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Managing Chronic Graft-Versus-Host Disease with CSF1R Inhibition

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 potential of CSF1R inhibition in managing chronic graft-versus-host disease, or cGVHD for short, is Dr. Andrew Harris. He's a pediatric hematologist/oncologist and bone marrow transplant specialist at Memorial Sloan Kettering Cancer Center in New York City, as well as the Director for the MSK Kids Multidisciplinary GVHD Clinic.

Dr. Harris, it's great to have you here today.

Dr. Harris:
Thanks. It's a pleasure being here.

Dr. Caudle:
Of course. So, to start, could you tell us how conventional immunosuppressants work in cGVHD and why they've fallen short in producing durable responses?

Dr. Harris:
Sure. So, when we talk about conventional immunosuppressants, typically we're talking about steroids or corticosteroids, to be specific. These are anti-inflammatory drugs that, when given at higher doses, can also kill lymphocytes, which are thought to be some of the immune effector cells that are part of the driver for chronic graft-versus-host disease.

Now, chronic graft-versus-host disease is a very immunologically complex disease process, where the immune cells that are given as part of that bone marrow transplant attack the tissues of the recipient of the transplant. And we see this typically later after transplant, and then there's an earlier form called acute graft-versus-host disease.

Now, chronic graft-versus-host disease involves a lot of different immune effector cells; it involves lymphocytes, it involves monocytes and macrophages, and it involves natural killer cells. So, it involves a lot of different portions of the immune system. We don't fully understand why some patients respond well to steroids and others do not. There are a few different theories about this. Some feel that there may be distinct, different biologic processes that are all falling under this catch-all term called chronic graft-versus-host disease, and others think that because of all these different cells that are involved, some may be more driven by the lymphocytes and may respond better to steroids, while as others may now be more driven by macrophages and may need other agents as well.

So we don't have a great grasp on the full biology of this and why some patients respond well and others do not. But for patients that do respond, one of the challenges that we have is that one of the hallmarks of chronic graft-versus-host disease is fibrosis, so even after the immune attack on these tissues stops, sometimes there is long-standing fibrosis and scarring for these patients that takes years to remodel, and in some patients, it does not completely reverse.

Dr. Caudle:
With that in mind, what makes the CSF1/CSF1R access such a critical driver in the pathogenesis of chronic graft-versus-host disease?

Dr. Harris:
So the CSF1/CSF1R access, or CSF1-receptor access, really is an interplay between monocytes and macrophages that polarizes the macrophages to an M2 phenotype, also known as an alternatively activated macrophage phenotype. These macrophages are known to

cause chronic inflammation and tissue damage, and this also leads to dysregulated tissue healing and ultimately, to the fibrosis that we see, which is a hallmark of chronic graft-versus-host disease.

So, if we can impact this CSF1/CSF1-receptor access and disrupt it, we may be able to keep these macrophages from causing this fibrosis that leads to scarring and reduction of mobility, to progressive emphysema in our patients in their lungs when it affects the lungs, and a lot of other disease symptoms that really significantly impaired patient quality of life and lead to a lot of symptom burden for them.

Dr. Caudle:
Thank you. For those of you who are just tuning in, this is *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Andrew Harris about the evolving role of CSF1R inhibition in chronic graft-versus-host disease management.

So, Dr. Harris, let's shift gears and talk about axatilimab, which targets CSF1R-dependent macrophages. What's the significance of this mechanism of action in the chronic graft-versus-host disease treatment landscape?

Dr. Harris:
So axatilimab is one of the most recently approved medications for the treatment of chronic graft-versus-host disease. The current FDA indication is as third-line therapy for patients that have failed two prior lines of therapy and that weigh more than 40 kilograms in weight. So, this is the first time, for which I'm aware, that the FDA has given an indication for an agent not based on age, but based on minimum weight. So, this opens up the doors for some of my larger pediatric patients where many of the other agents are only approved down to 12 years of age.

