CLINICAL VIGNETTE

Efficacy of Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

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A 50-year-old woman had been in generally good health until she developed progressive fatigue and was found to be pancytopenic. She was initially seen by another hematologist who obtained an unrevealing laboratory evaluation and performed 2 separate bone marrow aspirates and biopsies (BM BX) which showed mild dysplastic changes but no abnormal molecular markers and no convincing evidence of myelodysplastic syndrome (MDS) or aplastic anemia (AA). She had received over 30 packed red blood cell (RBC) transfusions.

She presented for a second hematology opinion and I ordered flow cytometry for CD 55 & CD 59, a screen for paroxysmal nocturnal hemoglobinuria (PNH), which was positive. Her bone marrow was repeated with additional next generation gene sequencing. Bone marrow morphology was mildly hypocellular and erythroid predominant with mild dysplastic changes in erythroid and myeloid progenitors. However, the morphology was not diagnostic for myelodysplastic syndrome (MDS) and the cytogenetics were normal and her MDS fluorescence in situ hybridization (FISH) panel was negative. Two molecular markers present in 50% of bone marrow cells were variants of unknown significant in JAK (Janus activated kinase) 2 and MLL 2 (mixed lineage leukemia).

She was treated with pneumococcal and meningococcal and Haemophilus influenza vaccinations and started on intravenous eculizumab.[1] Evidence for intravascular hemolysis resolved within weeks of starting eculizumab but her pancytopenia and RBC transfusion dependence persisted, with less frequent transfusions.

Her secondary hemochromatosis due to her prior and ongoing RBC transfusions was treated initially with oral deferasirox[2] with a gradual decline in her serial ferritin levels, as a measure of body iron stores. She had mild but manageable nausea and diarrhea on deferasirox. Approximately 9 months into eculizumab therapy her serial complete blood counts (CBCs) showed some improvement which was accelerated by a 33% increase in eculizumab dose. After one year of therapy she did not require further RBC transfusions.

Her pancytopenia continued to improve but a repeat PNH flow cytometry assay after 2 years of therapy showed continued high level persistence of the PNH clone with 78% of RBCs demonstrating type 2, or partial loss of CD 55 & CD 59 expression, and 8% of RBCs demonstrating type 3, or complete loss of CD 55 & CD 59 expression. Her anemia was further improved by elective hysterectomy for menorrhagia and after 2 ½ years of eculizumab therapy she was able to start elective monthly phlebotomy in addition to deferasirox for her transfusion and hemolysis related hemochromatosis. Several months later she had serially normal ferritin levels and was able to stop deferasirox initially and later phlebotomy. Over the next 5 years of follow up she showed sustained mild thrombocytopenia with platelets greater than 100 x 10-3/ uL and no evidence of hemolysis or venous thromboembolic event (VTE).

Discussion

PNH is due to an acquired somatic hematopoietic stem cell mutation in the glycosyl phosphatidyl inositol (GPI) gene which encodes a protein involved in linking other proteins to the hematopoietic cell membrane, in particular CD 55 and CD 59, which inhibit complement mediated lysis of RBCs.[3] PNH cells which are derived from the GPI mutated stem cell appear to have a survival advantage likely due to an autoimmune attack on hematopoietic progenitor cells and gradually replace normal stem cell derived cells.[3] The classic triad of clinical consequences of PNH include intravascular hemolysis, pancytopenia and an increased incidence of VTE.[3] There is a significant chance with PNH of development of either MDS or AA.[3] Fortunately, this patient's presenting pancytopenia was not due to MDS or AA and over time her blood counts nearly normalized despite the 50% presence of an MLL2 mutation, described in several malignancies particular follicular and diffuse large cell B cell lymphomas,[4] and 50% presence of JAK 2 mutation, not the V617F associated with myeloproliferative neoplasms (MPN).

PNH patients for a variety of complex reasons are at increased risk of VTE. Overall 29-44% of PNH patients suffer at least one VTE.[5] VTE tend to occur in unusual venous sites, including cerebrovascular and intra-abdominal, including hepatic, mesenteric and portal veins.[5] There are several potential mechanisms for hypercoagulability including platelet activation, decrease in the potent vasodilator nitric oxide (NO) levels with chronic hemolysis, possible decreased fibrinolysis and increased inflammation.[5] There is no standard treatment for prevention of VTE. To date, our patient has not suffered a VTE and has suppressed hemolysis on eculizumab confirmed by consistently normal haptoglobin levels.

Eculizumab and related monoclonal antibodies target the C5 component of the complement cascade and so inhibit the membrane attack complex (MAC) induced lysis of effected RBCs to which PNH RBCs are more susceptible.[1] The therapy does not address the defective hematopoietic stem cell or alter the selective survival advantage of PNH hematopoietic precursors. Allogeneic bone marrow transplant (allo BMT) after myelo-ablative therapy is the only potentially curative therapy.[3] Allo BMT is generally reserved for younger patients with PNH associated with AA. Hence patients like this require lifelong eculizumab type therapy.

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