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Breakthroughs and Innovations: Managing Complex Cases in Graft-versus-Host Disease

Announcer:
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Your host is Dr. Paul Doghramji.

Dr. Doghramji:
Acute graft versus host disease is a common complication of allogeneic hematopoietic stem cell transplantation, and is a major cause of morbidity and mortality. And while systemic corticosteroids are traditionally the first-line treatment for acute graft versus host disease, about half of patients are resistant to this kind of therapy. So, what other options are available for the treatment of steroid-refractory acute graft versus host disease? Welcome to CME on ReachMD. I'm Dr. Paul Doghramji, and joining me today are Drs. Doris Ponce and Corey Cutler. Dr. Ponce is an Associate Professor of Medicine at the Weill Cornell Medical College, and Associate Member at Memorial Sloan Kettering Cancer Center. Dr. Ponce, it's great to have you with us.

Dr. Ponce:
Thank you very much. Thank you for having me.

Dr. Doghramji:
And Dr. Corey Cutler is an Associate Professor of Medicine at Harvard Medical School, as well as the Medical Director of the Stem Cell Transplant Program at the Dana-Farber Cancer Institute. Thanks for being here today, Dr. Cutler.

Dr. Cutler:
My pleasure. Thanks very much.

Dr. Doghramji:
Let's begin by gaining a deeper understanding of graft versus host disease. Starting with you, Dr. Ponce, can you give us a brief overview of the disease?

Dr. Ponce:
Yes, of course. So, graft versus host disease remains a major cause of non-relapse mortality after allogeneic stem cell transplant, and graft versus host disease can be either acute or chronic. And, timing before Day 100 or after Day 100 does not really define if you could have acute or chronic – occurs in approximately 40-60% of our patients defied adequate prophylaxis. The principle target organs affected by acute graft versus host disease includes the skin, the liver and the GI tract. The severity of graft versus host disease is on a scale from 1 to 4. In chronic graft versus host disease, other organs can be affected, and the severity goes from mild, moderate, to severe. The staging and grading of acute graft versus host disease, and, a defined classification, the most commonly used has been

modified Glucksberg criteria, MAGIC criteria, IBMTR and more recently, the standard versus hybrid, by Minnesota risk score.

Dr. Doghramji:
And if we zero in on our patients living with graft versus host disease for just a moment, Dr. Ponce, can you share what you consider to be a challenging case scenario?

Dr. Ponce:
Treatment of graft versus host disease can be challenging, for example, patients who are intolerant of the corticosteroids, or those who are unable to keep on corticosteroids for a long period of time. uncontrolled diabetes or overweight patients who require higher doses of steroids. patients who might require an additional line of therapy, having cytopenia or having issues with clotting could limit their future line of therapy.

Dr. Doghramji:
Turning to you, now, Dr. Cutler, what are the goals of therapy, and is there a standard of care for the management of moderate to severe acute graft versus host disease?

Dr. Cutler:
So that's a good question. The main goal in therapy of acute graft versus host disease is obviously to turn off the alloimmune inflammatory process that's causing inflammation in the target organs, such as the skin, the GI tract and the liver. When we do that, we often use drugs like steroids, which lead to a number of long-term complications, as Dr. Ponce just described. And so, one of our goals in GVHD therapy is to minimize, or limit the rate of long-term complications, and in doing so, we try to maximize quality of life for patients who are suffering with acute graft versus host disease. Of course, at the end of the day, since GVHD can be a life-threatening, or life-ending process, the goal really is to improve overall survival. When we talk about treating acute graft versus host disease, for skin-limited disease, confined to less than 50% of the body's surface area – which we would call Stage 1 or Stage 2 skin, and overall Grade 1 skin GVHD – we sometimes can get away with topical corticosteroids alone, but if the skin involvement is extensive enough, then we do use systemic corticosteroids. The typical starting dose of systemic corticosteroids for skin-only disease, uh, generally has been considered to be 2 mg/kg of steroids, but many investigators choose to– use lower doses, as little as 1 mg/kg per day of corticosteroids. In addition, for patients with very limited GVHD, that require immune suppression, systemic sirolimus has now been shown, in a randomized trial, to be equally effective as steroids in this setting, for patients who have favorable risk based on biomarkers. When you get into higher degrees of skin involvement – so skin, stages three or four, or any degree of visceral involvement – that is, GI or hepatic involvement – then we need to use systemic corticosteroids, and we generally start at a dose of 2 mg/kg per day. Steroids are both our friend and our enemy. They are very potent anti-inflammatory agents, but in being so potent, they are often associated with toxicities and a higher risk of infection. So anything that we can do to limit exposure to corticosteroids is really, uh, one of our goals in GVHD therapy today.

Dr. Doghramji:
If you reflect on your own practice, Dr. Ponce, how do you define a treatment response for acute graft versus host disease?

