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Chronic GVHD Care: Identifying and Addressing Unmet Needs

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss unmet needs in the management of chronic graft-versus-host disease, or GVHD, 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, Dr. Turck, and thank you to the ReachMD community for having me. I appreciate the kind invitation and am looking forward to our conversation.

Dr. Turck:
Well, let's start by focusing on the challenges posed by fibrosis. Would you tell us about its role in chronic GVHD progression?

Dr. Ponce:
Yes, and thank you for that question. So as we know, graft-versus-host disease is a complex disease, and fibrosis is one of the consequences of the graft-versus-host disease process. So a patient can go into different phases through their development of chronic graft-versus-host disease: early inflammation, tissue injury, then followed by chronic inflammation and a dysregulated immunity, and then unfortunately, the phase of fibrosis and improper tissue repair, which can be associated with some of the long-term consequences of graft-versus-host disease that can limit patient mobility and cause other limitations as well.

Dr. Turck:
And as a follow-up to that, how can fibrosis impact a patient's quality of life, both in the short and long term?

Dr. Ponce:
Right. So as you can imagine, having fibrosis can impact your quality of life from beginning to end during the day. In the short term, your routine daily activities can be limited. For example, you want to tie your shoes, you want to shave, or you want to brush your hair, and those mobilities you do, arms and legs, can be impacted, even getting out of a chair or walking around. So as you can imagine, a patient having limitation with their range of motion can be quite impactful. We can also have fibrosis affecting the lungs, so we can also add that layer of complication with shortness of breath and general respiratory symptoms that can limit your activity even more.

In the long term, what we see is that many of these patients will have fibrosis in the long term where it hasn't been reversed, despite being on therapy. And that's another area where not only the physical limitation takes part, but also psychologically, it could be quite challenging for a patient to adapt to this new reality where they are cured from their cancer, but now you're dealing with limitations in range of motion, shortness of breath in a more permanent, long-term situation. So adaptability into ourselves, and there are things that can improve mobility—devices or having a strong social support—I think you can help that patient navigate this journey, and hopefully with newer drugs, we might be able to help in the long-term issue of having fibrosis.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking to Dr. Doris Ponce about the unmet needs and often overlooked aspects of the management of chronic graft-versus-host disease, or GVHD.

Now if we switch gears a bit and focus on treating chronic GVHD, Dr. Ponce, what are the limitations of current therapies?

Dr. Ponce:

So some of the limitations with current therapy is that we have newer drugs that are developed for the treatment of graft-versus-host disease. But these drugs, first of all, are approved for second or beyond line therapy, which means that upfront treatment remains steroids. And steroids have many, many side effects. So most of our patients will be exposed to systemic corticosteroids with all their side effects.

Then, another limitation is that with the new drugs that we now have in our armamentarium for the treatment of graft-versus-host disease, we see that each one has a particular mechanism of action. And I'll say with one of the drugs, it will contribute more into the B-dependent process and the other into the T-dependent process. So they don't necessarily overlap with their mechanism of action, which can mean that maybe one drug, while it could contribute to the improvement of graft-versus-host disease, it's not really tackling the entire process that is causing graft-versus-host disease. So I think a limitation is that we have multiple processes happening, and we have a drug that is tackling one particular pathway or one mechanism of action.

And the other thing is that as this disease is so complex and we consider treatment at a certain time and then we could go to different treatments and so on, being exposed to multiple lines of therapy, we're also looking into the long-term side effects of medications or the immediate side effects that patients will experience with all these medicines, as well as the financial burden of taking all these medicines. And psychologically as well; patients that were picturing being cancer free and without any treatment are now in this big burden where your immunity is not great. So with all the additional immune suppression that we're using, physically, they're not feeling well.

Dr. Turck:
Now zeroing in specifically on T-cell and B cell-directed therapies, why else do some patients fail to achieve optimal outcomes? And are there any emerging treatments that might address some of the shortfalls associated with existing treatments?

Dr. Ponce:
Right. So as we mentioned, we have different drugs approved with a particular mechanism of action, and it is possible that after failure to steroids and then taking one of these drugs, one particular process that a drug is addressing might not be the sole mechanism that is involved in the process of graft-versus-host disease. So part of the limitation is how do we address or how do we treat a patient if, let's say, the patient had multiple processes happening at the same time that are contributing to their graft-versus-host disease?

Another thing that we face as an enormous challenge is the ultimate tissue repair and fibrosis that the patient experienced after chronic inflammation and dysregulated immunity. And it's particularly challenging because the reversibility of fibrosis is limited. Therefore, and as we see in our patients, a majority of the patients achieve a treatment response that is only partial and not complete; what that means is that a patient gets better, they have a partial response, but they're still symptomatic, so they still have the affection, it's just better. So even though you could improve in some way, you're still going to have symptoms. And that's a big limitation in how a patient would like to feel after starting treatment.

And so then we have another drug added to the armamentarium for the treatment of graft-versus-host disease, which is axatilimab, that I think is important to highlight because this drug has an antifibrotic pathway mechanism. Is an anti-CSF1R drug. So it's a new treatment class, and it was specifically developed to tackle the pathway of fibrosis that is activated by macrophages. And in the clinical trial that led to the approval of the drug, they observed improvement in patients with advanced graft-versus-host disease. So I think it's important to highlight that we have a new class drug, and maybe it could help with those limitations of achieving reversibility of fibrosis that we see very often in GVHD.

Dr. Turck:
Now just to bring this all together before we close, Dr. Ponce, what else can we do to help address the unmet needs we discussed today? And what kind of impact can that have on our patients with chronic GVHD?

Dr. Ponce:
So patients with chronic graft-versus-host disease, again, they have a complex disease with multiple pathways and mechanisms involved that can cause injury and organ affection. So some of the limitations we can address in the future is how can we customize treatment? We have patients that might have a more aggressive pattern than others, or we have patients with certain organs involved that are different than others. So should we treat the patient differently? Should we customize therapy? Should we combine treatment with complementary mechanism of action? That is still a research question we will need to study to see if those approaches will be valid. But I think it could address some of the unmet needs of complementary pathways addressing fibrosis with decrease in inflammation if we combine treatment, etc.

Another thing that we need to remember is that patients should be treated as a whole in terms of, yes, we are addressing graft-versus-host disease, but they can also have other clinical needs. For example, how can we improve their mobility? Do they have a proper

physiatrist? Do they have a proper physical therapist? How can we improve their nutrition? Do they have issues with oral changes, oral affection, taste disturbances, and how can we address that? So that's another thing: think of patient as a whole. Bone health, do they need any anti-affective treatment during the course of graft-versus-host disease treatment, for example. So we just have to remember that while graft-versus-host disease has a new armamentarium of drugs, we also need to consider the patient as a whole where we will address other issues to improve their overall quality of life, which is quite relevant. And nonetheless, we also involve our social workers, psychiatrists, and psychologists because our patients can be going through many, many challenges in the process of the treatment of graft-versus-host disease with affection of their quality of life. So each one of the team members are quite helpful to help the patient navigate their journey.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Doris Ponce, for joining me to share how we can address unmet needs in chronic graft-versus-host disease care. Dr. Ponce, it was great having you on the program.

Dr. Ponce:
Thank you, Dr. Turck. I appreciate all the questions and the opportunity to be here, and thanks to the ReachMD community as well. Thank you.

Dr. Turck:
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