blood® Editorial

Introduction to a How I Treat series on acquired hemolytic anemia

There are many possible causes of acquired hemolytic anemia, and the differential diagnosis is often difficult.[1] One major group is represented by the autoimmune hemolytic anemias, in which increased red cell destruction is due to agglutinins that bind to antigens on the red cell surface.[2] The best characterized subtypes are warm autoimmune hemolytic anemia and cold agglutinin disease. Warm agglutinins are typically immunoglobulin G antibodies that bind to red cell antigens at a temperature of 37°C and determine accelerated extravascular hemolysis, whereas cold agglutinins are immunoglobulin M autoantibodies that bind at lower temperatures and cause complement-mediated hemolysis. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder caused by the absence of glycosyl phosphatidylinositol (GPI)–anchored surface proteins in blood cells, which is in turn due to a somatic mutation in the *PIG-A* gene.[3] Microangiopathic hemolytic anemia (MAHA) is characterized by red cell fragmentation and hemolysis that result from abnormalities in the small blood vessels[4]; systemic malignancies are a potential cause of unexpected MAHA.[5]

The How I Treat series in this issue of *Blood* includes articles written by expert clinicians that offer guidance regarding the treatment of acquired hemolytic anemias:

- Wilma Barcellini and Bruno Fattizzo, "How I treat warm autoimmune hemolytic anemia"
- Sigbjørn Berentsen, "How I treat cold agglutinin disease"
- Robert A. Brodsky, "How I treat paroxysmal nocturnal hemoglobinuria"
- M. R. Thomas and M. Scully, "How I treat microangiopathic hemolytic anemia in patients with cancer"

For many years, steroids and splenectomy have been essentially the only therapeutic tools available for the treatment of warm autoimmune hemolytic anemia. Barcellini and Fattizzo show that although steroids still represent the mainstay of first-line treatment, rituximab has emerged as an important tool for both first-line and second-line treatment. Berentsen underscores that not all patients with cold agglutinin disease should be treated and recommends that only those with symptomatic anemia or other bothersome symptoms should be considered for treatment. He also emphasizes the importance of avoiding ineffective therapies, clearly stating that steroids should generally not be used to treat cold agglutinin disease. The first-line treatment should include rituximab alone or in combination with bendamustine, whereas the complement C1s inhibitor sutimlimab is an emerging option for second-line treatment. Brodsky shows that terminal complement inhibition is highly effective for treating intravascular hemolysis from PNH, virtually eliminating the risk of thrombosis, but it is not effective for treating bone marrow failure. He also discusses new complement inhibitors upstream of C5 that are in clinical development. Thomas and Scully describe their approach to the evaluation and management of the cancer patient with MAHA. This hemolytic anemia is more commonly seen as part of a thrombotic microangiopathy, that is, a syndrome defined clinically by microangiopathic hemolytic anemia and thrombocytopenia. Early exclusion of thrombotic thrombocytopenia purpura is vital, and a potential causative role of drugs used in the setting of cancer should be considered.

I hope that these articles will help *Blood* readers improve their knowledge of the optimal treatment of these anemic conditions.

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