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Patient Case: How Would You Treat a Newly Diagnosed PNH Patient?

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Dr. de Castro:
Hello. This is a discussion of a Patient Case: How Would You Treat a Newly Diagnosed PNH Patient? I'm Carlos de Castro. I'm a Professor of Medicine at Duke University in Durham, North Carolina.

Patients C is a 41-year-old female who presented 10 years ago with shortness of breath and heavy menstrual periods. She was found to be pancytopenic. Workup revealed aplastic anemia. She underwent treatment with immunosuppressive therapy using ATG and cyclosporine and had a complete count recovery. A bone marrow biopsy 1 year later was normocellular. She did very well until recently when she noticed more fatigue. Her lab showed a white count of 3.4, a hemoglobin that was down to 5.7, hematocrit of 17.5, and a platelet count of 142,000. Her reticulocyte count was elevated at 7.8% and an LDH was very high at 2645 units/L. A bone marrow biopsy was done which showed a 40 to 45% cellular marrow with erythroid hyperplasia, normal FISH, and normal cytogenetics and a peripheral blood flow cytometry test was positive for PNH.

So we asked the question of what therapy should you start with? Currently, there are 3 FDA approved drugs for treating PNH. These include the C3 inhibitor, pegcetacoplan, and the C5 inhibitors eculizumab and ravulizumab.

Pegcetacoplan has been out there for a little over 2 years since FDA approval. It's administered at home via subcutaneous pump twice a week, or now there is an on-body injector that is being used. C3 inhibitors have the advantage of blocking both intravascular and extravascular hemolysis. This leads to higher hemoglobin levels, and in many patients, a drop in fatigue. They feel better on this drug. C5 inhibitors, eculizumab and ravulizumab, have obviously been around a lot longer. Eculizumab was approved nearly 20 years ago, ravulizumab is a longer-acting form of eculizumab with modifications to the monoclonal antibody. We have long-term data regarding both the efficacy and safety of these drugs. And they're both very efficacious and very safe. They have to be administered in an infusion center, usually intravenously every 2 weeks for eculizumab, or every 8 weeks for ravulizumab. Ravulizumab has now been approved to be given subcutaneously, although I've not done that yet. It's also been approved in pediatrics.

Which therapy to start with is a very difficult question. Obviously, we have the C5 inhibitors that we're very comfortable with, we have long-term data with them, they do decrease the risk of blood clots significantly, and survival has likely improved because of this. They are very well tolerated. But some patients, and we estimate it to be 10 to 20%, have a suboptimal response to these drugs; that is, they remain anemic and/or needing transfusions. C3 inhibition with pegcetacoplan is again more efficacious because it blocks both intravascular and extravascular hemolysis. And we do see a rise in hemoglobin levels to near normal levels. It also seems to decrease the risk of blood clots, probably to the same extent as the C5 inhibitors. Now, patients who go on these drugs have to be monitored fairly frequently during initiation. I tend to watch them every 1 to 2 weeks and check their blood counts LDH and retic count, and I also ask them about fatigue scores and any other symptoms. Once they are stabilized and responding, they can be seen every 3 to 6 months,

again with the same labs and asking about the same symptoms. All of these drugs have a problem with breakthrough hemolysis, patients can get an infection or another complement-activating event. And this can lead to breakthrough with again a return of symptoms hemoglobinuria, abdominal pain, etc, and usually a rise in the LDH. With eculizumab and ravulizumab, we usually monitor patients. Sometimes we give them an extra dose of eculizumab if we need to, but we debate on what to do for these patients.

With pegcetacoplan, at least in the PEGASUS phase 3 trial, the incidence of breakthrough him also seem to be a little bit less than eculizumab. But the cases seem to be a little bit more severe. And that may have more to do with its efficacy and having more PNH red cells that are circulating in the bloodstream.

Other adverse events have been mild for both these drugs and they're both incredibly well tolerated. The choice of which one to pick may be patient-driven after a long discussion about the advantages and disadvantages of both drugs.

With that, I'd like to thank you for attending this talk.

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