Received: 26 June 2020 | Revised: 8 September 2020 | Accepted: 9 September 2020

DOI: 10.1002/pbc.28725

Pediatric Blood & Cancer

HEMATOLOGY: BRIEF REPORT

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 anecdotal experiences. There is mounting evidence that some patients have genetic defects that could be targeted with promising preliminary results. Here, we describe three very refractory pediatric ES cases treated on bortezomib without adverse effects. Two of the three patients had dramatic and long-lasting recovery that started following the initial doses of the drug. Clinical trials to assess the role of bortezomib in ES treatment are warranted.

KEYWORDS
bortezomib, children, Evans syndrome, recovery, steroid-refractory

INTRODUCTION

Evans syndrome (ES) is a rare childhood autoimmune disorder characterized by the destruction of at least two blood cell lineages without any underlying pathological associations, usually characterized by anemia and thrombocytopenia and frequently accompanied by neutropenia.[1] Autoantibodies target red blood cells, platelets, and neutrophils leading to autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and autoimmune neutropenia, respectively. Responses to a variety of immunosuppressive therapy (IST) approaches are often temporary; many patients experience a prolonged course and become refractory to a series of different IST interventions.[2,3] Treatment of ES has been largely through trial and error with differences in management between different centers.[4] Here, we present the course of three children with refractory ES treated with bortezomib.

Abbreviations: ES, Evans syndrome; AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura; IST, immunosuppressive therapy; IVIG, intravenous immunoglobulin; PRCA, pure red cell aplasia

CASE DESCRIPTIONS

Case 1: The initial course of this patient was previously reported.[5] A currently 15-year-old male was diagnosed with ES at 9 years of age and later developed panhypogammaglobulinemia and required regular intravenous immunoglobulin (IVIG) supplementation for the treatment of common variable immunodeficiency. He has had several lines of IST to control AIHA and ITP with initial responses followed by recurrences. He initially experienced long-lived remissions following rituximab therapy and later splenectomy. He later presented with hemolysis and was 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 allogeneic hematopoietic stem cell transplantation (Clinicaltrials.gov Identifier: NCT01930253). He experienced a dramatic clinical response with 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 1.3 mg/m^2, he achieved platelet count greater than

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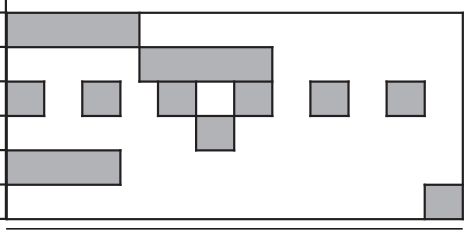
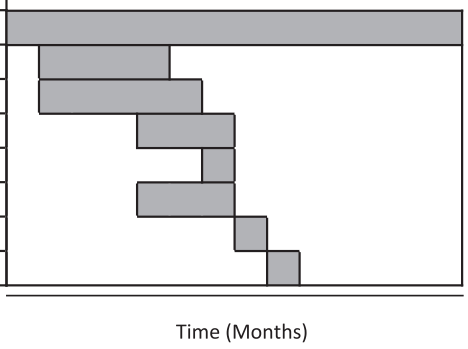
	Medication	Duration	Response		
			Hb	Plt	ANC
Patient 1	Prednisone	3.5 months	None	Temporary	Unaffected
	Mycophenolate	3.5 months	None	None	Unaffected
	IVIG	Monthly	None	Temporary	Unaffected
	Rituximab	1 dose	Temporary	None	Unaffected
	Sirolimus	3 months	None	None	Unaffected
	Bortezomib	5 doses	Sustained	Sustained	Unaffected



	Medication	Duration	Response		
			Hb	Plt	ANC
Patient 2	Prednisone#	14 months	Temporary	None	None
	IVIG	4 months	None	None	None
	Neupogen	5 months	None	None	Temporary
	Elthrombopag	3 months	None	None	None
	Rituximab	2 doses	None	None	None
	Sirolimus	3 months	None	None	None
	Dexamethasone	2 doses	None	None	None
	Bortezomib	4 doses	Sustained	Sustained	Sustained



	Medication	Duration	Response		
			Hb	Plt	ANC
Patient 3	Romiplostim	9 months	None	Temporary	None
	Prednisone	2 month	None	Temporary	Temporary
	IVIG	1 dose	None	None	None
	Rituximab-BS	4 doses	None	Temporary	None
	Bortezomib	5 doses	None	Temporary	None
	Dexamethasone*	6 months	None	Temporary	Temporary

