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Case Report

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"Luspatercept: a lifesaving therapy for transfusion-dependent thalassemia patients with alloimmunization complications"

Summary

This case demonstrates the benefits of luspatercept for thalassemic patients who are unable to receive adequate blood transfusions. It acts as a selective ligand trap and inhibits TGF-signaling via Smad2/3 to promote differentiation and maturation of late-stage erythroid precursors. Phase III clinical data showed that a 33% reduction in transfusion burden from baseline was achieved. The administration of luspatercept was a challenge due to the coexistence of antiphospholipid syndrome, portal vein thrombosis and splenectomy. Since initiating luspatercept, the patient has not experienced any adverse events and her general condition has improved.

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Introduction

In patients with thalassemia major the development of antibodies against red blood cells (both allo- and autoantibodies) remains a major complication. Based on donor-recipient homogeneity, RBC phenotype matching protocol, and age at transfusion beginning, alloimmunization rates vary in the literature. Alloimmunization rates in thalassemia were 4% to 50% and lower in homogenous groups.[1,2] Here, we present the case of a woman with β thalassemia and severe alloimmunization treated with luspatercept. Before luspatercept initiation this patient developed autoimmune hemolytic anemia presenting with severe hemolysis and a worsening of her general condition with any transfusion attempt.[3]

The case

A 50yrs old female with thalassemia intermedia diagnosed at the age of 5 years old with a Cd 39/δβSicilian genotype. She was then followed up at regular intervals in the pediatric hematology unit with no need for blood transfusions. The patient was transfused for the first time at the age of 23 due to a ruptured corpus luteum emergency surgery. Since then, she has maintained a hemoglobin of 9.5 g/dl without any need for transfusions. At the age of 29, she was diagnosed with severe splenomegaly with hypersplenism, worsening anemia, and thrombopenia, and she was referred to our adulthood unit for a scheduled splenectomy. Her blood type was A Rh+, and she had RBC, cc-, Ee - and K– phenotypes. She received two units of leukoreduced red blood cells intraoperatively. Postoperative portal thrombosis developed despite anticoagulant therapy. Antiphospholipid syndrome was detected with a thrombophilia test and treated with asenocoumarol. Twenty days postoperatively, the patient presented with fatigue, fever, jaundice, hemoglobinuria, and a significant drop in hemoglobin (4.1 g/L.) Anti globulin test performed both direct (DAT) and indirect (IAT) were present in association with unidentified autoantibodies.

She was hospitalized and given recombinant EPO injections (10.000 i.e. for 4 days) in combination with folic acid (10mg/day). Hb levels remained low, with a lower limit of 3.75 g/L, despite therapeutic measures. Intravenous immunoglobulins (2 g/kg total dose on days 1 to 5) were followed by methylprednisolone (250 mg/day) and anti-CD20 antibody rituximab (375 mg/m2 on days 1, 4, 8, and 12). To explain hyper hemolysis, screening tests searched for novel anti-erythrocytic antibodies. The patient has not been transfused since then and her hemoglobin level remained between 8.0 and 8.5 g/dl. She had fatigue and several extramedullary vertebral lesions. She also developed atrial fibrillation, resulting in left ventricular hypertrophy, left atrial dilatation, and diastolic dysfunction. From 2018 to 2019, her hemoglobin levels dropped below 6.5 g/dl, with no evidence of blood loss or hemolysis. Due to severe anemia and cardiac symptoms, 10,000i.u of erythropoietin was given twice a week in combination with 500mg of oral hydroxyurea. The patient initially responded with a transient increase in hemoglobin levels to 7.3 g/dl, but the extramedullary lesions subsequently progressed, causing neurological involvement with neuropathic pain and a T5 stress fracture. Patient's condition did not permit a second transfusion as any transfusion was followed by hyperhemolysis. With a baseline hemoglobin of 7.1g/dL, the patient was initiated on 1mg/kg luspatercept every 21 days as spc. The patient's hemoglobin increased and stabilized at 10 g/dL after the sixth luspatercept cycle. Her overall clinical condition significantly improved, fatigue was relieved and an MRI performed six months after she started luspatercept revealed a slight decrease in extramedullary foci.

Discussion

β-thalassemia is a hereditary hemoglobinopathy caused by over 400 identified mutations 3 of the β-globin gene or promoter region that reduce or prevent the expression of the β-globin subunit of hemoglobin in erythroid precursors. Because of the defect in Hb production, patients with b-thalassemia present with ineffective erythropoiesis, anemia, hypoxia and iron homeostasis dysregulation.[4] This case highlights the benefits of luspatacept in thalassemic patients who cannot receive suitable blood transfusions. Luspatercept[5] is a recombinant fusion protein comprised of a modified extracellular domain of activin receptor type IIB fused to the FC domain of human IgG1. Luspatercept acts as a selective ligand trap and preferentially binds to TGF-β superfamily ligands, such as GDF11, GDF8, and activin B, in vivo. The resulting potent inhibition of the TGF-β signaling via Smad2/3 has been shown to promote differentiation and maturation of late-stage erythroid precursors, such as erythroblasts. Importantly, the phase III clinical data of luspatercept demonstrated that a significantly greater percentage of patients receiving luspatercept achieved the primary endpoint of a ≥33% reduction in transfusion burden from baseline during Weeks 13–24, with a reduction of ≥2 RBC units compared with placebo. In this case, the patient was splenectomized and had developed portal vein thrombosis and antiphospholipid syndrome. Furthermore, she had severe neuropathic pain due to extramedullary foci and life-threateting anemia. Treatment with erythropoietin did not improved the patient's condition and worsened the neuropathetic pain. Transfusions were not an option due to the presence of auto and allo-antibodies and history of severe hyper-hemolysis. The administration of luspatercept was a great challenge because in phase III BELIEVE study 6 among the adverse events of special interest were the thromboembolic events. All thromboembolic complications occurred in individuals who had undergone splenectomy and had at least one other risk factor such as a history of venous thrombosis or thrombocytosis at baseline.[6]

The coexistence in this case of antiphospholipid syndrome, portal vein thrombosis and splenectomy were important risk factors to consider. However, the patient was on acenocoumarol for a long time, with great control and routine INR testing. Furthermore, she had not developed a new thrombosis or a new risk factor over time. Since initiating luspatercept the patient has not experienced any adverse events typically associated with this medication. Her general condition steadily improved as her hemoglobin levels raised and anemia was corrected. The patient did not acquire any new vertebral fractures or worsen any of her comorbidities. Furthermore, after 6 months our patient's extra medullary lessions improved, the neuropathic pain disappeared, and she discontinued the pain medications. In everyday clinical practice patients encounter several challenges from their disease, and alloimmunization in transfusion or inability to transfuse due to autoimmunity has been a dilemma for physicians and patients.

In this case the challenge to use luspatercept was a difficult decision. From one hand she had severe life-threatening anemia with many complications and an antiphospholipid syndrome related portal vein thrombosis and from the other hand treatment with erythropoietin and /or transfusions were inadequate, problematic or contraindicated. Treatment with luspatercept had a great impact in our patient medical problems and solved her failure to receive a transfusion. Thus, luspatercept is an emerging treatment option in adults with transfusion-dependent anemia due to β-thalassemia who cannot be transfused due to alloimmunization.

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Conflicts of interest

The author declares that there is no conflict of interest.

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