ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Update in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, MD, PhD
Consultant Haematologist
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

H&O What is paroxysmal nocturnal hemoglobinuria?

PH Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disease that results in intravascular hemolysis, which is associated with profound symptoms. Approximately half of PNH patients develop thromboses. Approximately one third of patients have a preceding diagnosis of aplastic anemia, and the other two-thirds of patients have some laboratory evidence of aplasia. Most, if not all, PNH patients have an underlying bone marrow problem. The disease is most commonly diagnosed in young adulthood, although patients can present at any age.

PNH results from a clonal somatic mutation, which results in an abnormal hematopoietic clone. The mutation occurs in the *PIG-A* gene, which is critical for the biosynthesis of glycosylphosphatidylinositol (GPI) anchors, and results in the deficiency of cell surface molecules that are normally tethered to the membrane by a GPI anchor. *PIG-A* mutations are common and occur in almost everyone at some point. In most people, the cells that are created by the mutant cell never expand above a very low level. Typically, there are up to 10 cells in a million, and they do not grow into anything that would be detectable routinely. It is only in patients with bone marrow failure that these cells expand due to either a growth advantage or a survival advantage over the normal bone marrow. In many patients with severe PNH, most, if not all, of the bone marrow is replaced by the PNH cells.

The epidemiology of PNH follows that of aplastic anemia. The red cells are unable to protect themselves from complement, which is part of the immune system. They lack the protein, CD59, that prevents terminal complement from attacking the cells. The red cells, and probably also the platelets, are very sensitive to being attacked by their own complement, and therefore they burst intravascularly inside the vessels, resulting in the release of free hemoglobin, which overflows in the urine and turns it dark—hence the name *paroxysmal nocturnal hemoglobinuria*. Typically, patients have episodes of dark, or even black, urine. It usually appears first thing in the morning, fades throughout the day, and lasts for a few days. Sometimes it is triggered by infection. Even when patients are not experiencing a paroxysm, they still have evidence of intravascular hemolysis, with high levels of lactate dehydrogenase (LDH) and, often, bilirubin. The hemolysis in PNH leads to profound symptoms of anemia, which may require transfusions. Patients can also experience abdominal pain, severe lethargy, difficulty swallowing, absolute dysphagia, and, in men, erectile dysfunction. Lethargy is a prominent aspect of the disease for many patients; it can be disabling and interfere with normal daily activities.

H&O How is PNH diagnosed?

PH PNH is diagnosed using flow cytometry, which can identify the absence of GPI-anchored antigens that are missing from PNH cells. Flow cytometry is used to look for those antigens on at least 2 lineages; red cells and granulocytes would be the typical finding. Usually, the proportion of PNH cells is higher in the granulocytes than in the red cells because there is a selective loss of PNH red cells due to hemolysis and patients are often transfused with normal cells. Historically, complement sensitivity tests, such as the Ham test, were used to demonstrate the sensitivity of PNH red cells to activated complement. Such tests are seldom used now.

H&O What is the prognosis in this disease?

PH About 20–30 years ago, with only supportive care available, approximately half of patients with PNH died from the disease, usually as a consequence of thrombosis. The median survival was approximately 10 years. More recently, survival had improved toward a median of approximately 15 years, and this was before the advent of novel therapies, such as eculizumab (Soliris, Alexion Pharmaceuticals). Some patients with PNH improve without treatment and achieve a spontaneous remission, usually 10–20 years after the diagnosis. In a previous study of 80 PNH patients, we reported that 12 patients eventually effectively cured themselves of the disease.

H&O How is eculizumab used in the management of PNH?

PH Treatment of PNH historically relied on supportive care with transfusions, management of cytopenia, and management of bone marrow failure with cyclosporine and other immune-specific drugs. Folic acid replacement and iron replacement have been used. Eculizumab, an anti-complement drug, was approved in 2007, and it has become the standard treatment for patients who are severely affected with hemolytic or thrombotic PNH. Eculizumab blocks the activation of C5, the fifth complement component, which plays a pivotal part in the complement cascade by preventing the activation of terminal complement and protecting the PNH cells from lysis.

The clinical data for this drug in PNH are very impressive; in virtually every patient, it stops intravascular hemolysis. In PNH patients with hemolysis, it usually stops the need for transfusion and improves all symptoms, including lethargy, abdominal pain, dysphagia, and erectile dysfunction. It has been almost 10 years since the first trial, and many of the original patients remain on eculizumab and continue to benefit from it.

Eculizumab is also effective at preventing thrombosis. We have used eculizumab with anticoagulants to effectively treat a number of patients with serious thromboses. Eculizumab will not effectively treat bone marrow failure leading to anemia in PNH. The bone marrow failure must be treated separately.

In the United Kingdom, we use eculizumab in PNH patients who are transfusion dependent, defined as 4 or more transfusions in the past 12 months; patients who have thrombosis due to PNH; patients who have renal failure due to PNH; and PNH patients who are pregnant. We recommend that women with hemolytic PNH who are not receiving eculizumab receive treatment throughout pregnancy and for at least 3 months postpartum. Eculizumab is also administered to severely hemolytic patients with a recent diagnosis who have a low hemoglobin and therefore a very high LDH—even if they were transfused fewer than 4 times in the past 12 months. There are other exceptional cases in which eculizumab is used, including PNH patients who are profoundly symptomatic with hemolysis but do not need transfusions.