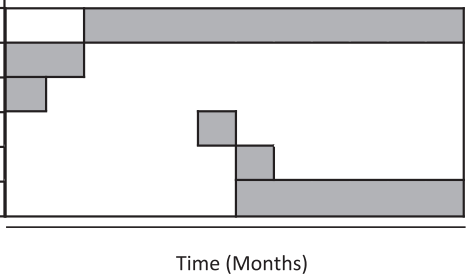


FIGURE 1 Schematic illustration of response to various treatments in three patients presented. Therapeutic interventions used in the first case were limited to 6 months before the first bortezomib treatment in the figure. The first patient did not have neutropenia. Abbreviations: IVIG: intravenous immunoglobulin; BS: biosimilar; Hb: hemoglobin; Plt: platelets; ANC: absolute neutrophil count. #Prednisone has been tapered during and following bortezomib therapy. *Dexamethasone was used intermittently during episodes of severe neutropenia at a pulse dose of 20 mg for 4 days

100×10^9/L in 2 weeks providing an ongoing remission of 7 months so far (Figure 1, Table 1). He continues to have regular IVIG infusions. No genetic testing is available on this patient.

Case 2: A currently 2-year-old male child presented at 6 months of age with fever, severe anemia with hemoglobin of 2.1 g/dL, reticulocytes 0.1%, absent neutrophils, and mild thrombocytopenia. Coombs test and anti-neutrophil antibodies were positive, and IgM was elevated at 351 mg/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, and later whole exome sequencing did not identify a pathogenic causative mutation.

He became refractory to various IST and remained blood transfusion dependent due to continuing PRCA. Several episodes of infections associated with severe neutropenia requiring admission responded to filgrastim therapy. Later, platelets dropped to $1–2 \times 10^9$/L with active multisystem bleeding requiring several admissions with further elevation in IgM to 495 mg/dL. Due to continued life-threatening bleeding for months without any response to rituximab, bortezomib therapy (four doses total) was given. After the second dose, he showed an increase in platelets; all counts normalized with reticulocytosis 2 weeks from the first dose. Since he received rituximab therapy 6 weeks prior to bortezomib treatment, serum immunoglobulins and B cells were declining rapidly. He became panhypogammaglobulinemic and completely B cell depleted, so he was given IVIG supplementation. He continues to have normal counts and immunoglobulin levels with negative Coombs test a year following bortezomib therapy (Figure 1, Table 1).

Case 3: A 15-year-old male patient presented with persistent bleeding and was found to have pancytopenia with positive Coombs test

TABLE 1 Case clinical and laboratory finding summaries

Case	Age@Dx	Case characteristics	Genetic test findings	Treatment	Current findings
1	9 years	Hemolytic anemia Thrombocytopenia Positive Coombs test CVID	No genetic tests are available	Transfusions Steroids Rituximab Mycophenolate IVIG Sirolimus Splenectomy Bortezomib	Positive Coombs test Low IgG and IgM Low B cells Clonal T-LGL expansion
2	6 months	Thrombocytopenia Anemia Reticulocytopenia Neutropenia PRCA Positive Coombs test Positive anti-neutrophil Ab Elevated IgM Elevated IgA G6PD deficiency HbC trait Duffy null phenotype	VUS–HBB c.19G>A [Heterozygous; consistent with HbC trait] VUS–ELANE c.778C>A [Heterozygous; likely to be benign]	Transfusions Steroids Filgrastim IVIG Filgrastim Eltrombopag Rituximab Sirolimus IV pulse MPD Bortezomib	Negative Coombs test Positive anti-neutrophil Ab Normal immunoglobulin levels Normal lymphocyte subsets
3	15 years	Thrombocytopenia Neutropenia Positive Coombs test Positive anti-neutrophil Ab Elevated IgG Elevated IgA Obesity Acanthosis nigricans	VUS–WAS exon 10 c.1144C>T →p.Pro382Ser. [maternally inherited; hemizygous deletion; not likely to be destructive] VUS–FLT4 exon 20 c.2810A>G →p. Asn937Ser. [maternally inherited; heterozygous; possibly damaging]	IVIG IV pulse MPD IV pulse DXM Oral steroids Rituximab-BS Romiplostim Bortezomib	Positive Coombs test Positive anti-neutrophil Ab Low IgM level Low B cells Clonal T-LGL expansion

Abbreviations: Ab, antibody; BS, biosimilar; CVID, common variable immunodeficiency; Dx, diagnosis; DXM, dexamethasone; G6PD, glucose 6-phosphate dehydrogenase; HbC, hemoglobin C; IV, intravenous; IVIG, intravenous immunoglobulin; MPD, methylprednisolone; PRCA, pure red cell aplasia; T-LGL, T-cell large granular lymphocyte; VUS, variant of uncertain significance.

