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Treating Steroid-Refractory Chronic GVHD: How to Transition to Second-Line Therapy

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss how we can modify treatment approaches for patients with steroid-refractory chronic graft versus host disease, or GVHD for short, are Drs. Ned Waller and George Chen.

Dr. Waller is the Director of the Regenerative Medicine Program at the Winship Cancer Institute of Emory University and a Professor in the Departments of Medicine, Pathology, Hematology, and Medical Oncology at Emory University School of Medicine in Atlanta. Dr. Waller, thanks for being here today.

Dr. Waller:
You're welcome.

Dr. Turck:
And Dr. Chen is an Associate Professor of Stem Cell Transplantation at the MD Anderson Cancer Center in Houston. Dr. Chen, it's great to have you with us.

Dr. Chen:
Thank you. Thank you for inviting me.

Dr. Turck:
Starting with some background, Dr. Waller, about how many patients with chronic GVHD are refractory to steroids?

Dr. Waller:
There are about 10,000 patients transplanted in the U.S. every year with an allogeneic stem cell product, and about half of them will develop some form of chronic GVHD. Among those patients, half will respond initially to steroids, but the fraction of patients with a durable response is only about a third.

Dr. Turck:
Well with that in mind, Dr. Chen, what are the signs that steroid refractory patients may exhibit?

Dr. Chen:
The steroid refractory is defined by the dose of steroids that the patient is using, and in the trials, it's usually been anywhere from 1 or more mg/kg per day of prednisone for 1 to 2 weeks with progressive disease or stable symptoms on 0.5 or more mg/kg per day of prednisone for 1 or 2 months. So unfortunately, that kind of approach is very retrospective, and the diagnosis of steroid refractory is delayed if you go by that. So another way to determine if the patient is steroid refractory is to determine if there's any progression in the signs or symptoms of chronic GVHD. So on physical exam, this could be range of motion in a joint, which becomes further restricted, or it could be more involvement of the total body surface area that is involved by the skin changes. It could be change in the texture of the skin, such as progressive thickening or becoming more leathery over time. And then it could be other symptoms that are associated with chronic graft versus host disease, like eye dryness or mouth pain that worsens.

Dr. Turck:
Now coming back to you, Dr. Waller, would you walk us through the NIH consensus criteria on when we should transition steroid

refractory patients to second-line therapy?

Dr. Waller:
Sure. So the NIH criteria were developed through a series of consensus conferences at the NIH organized by Steve Pavletic. They really map out patients' symptoms of chronic GVHD according to various target organs where GVHD can cause dryness, organ dysfunction, or contractures. And patients complain of a variety of different GVHD manifestations, particularly dry eyes, mouth sores, trouble swallowing, lung dysfunction, joint contractures, and these are used to define the overall severity of chronic GVHD as well as to map responses.

As Dr. Chen indicated, the initial therapy for chronic GVHD is a dose of steroids, which is pretty substantial. One mg/kg or 1.5 mg/kg is a dose that will long-term lead to significant side effects, like cushingoid features, diabetes, weight gain, and osteoporosis. So the goal for initial treatment of chronic GVHD is to establish some relief of the patient's symptoms, improvement in the thickening of the skin, lessening of mouth ulcers, improvement of dry eyes or joint contractures, and at the same time, initiate a plan to taper steroids so that we can avoid some of the long-term consequences. Tapering steroids is usually done over about a 6-month period, and there may be ups and downs of steroid dose during that period, but the long-term goal is to control the disease, remit the symptoms, and ultimately get patients off steroids.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and I'm speaking with doctors Ned Waller and George Chen about treatment approaches for patients with steroid-refractory chronic graft versus host disease, or GVHD.

So, Dr. Chen, if we look beyond the guidelines that Dr. Waller just talked about, what other strategies can we use to ensure a seamless transition to second-line therapy?

Dr. Chen:
You know, I think just being on top of the signs and symptoms of the patient and doing a consistent exam from visit to visit so that changes can be quickly noted and act upon is a very good strategy. And other strategies may include asking the patient to monitor him or herself. It's possible to give the patients a worksheet that can be used to monitor their own symptoms. So, for example, they could have a close friend or relative assess their range of motion over time, and in that way, they can get many serial measurements with which to track their progress or lack of progress on therapy. Other tools include measuring the symptomatic burden of their chronic graft versus host disease and tracking that over time. I think those are the main things that I would do to help patients and to help myself as a practitioner be on top of whether or not a patient is responding or not to chronic graft versus host disease.

Dr. Turck:
Now before we close, I'd like to hear some key takeaways from each of you on how we can better manage patients with steroid-refractory chronic GVHD. Dr. Waller, let's start with you.

Dr. Waller:
So I think the focus in managing patients is indeed the patient and the symptoms that are most bothersome to them. There's a certain amount of empiricism in GVHD therapy as to which drug might be most appropriate for which patients. The three FDA-approved drugs have different mechanisms of action. They all target tyrosine kinases, but different tyrosine kinases in the pathogenesis of GVHD. Ibrutinib targets B-cell signaling. Ruxolitinib targets T-cell activation through JAK kinases. And belumosudil targets the ROCK kinase, which allows cells to respond to cytokines. With patients who have a more inflammatory manifestation of chronic GVHD, they might get the best benefit from ruxolitinib, although patients with poor hematological reconstitution might have more toxicity. On the other hand, patients with a more sclerotic manifestation of graft versus host disease might benefit more from belumosudil or ibrutinib. And patients who have preexisting heart problems, particularly atrial fibrillation or bleeding problems, you might not want to use ibrutinib in that subgroup.

That being said, there's still a back and forth as to which drug will work best for any particular patient, and it has to be a conversation between the physician team and the patient as to how they're responding to any particular therapy.

Dr. Turck:
Thanks, Dr. Waller. And Dr. Chen, I'll give you the final word.

Dr. Chen:
I think the key is to carefully track the patients to see how they're doing because the response can be often very delayed to these second-line agents or even to the primary agents. And very often in the day-to-day management of the patients, it's not possible to really notice the changes that are happening, and it's only when one compares to a visit a week ago, many weeks ago, or many months ago and sees that the chronic graft versus host disease symptoms are progressing on the current therapy, that's when you realize that the

patient isn't responding and needs to change. So I would emphasize doing careful consistent exams, serially as often as possible.

Dr. Turck:
Thank you both for sharing those key takeaways. And as that brings us to the end of today's program, I want to thank my guests, Drs. Ned Waller and George Chen, for joining me to discuss modifying treatment for patients with steroid-refractory chronic graft versus host disease. Dr. Waller, Dr. Chen, it was great having you both on the program.

Dr. Waller:
It's been my pleasure.

Dr. Chen:
Thank you so much for having me.

Announcer:
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