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Improving PNH Patient Outcomes

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Apellis. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss how we can improve outcomes in paroxysmal nocturnal hemoglobinuria, or PNH for short, is Dr. David Dingli who's a professor of medicine in the Department of Hematology at the Mayo Clinic Comprehensive Cancer Center in Rochester, Minnesota. Dr. Dingli, thanks for being here today.

Dr. Dingli:
Thank you, Dr. Turck, for inviting me.

Dr. Turck:
To get us started, Dr. Dingli, would you give us a quick rundown of the treatment options available for PNH?

Dr. Dingli:
Yeah, thank you for this question. So currently, we have three drugs that are approved for the therapy of patients with PNH. We have two drugs that inhibit C5, which is just proximal of the formation of the membrane attack complex. These are eculizumab and ravulizumab. Eculizumab was the original compound that has been approved now for more than a decade and really changed the life of patients with PNH. It's a very good drug at inhibiting C5 in many patients, not all, and I'll come to that in a minute. It's very effective at preventing intravascular hemolysis. It used to be given intravenously every two weeks. Ravulizumab is a second generation C5 inhibitor. It has a much better pharmacokinetic profile. It undergoes endosomal recycling, and it has a lifetime of several weeks, so it only needs to be given every eight weeks. The advantage of ravulizumab is not only that it is given every eight weeks, but also, the risk of so-called breakthrough hemolysis appears to be less compared to eculizumab. I mentioned that a subset of patients will not respond to eculizumab or ravulizumab, and these are patients mainly from southeast Asia who have a polymorphism in C5 that renders them unable to bind the antibody, so these patients will not respond. The more recent entry in the field of PNH therapeutics has been pegcetacoplan, which is a C3 inhibitor, a more proximal complement inhibitor. The drug has to be given subcutaneously twice a week, and the patient can give the drug to themselves. It has to be kept refrigerated. The advantage of a C3 inhibitor are the following: there is a subset of patients that I mentioned that cannot respond to a C5 inhibitor, but more importantly, many patients with PNH who are on a C5 inhibitor continue to have residual anemia in part because they develop extravascular hemolysis. So while we think of PNH as being the quintessential acquired hemolytic disorder due to intravascular hemolysis with therapy using a C5 inhibitor, the red blood cells would accumulate C3, which cannot be controlled by eculizumab or ravulizumab. And accumulation of C3b on the surface of red cells renders them opsonized for destruction in the articular endothelial system. Pegcetacoplan prevents this, so it can prevent both intravascular as well as extravascular hemolysis in PNH. As a result, the patient who continues to be transfusion-dependent and continues to have symptomatic anemia because of hemolysis in PNH can see an improvement in hemoglobin and a reduction in transfusion requirements if not elimination of transfusion requirement with the use of pegcetacoplan.

Dr. Turck:
And what are some challenges associated with those treatment options that patients may face?

Dr. Dingli:
Therapy with these agents is parenteral. Eculizumab is given every two weeks, ravulizumab is given every eight weeks. Now ravulizumab can be given subcutaneously with a device that can be placed on the skin. And of course, pegcetacoplan is to be given twice a week, and the product has to be refrigerated. I mentioned there's a small population of patients with polymorphism in C5 that will

not respond to eculizumab and ravulizumab. Both classes of drugs are associated with some risk of infections, in particular with encapsulated bacteria, such as Neisseria, streptococcus, and Haemophilus and patients are required to be immunized against these. Other challenges include the fact that patients on C5 can continue to have evidence of hemolysis, and they need to continue with transfusions and may continue to have symptoms related to both hemolysis and the anemia, and of course, the burden associated with the continued need of transfusions.

Dr. Turck:
So with that in mind, how could we modify our approach to address suboptimal patient outcomes when they happen?

Dr. Dingli:
First we need to understand why the patient is having a suboptimal response. Is the issue related to breakthrough hemolysis, which generally means that perhaps the drug, especially C5 inhibitors, they are not being given as frequently as necessary or at the right dose that inhibits hemolysis. And this is something that we can easily check by looking at the level of complement inhibition just before the next dose is given.

