Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/transfusionshow-important-are-they-for-pnh-patients/14305/

Released: 08/12/2022
Valid until: 08/12/2023
Time needed to complete: 1h 54m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Transfusions…How Important Are They for PNH Patients?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. de Castro:
Hi, my name is Carlos de Castro, and I am a professor of medicine at Duke University Medical Center in Durham, North Carolina. This talk is entitled "Transfusions, How Important Are They For PNH Patients?" And my goal is to talk a little bit about how transfusions are used for patients with PNH. The anemia in PNH is a very complex topic 'cause it can be caused by a lot of different things. Coombs negative hemolytic anemia is the clinical hallmark of PNH, but the disease usually has a component of bone marrow failure. So there's a production problem. And there can be other causes of anemia also, including iron deficiency and bone marrow failure problems.

In the old days before we had effective treatment for PNH, patients would have to undergo transfusion therapy if they needed it. Other treatments included steroids, which could be given intermittently at low doses, and only a few patients could stay on chronic steroids, but it had all the side effects. Iron and folate supplementation were a usual part of how we treated patients in the old days. And splenectomy was very controversial with only anecdotal evidence that it would help. So transfusions were really a mainstay of patients with severe anemia who needed blood product support. Whenever a patient had any sort of complement activation, and this could come from infection, especially viral infections, surgery, or really any sort of stress, flares would be common with hemolysis, dark urine and marked symptoms, including fatigue and just feeling overall horrible, abdominal pain, et cetera. Transfusion was a way to ameliorate the anemia, but theoretically could also ameliorate some of the hemolysis because you wouldn't need so much erythropoiesis and manufacturing of PNH cells. Washing of red cells to prevent complement activation was found really not to be helpful and was really a waste of time and product, but hemofiltration is certainly recommended to prevent transfusion reactions and antibody formation.

Shown in this table, from a paper in 2015 talking about the role of blood transfusions, was how we managed anemia in PNH patients other than using eculizumab. And in those days, we, again, would give folic acid to help with the erythropoiesis. We would look at iron studies, and many of these patients were iron deficient 'cause they were losing it in their urine, so we would give iron. We would assess how much anemia the patient could tolerate. And that was a very subjective finding. And based on this, some patients clearly needed blood transfusions. This varied widely from patient to patient. And it also varied widely over the course of time in the same patient because these patients were making red cells. And so as soon as the complement levels would fall back down, their hemoglobin would usually rise back to their baseline. As I mentioned before, washing the red cells is not necessary. And all we need to do is filter the cells. And in some patients, especially those with aplastic anemia or those on immunosuppressive therapy, we can consider radiating the blood product.

Now, once we had an effective treatment, and that came in the form of eculizumab, the C5 inhibitor, transfusion requirements clearly fell. This is shown in this slide here where patients were put on eculizumab versus placebo and you can see the transfusion requirement in the orange bars there, both before and then after eculizumab, fell dramatically. Whereas those on placebo, there was really no change in their transfusion requirement over the 26-week period.

Now, despite the success of C5 inhibition, the responses to eculizumab, and now ravulizumab, can be very heterogeneous. Most patients still exhibit continuous low-level hemolysis likely through extravascular mechanisms. And up to 25 to 35% are estimated to still require an occasional red cell transfusion. Eculizumab prevents intravascular hemolysis, but in doing so, it unmasks this low level of extravascular hemolysis that is mediated because all of these red cells that are now surviving are being coded with C3 fragments and these PNH red cells have no way to remove those fragments. And this will lead to eventual uptake in the reticulo endothelial system and extravascular cell clearance. There is an incredible heterogeneity in the amount of degree of this clearance and how much hemolysis patients will undergo. So some patients on eculizumab or ravulizumab are doing very, very well and are not getting that anemic. Whereas others are still quite anemic and requiring red cell transfusions again.

In this one paper by Antonio Risitano, you can see that patients who are on eculizumab in Italy, 63 had a suboptimal response, 20% still required at least three or more transfusions during the year. All of them had evidence of C3 coding of their red cells and opsonization. And of the three patients that underwent further testing because of these suboptimal response, they showed that these all had decreased red cell half-life, an increased red cell turnover in the liver and the spleen where they were being taken up, and they had one patient who actually underwent a splenectomy and became transfusion independent, but were not recommending that as a standard therapy at this time.

So we now have the C3 inhibitor pegcetacoplan that is FDA approved in the United States. This is data from the EHA Conference in abstract form and will be published hopefully shortly. Here, we see now up to 48 weeks that patients who were on pegcetacoplan and even those that were switched over from eculizumab to pegcetacoplan showed a marked increase in their hemoglobin levels irregardless of the number of transfusions they had had prior to study entry. And the number that remained transfusion-free, were those that were less than four transfusions, was in the 80 to 88% range. Those that had an even higher transfusion requirements remained transfusion-free in 61 to 67% of these patients. Again, showing a dramatic improvement in patients with PNH once they're on a C3 inhibitor and we block extravascular hemolysis.

So, in conclusion, transfusion of red cells for patients with PNH is always going to be a necessity for some patients despite marked improvement in treatment using complement inhibitors. The etiology of any ongoing anemia should be investigated because we can have things like bone marrow failure, or we can have extravascular hemolysis due to C3 coating of red cells. And it's important to distinguish these because we treat them quite differently. Red cells should be filtered and in some cases, radiated. Washing is not necessary. And principles of blood conservation in these patients are still important. So a patient has a low hemoglobin, but is not symptomatic, they don't necessarily need to be transfused at that time. Thank you for your attention.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.
To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.