

Spotlight Session Illuminates Diagnosis and Treatment of Hemolytic Anemias

By Ruben Mesa, MD

Paroxysmal nocturnal hemoglobinuria (PNH) is one of those classic hematologic ailments that has long fascinated internists, scientists, and hematologists. Although a rare disease, PNH is part of the differential diagnosis of problems as diverse as hemolysis, anemia, thrombocytopenia, portal vein thrombosis, and even aplastic anemia. PNH now takes on a new role as a prime example of a disease for which targeted therapy is making a therapeutic difference.

Curiosity about the peculiar clinical phenomenon of nocturnal hemolysis led to discovery of the fundamental pathogenetic process in PNH: somatic mutation of the X-linked *PIG-A* gene, resulting in failure to anchor CD55 and CD59 on red-cell surfaces and increased susceptibility of these cells to hemolysis. The desire to overcome this complement-mediated lysis led to the development of a targeted therapy, eculizumab, a monoclonal antibody against the terminal complement protein C5 that inhibits complement activation. The evolving therapeutic options for PNH and other hemolyzing disorders were the focus of Monday's Education Spotlight Session on Hemolytic Anemia: PNH and Hemolytic Anemia.

The session began with a discussion by Dr. Samuel Lux, of Children's Hospital Boston, Harvard Medical School, who used a series of case-driven discussions to highlight various aspects of hemolytic anemias. Dr. Lux discussed the distinctions between immune and non-immune as well as between intravascular and extravascular hemolysis, interpretation of blood smears, and situations that mask hemolysis or otherwise complicate diagnosis.

PNH was then placed in the "spotlight" by Dr. Peter Hillmen, of Leeds Teaching Hospitals, Leeds, UK, who has long played a key role in our growing understanding of this disorder. Dr. Hillmen first reported the efficacy of eculizumab in patients with PNH. In the first report in the *New England Journal of Medicine* (NEJM) in 2004, the initial cohort of red cell transfusion-dependent patients experienced decreased anemia, markedly diminished hemolysis, and improved quality of life. Subsequent clinical trials (NEJM 2006) confirmed the efficacy of this agent and suggested that, in addition to ameliorating hemolysis, eculizumab may also decrease the associated risk of thrombosis.

Eculizumab was approved for PNH this spring in the United States and this summer in the European Union. Dr. Hillmen stated that many questions still remain, both for clinicians treating PNH patients and for investigators studying this and related marrow disorders. Dr. Hillmen said, "Eculizumab is changing PNH markedly and creates new issues, such as how to dose the drug optimally, how to manage breakthroughs, how to manage pregnancy, and for whom hematopoietic stem cell transplant should be considered." Dr. Hillmen used a series of challenging cases to illustrate these problems. He also reviewed current thinking on the role of free hemoglobin and nitric oxide consumption in the symptomatology of PNH, as well as the potential role for targeting PNH clonal cells with eculizumab in other disorders, such as aplastic anemia and myelodysplastic syndrome.