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Strategic Sequencing in Steroid-Refractory Chronic GVHD: Adapting to a New Landscape

Announcer:
This is *Project Oncology* on ReachMD. And now, 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 treatment landscape for steroid-refractory chronic graft-versus-host disease, or GVHD for short, is Dr. Doris Ponce. She's the Director of the GVHD Program and Co-Chair of the Center for Hematologic Malignancies Translational Research Council at the Memorial Sloan Kettering Cancer Center in New York City. Dr. Ponce, it's great to have you with us today.

Dr. Ponce:
Thank you so much, and I am excited to be here and be talking about graft-versus-host disease and about some exciting updates that we have in terms of our treatment options for our patients.

Dr. Caudle:
Thank you. And so let's just jump right in, Dr. Ponce. Could you tell us a bit about the treatments that are available for steroid-refractory chronic GVHD and how their mechanisms differ?

Dr. Ponce:
Yes, thank you for that question. So right now, it's an exciting time to talk about this because 10 years ago, we didn't have much to talk about, but now, we have an approval of four medications for the treatment of chronic graft-versus-host disease: ibrutinib, belumosudil, ruxolitinib, and axatilimab. And I put them in this order as they've been FDA approved.

So let's talk about the first one and talk a little bit about the mechanism of action. Ibrutinib has a very particular mechanism of action where it inhibits the BTK, or Bruton's tyrosine kinase, receptor in B cells and also interleukin-2-inducible T cell kinase. And with that, we see that the effect is that ibrutinib can decrease cell survival proliferation and autoantibody production that has been implicated in graft-versus-host disease.

The second medication I want to talk about is belumosudil. Belumosudil is a ROCK2 inhibitor. And with that, it does cause downregulation on a proinflammatory response. And the effect that we see is decrease in cytokine production. There are inflammatory cytokines. We also see decrease in proliferation, especially in these T helper cells and Th17 cells in general. And there is an upregulation of T-reg associated with belumosudil. Belumosudil has been reported as a dual effect as anti-inflammatory and also anti-fibrotic.

Then the other medication that we have approved is ruxolitinib. This medication is a JAK1/JAK2 inhibitor. And with that effect, it downregulates the proinflammatory JAK-STAT pathway. And with that effect, we also see cytokine production decrease, decrease in proliferation in Th17 cells in general, and upregulation of T-regs.

And the last one is axatilimab. So axatilimab is an antibody that targets the CSF-1 receptor. And with that mechanism of action, it does regulate the expansion and infiltration of macrophages that are the one that champions fibrosis. So it's believed that the axatilimab mechanism of action really targets the key role in fibrotic disease in graft-versus-host disease.

Dr. Caudle:
And to expand on what you talked about, what do we know about the efficacy and safety of each approach?

Dr. Ponce:
So what we know from ibrutinib is that the medication does have some adverse events associated with it. And the most common ones are fatigue, diarrhea, various muscle cramping, and there's also some increased risk of upper respiratory infection and pneumonia. An additional less common but real adverse event with ibrutinib is cardiac arrhythmia and increased risk of bleeding.

In terms of belumosudil, the treatment is being well tolerated. The main side effects patients have are fatigue and headaches; some of them can have GI symptoms like abdominal discomfort or diarrhea, and there is some increase in pneumonia.

The side effects described with ruxolitinib are mainly cytopenia, common anemia and neutropenia, and a risk of infection, including pneumonia. We have seen some viral reactivation as well.

And then with the last drug axatilimab, which is the most recent one, we saw that the dose that was approved by the FDA, which is the lowest dose, was the one that was associated with less of the adverse events, which is great. But the most common one described even for this dose, was liver enzyme abnormalities. So something to monitor for these patients. Also amylase increase. There is an increased risk of headaches. And something very unique was periorbital edema, though it was observed, again, less in these patients taking the lower dose but were still reported.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Doris Ponce about therapeutic options and sequencing for steroid-refractory chronic graft-versus-host disease, or GVHD.

So, Dr. Ponce, if we switch gears now and focus on treatment sequencing, how might patient-specific factors like organ involvement, disease severity, and prior therapy response influence decision-making?

Dr. Ponce:
We follow the FDA guidelines in terms of the medications that had been approved for a certain line of therapy. So, for example, the treatment that we have after failure to steroids—so it would be considered second line or immediate second line—as of right now are ibrutinib and ruxolitinib, whereas belumosudil and axatilimab are approved after failure of another line of therapy, so it would be next after the ibrutinib or ruxolitinib line. Saying that, as of this point, we don't customize treatment. Let's say you have skin or ocular involvement, should I pick a different drug for you? As of right now, we don't do that. We take into account a patient's comorbidities, a patient's ability to take treatment, and where they are in their treatment paradigm—if they are experiencing failure to steroids, if they're starting treatment, or if they have received other lines of therapy before. For example, if somebody has significant diarrhea and cardiac issues, you'd try to avoid ibrutinib. If you have preexisting cytopenias that are severe, you will consider avoiding ruxolitinib if possible. If you have very high liver function test, you want to might to avoid belumosudil and axatilimab. On the other hand, if our patient has history of myelofibrosis or JAK2-driven disease, ruxolitinib could be a consideration and is actually preferred for those patients. And if you have a prior B-cell malignancy, ibrutinib will be preferred over others. And then we take other issues into account, like logistics. Can the patient come and get treatment? Do they need to come to the center? Is it an IV medication? Is it oral? Which now comes into play with the approval of axatilimab, which comes as an IV formulation.

Dr. Caudle:
Excellent. And what are some best practices for communicating with patients about their treatment sequencing?

Dr. Ponce:
What we do in our practice is that we do an overall view about what graft-versus-host disease is and what our goals are. So some of these patients come into this moment of the diagnosis of chronic graft-versus-host disease after experiencing acute graft-versus-host disease, for example; it's not uncommon in that situation. And it is important to provide education and explain that chronic graft-versus-host disease has a lengthy period of time for treatment as well as for treatment response. So in acute, if they respond after 3 to 5 days of starting treatment, the expectation in chronic will be the same. So we usually provide teaching that the time it takes to start feeling better or having benefit can be longer, so they don't get disappointed or frustrated at the start of treatment.

It's also important to emphasize some of the side effects that they could experience with treatment. So that's explained to the patient. And what do we expect? What are our goals in treatment? So I usually explain to them that initially, our first goal is to stop the progression of symptoms. And then our second goal is improvement.

I also explain to my patients that many of these drugs are associated with a treatment response being partial, which means that the symptoms don't completely go away in the majority of the cases. So that also help us to create expectations for them in what they will see with treatment. So yes, it will get noticeably better, but you still may have some residual symptoms of your chronic graft-versus-host

disease.

We also emphasize treatment compliance; that is important. And we alert them to provide updates if they have any side effects, and some of them are things that we could try to improve if they have side effects. Let's say they have diarrhea; you can provide like anti-motility agent, for example.

Dr. Caudle:
And as we wrap up our program, Dr. Ponce, are there any final thoughts you'd like to share with our audience?

Dr. Ponce:
I think my take-home message is that when we look into patients with this diagnosis, look at them as a whole and try to provide support that ultimately will bring them not only response, but improvement in quality of life and insert the patients back to the community where they could feel supported as well.

Dr. Caudle:
With those key takeaways in mind, I'd like to thank my guest, Dr. Doris Ponce, for joining me to discuss treatment sequencing strategies for steroid-refractory chronic graft-versus-host disease. Dr. Ponce, thank you so much for joining us.

Dr. Ponce:
Thank you so much.

Announcer:
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