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Optimizing cGVHD Treatment Decisions in the Second- and Third-Line Settings

**Dr. Turck:**
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss second- and third-line treatment decisions for chronic graft-versus-host-disease, or chronic GVHD for short, is Ms. Stephanie Gregory. She serves as lead nurse practitioner at the Blood and Marrow Transplant Program at Northside Hospital Cancer Institute in Atlanta, Georgia. Ms. Gregory, thanks for being here today.

**Dr. Gregory:**
Thanks for having me.

**Dr. Turck:**
Well, to set the stage for us, how do you currently think about sequencing therapy in chronic graft-versus-host disease once patients move beyond first-line treatment?

**Dr. Gregory:**
There is, as of yet, still no standard approach in how we sequence therapies. And there's a lot of research that still needs to be done in that aspect. Without strong guidelines that are giving approaches with head-to-head comparisons, then steroid-refractory chronic graft-versus-host-disease therapy is often just chosen based on the provider experience and patient-specific factors. Most clinicians do not wait until that definition of steroid refractoriness that you see in clinical trials before we move on to second-line therapy.

And I can say that's reflected in my own program as well. The idea behind that being that we're optimizing that initial response we're getting from steroids but also getting them tapered off steroids as quickly as possible to avoid the toxicities that we're all very familiar with that are associated with long-term steroid use. So we're really being more proactive rather than reactive in our management.

Another difficult question that we really haven't answered yet in clinical trials is whether or not it's best to really sequence these agents or to layer them. Even in my own program, we have some providers who very much prefer to sequence therapy, one at a time, and then we have some providers who layer therapies. And these are questions that are still unanswered. How do we balance that short-term control of disease but also preserve future treatment options? But also recognizing that the further down the lines of therapy we go, we know in the treatment of chronic graft-versus-host-disease, we see less effectiveness with shorter duration of response.

**Dr. Turck:**
Now, we often see repeated use of T- and B-cell targeted therapies early on, but what are the potential limitations of that approach as patients move on to later lines of treatment?

**Dr. Gregory:**
I think we can summarize those potentials with basically two primary limitations. First, the risks of repeated and/or layered use of agents like steroids, like antithymocyte globulin and rituximab, to patients is twofold. One, it can lead to prolonged immune deficiency. We see B-cell aplasias, and we see recurrent infections like pneumonia or CMV viremia. And an even bigger concern of that is loss of graft versus leukemia effect, which we correlate with risk of relapse.

On the flip side of that, repeated targeting of the same pathways can lead to diminishing clinical benefit, like steroid refractoriness or diminished response to steroids. So overlapping mechanisms can limit that downstream efficacy, which makes us worry about the development of resistance or the loss of that durable response that we achieve.

**Dr. Turck:**

And are there any special considerations about the role of mechanism of action when planning treatment beyond the second line, and how do you decide when it's time to move to a therapy with a different mechanism of action?

**Dr. Gregory:**
I think that diversifying the mechanism of action across lines of therapies can be very helpful. Beyond second line, especially, that mechanism of action is critical—moving to more targeted agents rather than more broad-spectrum agents with specific pathways, like ROCK inhibition or CSF-1R pathways, and thinking about predominant organ involvement and how we want to target those. Although, I tend to think that we really should be looking at changing based on mechanism of action and not necessarily the organ that's involved. And the reason I feel that is because I don't believe that, as of yet, we have clinical trial evidence that these agents are really organ specific, but more that they each have unique pathways.

Nevertheless, many providers feel certain agents have use for multi-organ disease, whereas others feel they have more benefit for sclerotic manifestations, like belumosudil, for example, lung or liver involvement with axatilimab, or even skin or mucosal involvement in the use of extracorporeal photopheresis, or ECP.

When it comes to deciding when to change therapy, I think we should really be basing this more on the clinical response rather than histologic response, so patient-reported improvement. And consider switching if the patient is steroid refractory, like there's evidence of clear progression of symptoms or if they exhibit persistent partial response but no further response after that. Or if there's toxicity to the therapy that they're receiving, like thrombocytopenia, recurrent infections, bleeding, or cardiovascular toxicities.

**Dr. Turck:**
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Ms. Stephanie Gregory about second- to third-line therapy for chronic graft-versus-host-disease, or chronic GVHD.