And if complement is inhibited, that is not a reason for the persistent anemia for example. We need to rule out that the patient is having iron deficiency or folate deficiency. Of course, I'm assuming here that the patient does not have a significant element of bone marrow failure associated with their PNH, and this can be figured out by looking at the reticulocyte count, the LDH, and the rest of the CBC. If the patient has a near-normal platelet count and a near-normal white cell count and the reticulocyte count is high, then clearly the patient does not have a significant element of marrow failure that is contributing to the ongoing anemia. In that situation, we need to rule out breakthrough hemolysis and we need to rule out extravascular hemolysis. And breakthrough hemolysis, as I mentioned, can be understood if the patient has elevated reticulocyte count and elevated LDH. And classically, we think that if the LDH is more than one and a half times above the upper limit of normal, at the trough level of the C5 inhibitor, then the patient is not having adequate intravascular hemolysis control. But if the LDH is well controlled, then we need to look for the possibility of extravascular hemolysis. And the way we do that is by obtaining monospecific Coombs test or antiglobulin test, which is characteristically negative in the patient with PNH because PNH is considered a Coombs-negative hemolytic anemia. It's not an immune-mediated process. But in this scenario, if there is significant extravascular hemolysis apart from the higher reticulocyte count, we will see that the red cells are coated with C3b, and this is what makes them opsonized.

Dr. Turck:
As a quick follow-up to that, what counseling strategies could we use to engage our patients in the treatment decision-making process?

Dr. Dingli:
So I think the patient needs to be quite involved in the decision on how we are going to treat their disease. First of all, they need to be informed about what the illness is because most likely they have never heard of it, and they don't know anybody with that disease, although with the arrival of the internet and chat rooms, many patients will ultimately meet many other patients, at least in the virtual environment. So they need to understand what this illness is and what we're trying to achieve by controlling their disease, namely that we want their hemoglobin to be better, we want to avoid transfusions, we want to avoid the life-threatening thrombotic events. We want to improve quality of life in these patients, and we know that with effective therapy, the lifespan of these patients can approach that of a normal population. So those are the goals. Then we need to discuss with them what the treatment options are and what the expectations of responses are. We need to talk about C5 inhibition in the form of eculizumab and ravulizumab. These have been around for many years, time-proven, highly effective at preventing thrombosis. And we also need to talk about pegcetacoplan, which is a more recent drug on the market.

The patient is to understand the importance of compliance with therapy and what will happen if therapy is withheld for some reason or if there is a condition that will be activating complement, for example infection, inflammation, surgery, or pregnancy, and what to look out for. They need to understand the risks of infections and the importance of being vaccinated against encapsulated organisms, and typically, I would recommend vaccination against Neisseria meningitidis, Haemophilus influenza, as well as the streptococcus. If I need to start therapy promptly in a patient, I will probably cover the patient with antibiotics while I give time for the vaccines to become effective. Then we should have a conversation about the pros and cons of these drugs, whether the patient prefers an infusion every two weeks intravenously, versus eight weeks, versus the patient who wants to take the control of their disease in their own hands. More or less, own the disease and receive therapy in the comfort of their home with a drug that they self-administer twice a week. And this is the beauty of humanity. We are all different. We perceive different benefits and risks differently, and as long as the patient is informed, together with the patient, we can make the right decision that fits with the lifestyle and with the value systems and with the expectation that each patient has.

Dr. Turck:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. David Dingli about improving outcomes for patients with paroxysmal nocturnal hemoglobinuria, or PNH.

So, Dr. Dingli, now that we have a better understanding of PNH treatment challenges, I'd like to zero in on C3-targeted therapy. What else could you tell us about it? And what more should we take into consideration when switching patients to it?

Dr. Dingli:
So the use of a C3 inhibitor has several potential advantages over a C5 inhibitor. First of all, we're inhibiting complement in a more proximal way, and we know that a C3 inhibitor can block intravascular hemolysis very effectively, but it also prevents this phenomenon of extravascular hemolysis, which has become increasingly recognized, and it is quite important in maybe 25 percent or more of patients and probably it is present in more patients. And this phenomenon occurs because the red cells now are surviving longer, and if the patient wants a C5 inhibitor, we are inhibiting the complement distally, but it does not prevent the accumulation of C3 on the surface of red cells. And this accumulation of C3 is what results in opsonization of red cells and ongoing extravascular hemolysis. And this can result in significant anemia that is important for the patient in the sense that it can cause shortness of breath, fatigue, decrease in quality of life, and some patients continue to require transfusions. So clearly, for the patient who is not having an optimal response to a C5 inhibitor, a C3 inhibitor can provide a very interesting opportunity.

Of course, the drug has to be self-administered twice a week compared to a drug that can be given every eight weeks, but for the patient who remains anemic, remains requiring transfusions, continues to have significant fatigue, the only drug currently available that offers a prospect of a hemoglobin that approaches normal, then it will be the use of pegcetacoplan in that context.

Dr. Turck:
Well with those final insights in mind, I want to thank my guest, Dr. David Dingli, for joining me to discuss how we can improve treatment responses in patients with PNH. Dr. Dingli, it was great having you on the program today.

Dr. Dingli:
Thank you again for the invitation.

Announcer:
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