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Managing PNH Patients: Addressing the Unmet Needs

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:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck. And joining me to discuss how we can address unmet needs in the management of patients with paroxysmal nocturnal hemoglobinuria, or PNH for short, is Dr. Brian Mulherin. He's a hematology and oncology specialist at Hematology Oncology of Indiana and Ascension St. Vincent Hospital in Indianapolis. Dr. Mulherin, welcome to the program.

Dr. Mulherin:
Thank you for having me.

Dr. Turck:
Let's dive right in, Dr. Mulherin. What are the current knowledge gaps when it comes to managing patients with PNH?

Dr. Mulherin:
There are a number; one is just making the diagnosis to begin with. It's not uncommon for years to elapse after someone first develops symptoms and before a formal diagnosis is made. And that's because symptoms can be quite vague and nondescript at the beginning, maybe a little fatigue, a little lightheadedness. Keep in mind, these are young adults, young, middle-aged adults; the average age at diagnosis is 39. So they may not have regular medical care, it may not be pursued as much. So all that can contribute to a delay in diagnosis. That's number one.

Number two, once the diagnosis has been made, what is the optimal management? We have three currently approved complement inhibitors and many more on the way. We have eculizumab, we have ravulizumab, and pegcetacoplan.

How does one choose? And which is the best approach to use in those cases? That is unknown right now. We have some patients who are well served by taking C5 inhibitors like ravulizumab, eculizumab, and others who are not. Some patients who may have very significant residual hemolysis, who may benefit from a more proximal complement inhibitor, but that's still an ongoing area of investigation.

Number three, how do we manage breakthrough hemolysis, especially in patients who are on inhibitors like pegcetacoplan or one of the many that are in development? What is the best way? What's the best way to do that? What is the natural history of that, especially in patients treated with pegcetacoplan or some newer drugs that are in development. The PNH clone size may expand to levels that previously have never before been seen, maybe to greater than 90 or 95 percent. What does that mean? Does that have any long-term implications? What do we have to do differently about that?

Another one would be what is the optimum management of PNH when it's associated as part of a bone marrow failure syndrome? So we know there's a very strong association of this disease with aplastic anemia, for instance, but any number of bone marrow failure syndromes can do that, and around 10 to 20 percent can go on to develop a myeloid malignancy, whether that's MDS, AML, or something else. How do we integrate complement inhibitor therapy into those conditions? What is the best way to do that?

Dr. Turck:
Now would you tell us about some barriers that may impact the effective management of these patients?

Dr. Mulherin:

So one barrier is actually just making the diagnosis. It's not uncommon for patients to have a diagnosis that's delayed for years in many cases because initially, the symptoms may be nondescript, just some day fatigue, some lightheadedness, maybe problems concentrating. Keep in mind, these patients are typically young adults, the average age of diagnosis is around 39. And it strikes men and women equally. There are no known risk factors associated with this. So just making the diagnosis can be a challenge.

Once patients have it, then figuring out which complement inhibitor approach is the best, is the most optimal and for the patient considering the type of disease they have, considering the patient's lifestyle, their preferences, maybe looking at insurance, and ability to be compliant. And then another would be, how do we manage breakthrough hemolysis? Which I've mentioned before. And do we give more of the drug? Do we switch to a different drug? This is especially an unknown if we are looking at newer drugs like pegcetacoplan and other agents that are in development, how best to manage this breakthrough hemolysis.

Dr. Turck:
Now, Dr. Mulherin, how does PNH disease burden affect patient outcome?

Dr. Mulherin:
So it's a little bit of a complicated question. So do we mean by looking at the clone size? For example, I think roughly, especially in people who are treated on C5 inhibitors like eculizumab or ravulizumab, there's roughly three categories of how they're going to respond.

Some patients are going to respond extremely well. They may not have any residual anemia. They may have minimal symptoms, and they can essentially resume or fairly close to resume their life to how things were before. That's the smallest category. There's another third of patients who are still anemic, but mildly anemic. So their hemoglobin maybe 11 or so. But in some cases, they can have significant residual symptoms, and we think that it has to do with the ongoing hemolysis, which is still ongoing.

And then there's the lower third of patients who are not well served by C5 inhibitors, patients who have significant residual anemia and may even be transfusion dependent. So especially in that group of patients, you think the burden of the disease is higher; those patients are debilitated by their condition. They may find it difficult to think, they may find it difficult to care for their child or to hold down a job. Keep in mind, these are people in their upper 30s and lower 40s, so in their prime working years. So it's a disease that affects a small amount of the population, maybe 4,000 or 5,000 cases just in the United States total. But relative to a sign that has a disproportionate impact on this population, working years, or productivity, and all those kinds of things.