So, Ms. Gregory, let's take a closer look at how therapeutic decision-making plays out in practice. Looking specifically at partial response, if a patient is showing some improvement but not a complete response, what factors influence whether you stay with that therapy or adjust your approach?

**Dr. Gregory:**
Sure, this one's a tough call. We know we have a limited number of options for chronic graft-versus-host-disease treatment. We also know that the further down the lines of therapy we go, the less effective they are in achieving response and in maintaining that response.

So the decision really is balancing the rate of improvement with minimal side effects and steroids that are hopefully tapering successfully. So if that patient is showing steady, gradual improvement with minimal side effects and you are able to taper those steroids quickly, then I would recommend staying the course. If improvement has plateaued, steroids can't be safely tapered without a flare of GVHD symptoms, or there are significant complications or toxicities related to the therapy, whether that's steroids or whatever agent you're trialing, then a shift is needed.

Keeping in mind that we want to give the therapy adequate time to demonstrate a response—so minimum of eight weeks, sometimes longer. Of course, the major caveat to giving it adequate time is if we have vital organs that are involved by this chronic graft-versus-host-disease like the liver or the lungs, in those situations, you might need a more aggressive or faster approach to changing therapy.

And then always take quality of life into consideration, even if that patient is technically improved. If they have persistent symptoms that are still affecting their functional status, then you may need to consider making a change to see if you can further improve their quality of life.

**Dr. Turck:**
And I was wondering if you could tell us a little bit more about how in challenging scenarios, like fibrotic or steroid-refractory chronic GVHD, a mechanism of action guides your therapy selection there?

**Dr. Gregory:**
Yeah, sure. So I think this is where the "art of medicine" and the importance of tailoring treatment to the individual really comes into play. In these situations that are typically very difficult with fibrosis or steroid refractoriness, selection of the therapy really shifts from broad immunosuppression to a more targeted agent approach, addressing specific pathways and specific mechanisms.

In diseases that seem more inflammatory in nature, you may choose inhibiting B-cell or T-cell activation, like with ruxolitinib, ibrutinib, or rituximab for example. But for those fibrotic or sclerotic features, then you're looking at more targeted pro-fibrotic signaling, like belumosudil, or macrophage activity, like axatilimab.

I think this question really also highlights the major areas of improvement that are needed in chronic graft-versus-host disease. A lot of

patients suffer from significant morbidity that is associated with severe chronic graft-versus-host-disease. They're on therapy for a really long time, and they experience a lot of toxicities related to graft-versus-host disease but also to the therapies that we are giving them. Even if they're responding to therapy, many only achieve a partial response. So we need more therapies that target alternative or downstream pathways. We need research into biomarkers or non-invasive tests that can help us identify chronic graft-versus-host-disease earlier in the process so we can optimize early therapy and hopefully halt or slow the progression to severe steroid-refractory and fibrotic disease.

**Dr. Turck:**
Before we wrap up our discussion, Ms. Gregory, let's take a look at the big picture. What are the key principles or best practices clinicians should keep in mind when sequencing second- to third-line therapies in chronic GVHD?

**Dr. Gregory:**
So I think first and foremost, because we still have such a long way to go when it comes to chronic graft-versus-host-disease, I think the key takeaway is prioritizing clinical trials when available—clinical trials that focus on how to sequence GVHD therapies, whether or not to combine therapies, and certainly looking at biomarkers or noninvasive tests to identify GVHD earlier.

I think also treating based on dominant clinical features, whether the process looks more inflammatory versus fibrotic, and avoid repeating reliance on the same immune pathways, so utilizing different mechanisms of action to get the best and most durable response.

And always take prior response and toxicities into consideration when choosing an agent. Of course, one needs to be mindful of the patient's comorbidities which may also contribute to selection of the next therapy. And the best way to achieve response while sparing steroids as much as possible should be considered.

**Dr. Turck:**
Helpful insights for us to think on as we come to the end of today's program. And I want to thank my guest, Ms. Stephanie Gregory, for joining me to talk about therapeutic sequencing in chronic graft-versus-host-disease. Ms. Gregory, it was great having you on the program.

**Dr. Gregory:**
Thank you very much for having me.

**Dr. Turck:**
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!