H&O How is eculizumab administered?

PH Eculizumab is given intravenously with a half-hour infusion. It is important that an adequate trough level is maintained to keep the complement blocked and prevent the hemolysis of PNH, so the drug is given weekly for the first 5 doses, and then every 2 weeks. Approximately 90% of patients with PNH will be adequately treated with a dose of 600 mg given once weekly for 4 weeks, and then 900 mg given every 2 weeks. A small number of patients need a higher dose, such as 1,200 mg every 2 weeks.

H&O Is eculizumab associated with any adverse events?

PH Approximately half of patients experience headaches—which can be severe—the day after the first dose. These headaches can usually be treated with simple analgesia. Headaches do not usually occur on subsequent days or with subsequent infusions. The major concern with blocking the complement is the risk of infection, in particular, *Neisseria* infection, leading to *N. meningitidis* (meningococcal) infection. The risk of a patient developing a meningococcal infection on eculizumab is about 0.5 cases per 100 patient years. We educate the patients in our practice about this concern. In the United Kingdom and France, patients receive prophylaxis with penicillin to prevent meningococcal infection. Patients are also vaccinated, and levels of the vaccine are measured. Unfortunately, we do not yet have vaccines for serogroup B.

H&O When is anticoagulant prophylaxis indicated for PNH patients?

PH As I mentioned, the biggest risk in PNH is thrombosis, which occurs in approximately 40–50% of patients and is associated with a larger PNH clone size. Historically, a third of PNH patients died as a direct result of thrombosis, making it the most common cause of death. The blood clots often happen in typical unusual sites, such as the hepatic veins, other intra-abdominal veins, and the cerebral veins, and manifest as hepatic vein thrombosis (Budd-Chiari syndrome), mesenteric vein thrombosis, and cerebral vein thrombosis. These central clots lead to strokes, myocardial infarction, and life-threatening thrombosis. In addition, arterial thromboses, such as myocardial

infarctions and cerebrovascular accidents, also occur more frequently in PNH. Many years ago, efforts were begun to try to predict which patients were at higher risk of clots in order to enact preventive strategies. The risk of clots is, to some extent, associated with the size of the PNH clone, particularly the neutral clone. We consider prophylaxis with warfarin or coumarin, to maintain an international normalized ratio between 2 and 3, in patients with a neutral clone size greater than 50% and an adequate platelet count (≥100,000/mL), who have no contraindications to this therapy. However, anticoagulant prophylaxis is not used in patients who are starting eculizumab therapy. Eculizumab will prevent thrombosis in most patients.

H&O Is there a role for bone marrow transplant in the management of PNH?

PH Bone marrow transplant is the only curative treatment for aplastic anemia and PNH. It has been studied in clinical trials in patients with a variety of types of PNH. In the last year, we have learned that the outcomes of bone marrow transplant in hemolytic PNH or thrombotic PNH are poor, almost certainly much poorer than treatment with modern therapies, such as eculizumab. We reserve allogeneic bone marrow transplant in PNH for patients who have profound bone marrow failure. The only exception would be the very rare patient who has an identical twin, in whom the risk of transplant is so small that we would advocate this procedure.

H&O Are there any other concerns for PNH patients?

PH Pregnancy has always been a major concern in PNH. Published studies suggest that more than 10% of women with PNH who become pregnant will die during pregnancy. Of course, there is a bias in such reporting, and the real number is probably lower. However, morbidity and mortality in pregnancy is much higher in PNH patients. In the past, many PNH patients avoided pregnancy because of the risks. There is also some evidence that there might be more fetal loss in women with PNH, but that finding is hard to explain and may be attributable to reporting bias. So far, we have administered eculizumab during pregnancy in 10 PNH patients, and the babies were born without any adverse events. Eculizumab does not cross the placenta. In general, these patients have fared much better by avoiding the thrombosis seen in patients not receiving eculizumab.

Another concern for PNH patients is renal failure. Approximately 20% of patients with PNH will have stage III–V chronic kidney disease. It results from several factors, including continuous intravascular hemolysis, with hemoglobinuria, and probably nitric oxide consumption through free hemoglobin. We know that eculizumab will effectively manage those factors, so renal dysfunction is one of the indications for treatment in the United Kingdom.

H&O What are some areas of research in PNH?

PH PNH is a very active research area, and has been for many years. Researchers are trying to optimize therapy. Two-thirds of patients become transfusion dependent, and most have a very good response. There is evidence, however, that some patients require more transfusions because of bone marrow failure. Extravascular hemolysis, necessitating transfusion, can occur in patients receiving eculizumab. There is much laboratory and clinical research under way to determine the optimal dose of eculizumab, identify the reasons that some patients still require transfusions or have a slightly low level of hemoglobin, and learn how to address the extravascular hemolysis associated with eculizumab.

Another area of research is examining why PNH occurs. We know that the PNH clones develop in patients with aplastic anemia. Both diseases are very rare, and that is not by coincidence. It seems that the aplastic process, which is an immune-mediated bone marrow failure, results in the selection of PNH clones, allowing them to grow in those patients with bone marrow failure. If we can elucidate the mechanism by which that growth occurs, we will gain a better understanding of why PNH occurs and may be able to develop a therapeutic approach to treating both PNH and other bone marrow failure syndromes.

Suggested Readings

Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011;117:6786-6792.

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