So our goal is to alleviate the burden as much as possible, understanding that we are not curing the disease, we're trying to minimize the hemolysis as much as we can, allow them to go on living life as best they can. But for some patients certainly with C5 inhibitors, that's just not possible. We're hoping that with newer drugs that may change the natural history of it.

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. Brian Mulherin about the barriers and knowledge gaps that may lead to the ineffective management of patients with PNH.

So, Dr. Mulherin, now that we have a better understanding of the challenges, let's turn our attention to some solutions. You touched on this just a little bit before, but how can we help ensure that patients receive an early and accurate diagnosis?

Dr. Mulherin:
That is a big challenge. I mentioned earlier, it's not uncommon for patients to go for years without having a diagnosis made. Now obviously, those patients are not the ones who have flaer PNH who have a hemoglobin of three. It's more of a chronic fatigue, difficulties concentrating, things like that. Hemoglobin of between eight, nine, 10, that's probably pretty common when people are diagnosed. But again, these are younger people, they may not be going to the physician on a regular basis.

So anyone who has, in this right age group especially, who has otherwise unexplained non-hemolytic anemia, maybe with some others cytopenias, that needs to be investigated and PNH ruled out. And there are very easy tests to do that. The current flow cytometric metrics are extremely accurate at making the diagnosis. The key is that the physician has to think about that it's a rare condition. Many of these patients are not going to present to a hematologist, they're going to present to their primary care physician. And so that's in common on other people earlier than a medical chain in the medical ecosystem before they get to us to recognize that there's something wrong, there's something that doesn't make sense, and that they have to pass it, and then they have to refer on from there.

I think having patients being diagnosed in the hospital because they're presenting with a PE or something, yes, that can happen. But that doesn't happen as often. It's more of these kinds of chronic fatigue problems, concentrating and the brain fog, those kinds of things that most patients are additionally presenting with. They may actually have some of the other symptoms, the paroxysms. So free hemoglobin is a potent scavenger of nitric oxide, so that can lead to smooth muscle dysfunction, which can cause the abdominal pain, it

can cause dysphasia, in men it can cause erectile dysfunction, but lots of things can cause all those things.

So I think it's just if someone has things that cannot be explained, that needs to be investigated, especially that triad that I mentioned earlier.

Dr. Turck:
And what are some strategies for managing patients and improving outcomes?

Dr. Mulherin:
So one is looking at compliance/adherence. So patients have to understand when they start this, this is a therapy that they're going to be on essentially indefinitely. These are complement inhibitors that patients are starting on, it is not changing the underlying genetic defects; the mutation in the PIG-A gene, which leads to loss of the GPI anchors, so patients don't have CD55 and CD59 in red cell surfaces, leaving them susceptible to complement-induced lysis, that process is still ongoing. So it's still there.

If patients stop therapy for whatever reason because they don't want to do it, because there's an insurance issue, and so the drug isn't available, they can, I don't want to say relapse, but you can have recurrent hemolysis. You can call it breakthrough hemolysis if you want. So if someone has an attack of breakthrough hemolysis, it's important to figure out why. Is it because they did not take their drug? Is it because more commonly if they're actually taking the drug as scheduled or able to take the drug as scheduled, it's usually because of a complement-amplifying condition. So when someone has a heightened inflammatory activity, so this could be acute illness, infection, trauma, pregnancy, COVID-19 as well. So yes, they need support from the complement inhibitor perspective, they may need transfusions as well, but you have to fix the underlying problem. So when someone truly has breakthrough hemolysis, we need to figure out what that is and try and treat it. If it's an infection, treat the infection, for example. And you're going to have much better outcomes and how to get patients through that acute episode much better if you could do that.

Dr. Turck:
And as we end our discussion today, Dr. Mulherin, are there any closing thoughts you'd like to add?

Dr. Mulherin:
This is a rare disease. This is considered an ultra-rare disease. There's only a few thousand cases in the United States, maybe 400-500 new cases per year. But there are a lot of effective treatment options available, and there are many, many more, which are on the way. There's a lot of drug development, a lot of exciting things that are happening, including some oral therapies that are in development. So there's a lot of hope for patients, a lot of hope that yes, while we cannot cure the underlying genetic defect, we are hoping that we can leave these people, many of whom are younger, they're early middle age, that they can still have as good a quality of life and have as good a functional status as they possibly can.

Dr. Turck:
Well, as those final insights bring us to the end of today's program, I want to thank my guest, Dr. Brian Mulherin, for joining me to discuss how we can address unmet needs in the healthcare journey of patients with PNH. Dr. Mulherin, it was a pleasure speaking with you today.

Dr. Mulherin:
Thank you very much for having me.

Announcer:
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