and anti-neutrophil antibodies, and elevated IgG level. He had poor responses to several different therapeutic interventions. Therapy with a thrombopoietin receptor agonist, romiplostim, resulted in platelet count recovery with continuing neutropenia and mild anemia. He developed several episodes of tonsillitis and tonsillar enlargement that resolved after rituximab-biosimilar treatment. He continued to be dependent on romiplostim therapy to maintain an adequate platelet count. Therefore, he was treated with the same regimen of bortezomib. However, due to lack of response, he was restarted on romiplostim. Serum immunoglobulins and B cells were trending down significantly due to rituximab-biosimilar therapy given 8 weeks earlier that continued following bortezomib treatment with low IgM, and absent B cells; no IVIG supplementation was given. Whole exome sequencing analysis did not identify a pathogenic causative mutation (Figure 1, Table 1). Bortezomib was tolerated well without any peripheral neuropathy or infections 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. Often, physicians are left to draw conclusions from case reports or series. Steroids alone are seldom effective in providing sustained remission; thus, these are considered an adjunct to other therapies. Rituximab induces complete/partial remissions in at least one cell line in approximately 76% of children.[6] Rituximab treatment carries the risk of infections, hypogammaglobulinemia, and multifocal leukoencephalopathy. Other therapies such as IVIG, mycophenolate mofetil, sirolimus, cyclosporine, and splenectomy have had variable success.[2]

Heterogeneity of treatment responses reflects variations in the underlying mechanism(s). Thus, it is likely that several different steps of the immune response may be involved in the development of ES, which has been evidenced by more recent demonstrations of various underlying mutations in immune response genes.[7] However, since autoantibodies play a terminal role in ES, the B-cell/plasma cell pathway has been the target of several current therapies. An inability of B-cell depleting rituximab to eliminate long-lived plasma cells lacking CD20 could be a clue to its failure in some cases. Thus, long-lived plasma cell eradication is a reasonable approach in such cases, which may be achieved with bortezomib given its success in multiple myeloma therapy targeting malignant plasma cells. Additionally, bortezomib has shown success in anecdotal cases of refractory ITP and ES and in vitro evidence suggested elimination of long-lived plasma cells.[5,8–10]

Two of three cases reviewed here showed a dramatic and long-lasting response to bortezomib therapy. We would like to stress three observations from our limited experience: (1) Initial response came rather quickly, raising the possibility of mechanisms involved beyond inhibition of autoantibody production through elimination of long-lived plasma cells, since the half-life of IgG is approximately 3 weeks and such autoantibodies tend to be high-affinity likely secondary to affinity maturation over time. This issue requires 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 fewer doses could be sufficient to induce responses. (3) Bortezomib has been well tolerated without any evidence of peripheral neuropathy (a frequent side effect in patients with multiple myeloma), infections, or any other adverse effects.

Increased recognition of underlying monogenic mutations in various immune response genes in ES patients raises the possibility of new targeted therapeutic interventions that would eventually prevent autoantibody production along with control of accompanying systemic processes.[11,12] Such novel targeted therapies are being currently investigated with some promising results.[13,14] However, many patients may not have access to genetic testing, including whole exome or genome sequencing. Several cases do not yet have described genetic etiologies despite testing as exemplified in the second and third cases in this report. Furthermore, even with some known underlying genetic abnormalities, targeted therapies may not be currently available.

We think clinical trials integrating bortezomib in ES treatment is reasonable in steroid-refractory patients, particularly if they failed rituximab therapy after reaching complete peripheral B-cell lymphodepletion. It is also prudent to have genetic testing for underlying immune dysregulation screening, if available. Patients receiving bortezomib therapy should be monitored for fatigue, weakness, peripheral neuropathy, nausea, vomiting, diarrhea, fever, constipation, thrombocytopenia and anemia, in addition to hypogammaglobulinemia. Bortezomib-responsive cases may avoid several potential adverse effects, and the social and financial burden of other interventions. Furthermore, biological correlates of bortezomib-responsive and refractory cases may help understand the various mechanisms of ES.

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How to cite this article: Beydoun SB, Persaud Y, Lafferty J, Callaghan MU, Savaşan S. Bortezomib treatment of steroid-refractory Evans syndrome in children. *Pediatr Blood Cancer*. 2020;67:e28725. https://doi.org/10.1002/pbc.28725