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Understanding the Role of the Alternate Complement Pathway in PNH

Announcer:
You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome *to Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss the role of the alternative complement pathway in paroxysmal nocturnal hemoglobinuria, or PNH for short, is Dr. Catherine Broome, who's an Associate Professor in the Department of Medicine at the Georgetown Lombardi Comprehensive Cancer Center. Dr. Broome, thank you so much for being here today.

Dr. Broome:
Thank you for having me.

Dr. Caudle:
We're excited that you're here. So to start us off, Dr. Broome, can you give us a brief background on the pathophysiology of PNH and its clinical presentations?

Dr. Broome:
Sure. So PNH is a relatively rare, acquired disorder, in which the stem cells become abnormally mutated and no longer produce a very important protein, which is the PIG-A protein. That protein is an anchoring protein that allows appropriate anchoring of glycoproteins, such as CD55 and CD59 to the surface of red blood cells. CD59 and CD55 are incredibly important at controlling complement activation. And if they are lacking on the surface of those red blood cells, complement activation will occur and the generation of the membrane attack complex will occur. And this will cause intravascular hemolysis, or basically, a rupture of the red blood cell within the intravascular space. As you might imagine, this kind of brisk intravascular hemolysis can cause quite a number of symptoms for patients. So PNH patients have anemia; they are significantly fatigued. And one thing that's quite unique about this disease is that the process by which these cells are destroyed through complement activation also significantly increases the patient's risk for developing thrombosis and intraabdominal, or Budd-Chiari syndrome, where there is thrombosis of mesenteric and our portal veins. These patients can also develop arterial thrombi; they can have a myocardial infarction; they can develop cerebrovascular accidents; they can develop pulmonary emboli and DVT.

Dr. Caudle:
Now if we focus in on the complement system, how does it normally function? And how is it different in patients with PNH?

Dr. Broome:
So the complement system is there in order to aid our natural immune system. It is an aid to help get rid of foreign invaders like bacteria or fungi. It's also there to aid our body and our immune system in getting rid of old or dead and dying tissues or cells through sort of a clearance mechanism. And because it needs to be ready, to be available to our immune system at a moment's notice, the alternative pathway in particular is sitting at the ready, kind of as your car would be parked in your driveway in a neutral position with the engine running just waiting for you to jump in and start it and go about your day. The alternative pathway is sitting there. The engine's running at a very low level and it's ready to jump in. And for most of us, this is not a problem. But for patients who have developed PNH, the problem is that the alternative pathway is generating complement components, which are binding to the surface of those red blood cells and without the control proteins, CD55 and CD59, attached to those red blood cells, that complement becomes activated. And it ultimately is going to generate the membrane attack complex, which is going to lyse or poke holes in the membrane of those red blood

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cells and cause intravascular hemolysis. In PNH, what happens then is that that intravascular hemolysis is generating red blood cell particles that then need to be cleared from the system. The body thinks, 'Oh my, I need to activate my complement system even further because I've got all this extra work to do.' Additional activation of the alternative pathway really just continues to drive this process in a very uncontrolled fashion.

Dr. Caudle:
And what can you tell us about the impaired regulation of the alternative pathway upstream in the complement cascade?

Dr. Broome:
So I don't know that it's actually impaired. But what we do know is that there are a variety of places upstream that we can interact with. We have been inhibiting the terminal portion of the complement pathway; we've been inhibiting the ability to generate that membrane attack complex. As we do so, as you might imagine, you block the very end of a pathway, those components that are proximal to where you're blocking are going to build up. And so in some patients with PNH, the buildup of these proximal components of this pathway allow for additional deposition on the surface of the red blood cells, proximal components, like C3b. And C3b is not a component that is going to cause lysis of the red blood cell, like the membrane attack complex does. But it is a very powerful opsonin. And our immune system is going to recognize cells that are tagged with this complement component as cells that need to be removed from the circulation. So even if these cells are surviving, they're not being lysed by the membrane attack complex; they're now being recognized by components of the monocyte-macrophage system as being tagged by the C3b for needing to be removed.

And so in PNH, we're noticing that while the therapies that we have been employing for our patients are very effective in stopping the lysis of the red blood cells, there may be other issues upstream in this alternative pathway that continue to provide a source of problems, a source of extravascular hemolysis, continued anemia, continued fatigue, and other issues for those patients.

Dr. Caudle:
I'd like to thank my guest, Dr. Catherine Broome, for providing insights on the alternative complement pathway. Dr. Broome, it was great having you on the program.

Dr. Broome:
Thank you. It was wonderful to be here.

Announcer:
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