One of the things that's very exciting about axatilimab is it is our only drug that targets the CSF1 receptor-dependent macrophage that's responsible for a lot of the fibrosis in our patients. So if we can disrupt those macrophages and deplete those macrophages, we may be able to not only stop the fibrosis that happens as part of chronic graft-versus-host disease, but we may even be able to facilitate reversal of some of that fibrosis. This is extremely important for our patients because the fibrosis is what leads to a lot of their symptoms and a lot of the impairment on their quality of life. If you're not able to fully move your arms at the shoulders or you're not able to close your hands and make a tight fist, that can significantly impair your ability to do your daily functions and things that make you happy on top of that. So, if we're able to disrupt this by depleting these macrophages, it certainly makes for a reason to have hope for our patients that we have this completely new tool that targets a new pathway that is identified in chronic graft-versus-host disease.

Dr. Caudle:
So, as a follow-up to that, what types of clinical responses are we seeing from CSF1R inhibition, particularly with axatilimab?

Dr. Harris:
There's been a few papers that have come out with clinical trials that led to the FDA approval for axatilimab, and so I'm going to really reference a lot of that data in this discussion. I have had a handful of patients myself that are treated with axatilimab, but pulling on the larger experience that's been published, I think, is most worthwhile.

So we have seen responses in all of the different target organs of chronic graft-versus-host disease. So this involves the eyes, the mouth, the skin, the GI tract, the lungs, and the liver as the primary targets, as well as the genitourinary tract, which can be affected as well. And when we look at the responses, there have been responses in all these different organs to patients that have been treated with axatilimab in these studies. And some have had complete responses, but more often than not, we see partial responses, again, in part because of this fibrosis that can take a long time to remodel.

More importantly, one of the things that was reported in these studies was that despite there being only partial objective responses, there was significant symptom improvement for our patients, which means that they're having a drastic improvement in their quality of life.

And so this and one of our other newly approved agents, belumosudil, both have shown that there was significant improvement in quality of life and reduction in symptoms, even though the overt responses that we were seeing on the things that we can test and the things that we can examine were not as robust as the patient's improvements in their symptoms. So this is a really big deal and it gives us reason to keep on giving our patients hope that we have additional tools that can help them with continued improvement in their disease.

Dr. Caudle:
And taking a bird's eye view, how do you think this approach may change the way we define treatment response?

Dr. Harris:
So this is a big challenge in these clinical trials: meeting this objective response. So this symptom response, quality of life response, and

fibrotic score response that we've been seeing in these clinical trials, I think, really is making us rethink some of the most important endpoints for these trials, knowing that this fibrosis may take months to years to reverse. Having these shorter-term improvements, symptom improvements in quality of life, reduction in fibrosis, and increases in mobility are all things that we can think of as meaningful outcomes because chronic graft-versus-host disease is a longstanding disease. And if we can improve the quality of life of our patients, I think it's a very meaningful outcome. And so, this is something that's probably going to be incorporated into all future clinical trials for chronic graft-versus-host disease.

Dr. Caudle:
And in the last few moments of our program, Dr. Harris, do you have any closing thoughts you'd like to leave with our audience?

Dr. Harris:
So chronic graft-versus-host disease is a really complex process. It's probably best managed primarily through transplant specialists, especially those that have a particular interest in chronic graft-versus-host disease. Having said that, we do rely on consultation from a lot of our sub-specialists in the areas where we know this disease can impact our patients. We work with dermatologists and pulmonologists, so care is often multidisciplinary for these patients. This can lead to a lot of time spent traveling to and from the hospital and time in the hospital. And one of the reasons that I developed this multidisciplinary clinic that we have for our children at Memorial Sloan Kettering is to bring all the sub-specialists to the patients instead of sending the patient out multiple times to different sub-specialists. I'm hoping that more centers are going to be able to adapt this approach to improve quality of life for our patients by reducing fatigue from the travel to and from visits.

Dr. Caudle:
Thank you. As those important insights bring us to the end of today's program, I'd like to thank my guest, Dr. Andrew Harris, for joining me to discuss how CSF1R inhibition is reshaping treatment in chronic graft-versus-host disease.

Dr. Harris, it was great having you on the program.

Dr. Harris:
It was a pleasure being here. Thank you for the invitation.

Dr. Caudle:
Thank you.

Announcer:
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