboembolism (VTE) prompting cessation of romiplostim. Her port was removed, and she was started on enoxaparin bridging to warfarin. She was admitted to our hospital shortly thereafter with hemoptysis, an acute right lower extremity VTE, and a platelet count of <5,000/ μ L. Given her history of heparin

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Conflicts of Interest Disclosure

The authors' have no financial conflicts of interest.

exposure, testing for heparin induced thrombocytopenia, including platelet aggregation studies, was performed and was negative. She was started on dexamethasone and IVIg with no response. She then underwent splenectomy.

Despite utilization of first and second line therapies, the patient continue to be severely thrombocytopenic with platelet counts $<10,000/\mu\text{L}$ over the next eight weeks. Additional diagnostic workup did not reveal other causes for thrombocytopenia, including a bone marrow evaluation which demonstrated no morphologic or cytogenetic abnormalities. She was restarted on romiplostim. Pulse IV cyclophosphamide was given and she was started on mycophenolate mofetil (MMF) and eltrombopag. Given continued refractory thrombocytopenia, she was retreated with rituximab. Despite these additional interventions, she continued to have significant thrombocytopenia and ongoing mucocutaneous and GI bleeding.

Therapeutic Challenge

Refractory ITP is an American Society for Apheresis (ASFA) Category IV indication for therapeutic plasma exchange (TPE), but in conjunction with her thrombosis and laboratory values, a stronger ASFA Category II/III indication was considered by our transfusion medicine service. She underwent three initial TPE procedures to ascertain if removal of her plasma-fraction element would improve platelet counts. All previous therapies were continued and steroids were resumed. Her thrombocytopenia improved after the TPE series; however this was not sustained (Figure 1A).

Solution

Bortezomib is a protease inhibitor used in treatment of multiple myeloma because it stimulates stress-induced apoptosis in plasma cells and reduces the activation of CD4+ and CD8+ cells by NF- KB^2 . Bortezomib has also been used successfully for treatment of relapsing thrombotic thrombocytopenic purpura in three case reports³⁻⁵. We started our patient on subcutaneous injections of bortezomib ($1.3 \text{ mg}/\text{m}^2$ subcutaneously days 1, 4, 8 and 11) following TPE. As Figure 1A demonstrates, the patient had an excellent platelet response with bortezomib with no adverse effects noted. She was discharged on hospital day eighty-eight on MMF, eltrombopag, prednisone, and weekly romiplostim. As an outpatient she achieved a platelet count of $>1,000,000/\mu\text{L}$, despite her outpatient provider tapering eltrombopag and stopping romiplostim. Unfortunately, the patient subsequently experienced a marked and rapid decrease in her platelet counts, for which she had her eltrombopag dose increased (Figure 1B). She was re-admitted to our facility with mucocutaneous bleeding and an undetectable platelet count ($<5,000/\mu\text{L}$). She underwent a second course of bortezomib therapy and received five additional TPE procedures (Figure 1C) while being maintained on MMF, eltrombopag, and weekly romiplostim. She was discharged with a robust platelet count and is being maintained on eltrombopag and MMF with intermittent need for romiplostim (Figure 1D).

The immune-mediated pathology of refractory ITP is poorly characterized. In this correspondence we report the novel utilization of proteasome inhibition with bortezomib in

refractory ITP. We acknowledge that the patient received several additional immunologic-directed treatments making it difficult to ascertain if bortezomib alone is responsible. However, this case supports the need for further research into the utilization of proteasome inhibition in refractory ITP.

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Figure 1. Hospital and Outpatient Interventions for Index Case

Interventions: Arrows and letters indicate interventions: a= therapeutic plasma exchange, b= bortezomib (1.3 mg/m² subcutaneously days 1, 4, 8 and 11, c= rituximab 375 mg/m² IV $\times$ 4 doses, d= dexamethasone 40 mg PO daily $\times$ 5 days decreased to prednisone 20 mg PO daily, e= eltrombopag, dose range 25–75 mg PO, f= romiplostim, dose range 2–10 mcg/kg. When e or f are used this indicates a change in dose or cessation of drug. A) patient was started on therapeutic plasma exchange dates indicated by arrow and letter. When platelet response was not sustained, bortezomib was started. B) after discharge patient had platelet counts monitored weekly. She was given weekly romiplostim until platelet counts were satisfactorily elevated, then eltrombopag was also decreased. She developed refractory thrombocytopenia. C) patient was admitted. She was continued on eltrombopag and received bortezomib and therapeutic plasma exchange. Romiplostim was resumed. On count recovery she was discharged. D) as outpatient she continues to have robust counts. She continues to take eltrombopag and gets romiplostim if platelet count decreases below 125,000/ μ L.