Fighting Fire with Fire: Antibodies Treat Hemolytic Anemias

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The exciting development in today's Education Session on Hemolytic Anemias (7:30 – 9:00 a.m. and 4:00 – 5:30 p.m.) is the effective use of monoclonal antibody therapy to treat various hemolytic anemias, including autoimmune hemolytic anemia (AIHA), cold agglutinin disease, and paroxysmal nocturnal hemoglobinuria (PNH).

Dr. Philip Hoffman from the University of Chicago detailed the use of rituximab (Rituxan®) and alemtuzumab (Campath®) in refractory AIHA. The underlying mechanism of AIHA involves immune system production of autoantibodies (usually IgG) targeting red cells, leading to extravascular hemolysis. Etiologies of AIHA can be quite varied, but the common goal of therapy remains mitigation of extravascular hemolysis through immunosuppression and possibly splenectomy.

However, what can clinicians use if corticosteroids, IV-Ig, or mycophenolate cannot maintain stable hemoglobin levels, or if a patient relapses after splenectomy? Currently available monoclonal antibodies rituximab and alemtuzumab specifically recognize B-cell restricted proteins CD20 and CD52, respectively, and can deplete the B-cell pool to dampen the autoantibody producing cells. In several reports of small patient cohorts, rituximab alone or in combination with other therapies safely achieved durable responses in a majority of patients. Although preliminary, the use of alemtuzumab also appears hopeful, with three out of four patients demonstrating response after therapy.

Cold agglutinin disease is also an extravascular hemolytic disease, but it is caused by an IgM autoantibody. Dr. Morie Gertz from the Mayo Clinic, Rochester, described recent reports that rituximab is able to achieve response rates of 45-54 percent, which is significantly higher than traditional therapies such as corticosteroids, purine nucleoside analogs, or alkylating agents. If rituximab is given in combination with fludarabine or interferon, response rates can be increased from 60 percent to 67 percent, 25 percent of which were complete responses.

Chronic intravascular hemolysis is characteristic of PNH, a rare disease involving the inability to prevent complement-mediated lysis of red cells. This phenotype arises from the lack of surface expression of GPI-linked proteins CD59 (membrane inhibitor of reactive lysis) and CD55 (decay accelerating factor), both of which normally protect red cells from spurious complement-mediated lysis. PNH arises from an acquired genetic defect at the hematopoietic stem cell level of phosphatidylinositol glycan class A (PIG-A), one of the subunits of the enzyme that catalyzes the first step in the biosynthesis of the GPI moiety. Inactivation of PIG-A leads to loss of surface expression of GPI-anchored proteins, such as CD59 and CD55. Complement-mediated lysis of red cells leads to free plasma hemoglobin and scavenging of nitric oxide. This results in the symptoms of PNH, such as fatigue, smooth muscle dystonias, and abdominal pain.

Eculizumab (Soliris™) is a monoclonal antibody that targets C5 and inhibits association of the membrane attack complex. Dr. Robert Brodsky from Johns Hopkins University detailed the recent TRIUMPH trial in which 87 patients with PNH were randomized to placebo or intravenous eculizumab for six months. Surprisingly, eculizumab-treated patients needed significantly less transfusions of red cells (median 0 versus 10) and had better hemoglobin stabilization (median 48.8 percent versus 0 percent) than placebo-treated patients. Furthermore, the eculizumab-treated patients simply felt better, perhaps due to reduced free hemoglobin and nitric oxide scavenging.

As these results show, monoclonal antibody therapy targeting the components of various hemolytic anemias appears very promising.