Bortezomib Treatment of Steroid-Refractory Evans Syndrome in Children

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Abstract

Treatment of refractory Evans syndrome (ES) remains a challenge in Hematology practice. Due to rarity of this condition, evidence-based approaches are limited and often treatment choices stem from small case series or anectodal experiences. Here, we describe three very refractory pediatric ES cases treated on bortezomib without adverse effects. Two of the three patients had dramatical and long-lasting recovery that started following the first doses of the drug. Clinical trials to assess bortezomib role in ES treatment are warrented and results may lead to inclusion of this drug as an option, even as a first-line therapy.

Introduction

Evans Syndrome (ES) is a rare childhood autoimmune disorder characterized by anemia and thrombocytopenia and frequently accompanied by neutropenia[1]. Autoantibodies target red blood cells, platelets (PLT), and neutrophils leading to autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP) and autoimmune neutropenia, respectively. Responses to variety of immunosuppressive therapy (IST) approaches are often temporary; many cases experience a prolonged course, become refractory to a series of different IST interventions. Treatment of ES is largely through trial and error-like approach with differences in management between different centers [2]. Here, we present the course of three children with refractory ES treated on bortezomib.

Case Descriptions

Case1. The initial course of this case was previously reported[3]. A currently 15-year-old male was diagnosed with ES at 9 years of age and later developed common variable immunodeficiency. He has had several lines of IST to control AIHA and ITP with initial responses followed by recurrences. He experienced long-lived remissions following rituximab therapy and later splenectomy. He presented with hemolysis and was then treated with bortezomib.

He received bortezomib at a dose of 1.3 mg/m^2 on days 1, 4, 8, 11, and 26 partially based on the clinical trial for refractory autoimmune cytopenias following hematopietic stem cell transplant (Clinicaltrials.gov Identifier: NCT01930253). He experienced a dramatic clinical response with near-immediate improvement within 4 days of the first dose providing him a remission that lasted for 22 months until he developed thrombocytopenia. Following a single dose of bortezomib at 1.3mg/m^2, he quickly achieved PLT count greater than 100x10^9/L in 2 weeks, providing an ongoing remission of 7 months so far (Table1).

Case2. A currently 2-year-old boy presented at 6 months of age with fever, severe anemia with a hemoglobin at 2.1g/dL, reticulocytes 0.1%, absent neutrophils and mild thrombocytopenia. Coombs test and anti-neutrophil antibodies (ANeA) were positive and IgM elevated at 351mg/dL (20-145). Bone marrow showed

a paucity of erythroid precursors, myeloid left shift, and increased megakaryocytes consistent with pure red cell aplasia (PRCA). Investigation for known genetic causes of PRCA, hyper-IgM syndrome, a broad immune dysregulation gene panel and later whole exome sequencing (WES) did not identify a potentially causative mutation.

He had become refractory to various IST and stayed RBC transfusion-dependent due to continuing PRCA. Several episodes of infections associated with severe neutropenia requiring admissions resolved on filgrastim therapy. Later, PLT dropped to 1-2x10^9/L with active bleeding requiring several admissions with further elevation in IgM to 495mg/dL. Due to continuing life threatening bleeding of months duration, bortezomib therapy (total of 4 doses) was given. After the second dose of bortezomib, he showed an increase in PLT; all counts normalized with reticulocytosis two weeks from the first dose. He continues to have normal counts and normal IgM level with negative Coombs test a year following bortezomib therapy (Table1).

Case3. A 15-year-old male patient presented with persistent bleeding was found to have pancytopenia with positive Coombs test and ANeA, and elevated IgG level. He had poor response to several different therapeutic interventions (Table1). Therapy with a thrombopoietin (TPO) receptor agonist (TRA), romiplostim resulted in PLT recovery with continiuing neutropenia and mild anemia. However, he later required higher and more frequent doses of romiplostim. He developed several episodes of tonsillitis and tonsillar enlargement that has resolved after rituximab-biosimilar treatment. After a short-lived improvement in PLT, he needed romiplostim again to maintain PLT count. Therefore, he was treated on the same regimen of bortezomib. However, after a temporary improvement in his PLT and neutrophils, he dropped counts and was restarted on romiplostim. WES analysis did not identify a causative variant that could be associated with ES development. Bortezomib was tolerated well without any observed adverse effects in all three patients.

Discussion

There are no clinical trials to validate the use of any second or third line therapies in steroid-refractory ES in children. More often, treating physicians are left to draw conclusions from anectodal or small series of cases. Steroids alone are seldom effective in providing sustained remission with significant long-term adverse effects; thus, are considered as an adjunct to other therapies. Rituxmab induces complete/partial remissions in approximately 60% of children with risk of infections, hypogammaglobeninema, and multifocal leukoencephalopathy. Other therapies such intravenous immunoglobulin, TRA, mycophenolate mofetil, siroliumus, cyclosporine, sand plenectomy have had variable success.

Heterogeneity of treatment responses reflects variations in the underlying mechanism in each case. Since ES is primarily mediated by autoantibodies, B cell-plasma cell (PC) pathway has been the target of several therapies. Inability of B cell-depleting rituximab in eliminating long-lived PC lacking CD20 could be the clue in its failure in some cases. Thus, aiming long-lived PC eradication is a reasonable approach in such cases, in light of successful outcomes of a proteasome inhibitor, bortezomib in multiple myeloma (MM) therapy targeting malignant PC[4]. Nevertheless, bortezomib has shown success in anectodal cases of refractory ITP and ES and in vitro evidence suggested elimination of long-lived PC by bortezomib[3,5-6].

Two of three ES cases reviewed here showed quite a dramatic and long-lasting response to bortezomib therapy. We would like to stress three observations from our experience: 1. Initial response came rather fast raising the possibility of mechanisms involved beyond inhibition of autoantibody production through elimination of long-lived PC, since half-life of IgG is approximately 3 weeks and such autoantibodies tend to be high-affinity likely secondary to affinity maturation over time. This is a very interesting point requiring further research. 2. In line with the rapidity of response and furthermore, lasting recovery after a single dose of bortezomib following a flare in the first case, smaller and/or lesser doses could be sufficient to induce responses. 3. Bortezomib has been well-toleated without any evidence of peripheral neuropathy, the frequent side effect in patients with MM.

We think clinical trials integrating bortezomib in ES treatment even as a front line therapy option is justifiable and responsive cases may avoid several adverse effects of other interventions. Furthermore, biological correlates of responsive and refractory cases may help understand the variability of mechanism of ES.

Conflict of Interest Statement

The authors have no conflict of interests to disclose.

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