Dr. Ponce:
That's a great question.One of the most critical time points as far as disease assessment is Day 28. And usually at that time, we assess if our patients responded or not, so our initial interventions, which typically on front-line treatment, is corticosteroids. We will call a patient responder to treatment where they either achieve a complete response, a very good partial response, or a partial response. So complete response is defined asresolution of all of the signs and symptoms of graft versus host disease, with no occasional intervening graft versus host disease therapy. A very good partial response, so it's almost close to a complete response, and so patients are tolerating food or enteral feeding, they predominantly have formed stools, and no abnormal GI bleeding or cramping, and no more than occasional nausea or vomiting. The partial response is basically an improvement of our initial stage in our graft versus host disease, without worsening of other target organs.

When do we consider patients to be failure? Day 28 treatment failure, consists of mixed response. So a mixed response – we have more than one organ affected by graft versus host disease. While one of them is improving, another organ is deteriorating. Now progression means thatour patients, have worsening graft versus host disease symptoms in at least one organ, without improvement in others. And non-response is absence of any improvement in acute graft versus host disease at this stage. To consider the treatment response, we will assess patients that have been properly treated for graft versus host disease. If a patient, receives a 2 mg/kg per day, for example, then, this should be applicable. Also I want to mention that there are other time points important to assess, if the patient is an early responder or not. We do offer treatment response at different timepoints, so like Day 5, Day 7, until it's critical. And also, for late responses, like after Day 28, we also want to see what is the duration of response.

Dr. Doghramji:

And if we zero in on steroid-refractory acute graft versus host disease, Dr. Cutler, can you tell us how you define it?

Dr. Cutler:
Of course. It's actually very important that we have common definitions that the transplant community accepts for these scenarios. We define steroid-refractory acute graft versus host disease as individuals who progress despite three to five days of 2 mg/kg of prednisone or its equivalents, those individuals who fail to respond at all within seven days of dosing at that level, and then individuals who fail to have a complete response by Day 28. There is also a scenario of steroid-dependence, and these are individuals who we can't taper prednisone below 2 mg/kg, or those patients who recur during a taper of their corticosteroids. And finally, we do define individuals as being steroid intolerant, and these are individuals who cannot tolerate the side effects of steroids. These represent a very distinct patient population, in comparison to those who are truly steroid-refractory or steroid-dependent.

Dr. Doghramji:
Well now that we have a better understanding on what steroid-refractory acute graft versus host disease is, let's focus on how we can treat it. Dr. Cutler, what's your approach to managing this disease?

Dr. Cutler:
So, steroid-refractory acute graft versus host disease is a very risky clinical situation associated with high morbidity and high mortality. Currently, there is only one drug that is approved for the management of steroid-refractory acute graft versus host disease, although there are a number of agents that are being tested in early, intermediate and late stage clinical trials. And for that reason, we very often recommend participation in ongoing clinical trials. Current management is with the drug ruxolitinib, when a clinical trial is not available. Ruxolitinib is a JAK2 inhibitor, and it was approved on the basis of the REACH1 study, although more recently, the REACH2 clinical trial, which was a randomized phase 3 study, was actually reported and was found to be a positive study. This was a trial in which just over 300 subjects were randomized to ruxolitinib or a control therapy deemed to be the investigator's choice, and the response rate at, Day 56 – so the durable response rate – was nearly 40% in the ruxolitinib arm, but only 22% in the control arm. That being said, responses in higher grade steroid-refractory acute GVHD are not great still, and therefore, there is plenty of work to be done in steroid-refractory acute graft versus host disease.

Dr. Doghramji:
And, how about you, Dr. Ponce? How does your approach differ from Dr. Cutler's, and do you have any thoughts, uh, you'd like to add on, uh, ruxolitinib as a second-line therapy for acute graft versus host disease?

Dr. Ponce:
I do not differ with Dr. Cutler. I, am, hopefully in agreement finally we have a drug approved by the FDA. So that is my, second line, first choice for patients. The point to highlight that Dr. Cutler mentioned – there's still a lot of room for improvementIt's important to highlight that there was no improvement in non-relapse mortality, so there is an area toconsider for improvement. Besides treating the patients for steroid-refractory graft versus host disease, it's important also to provide, um, additional supportive care, like for example, these patients could have issues with bone healthlow vitamin D, dental issues, diabetes and other things that could arise just due to the nature of the treatment. A multi-disciplinary approach for these patients is really critical to keep their quality of life to be optimal.

Dr. Doghramji:
For those just tuning in, this is CME on ReachMD. I'm Dr. Paul Doghramji, and I have the pleasure of speaking with Dr. Doris Ponce and Dr. Corey Cutler on the topic of steroid-refractory acute graft versus host disease. Looking at the current treatment landscape for steroid-refractory acute graft versus host disease, you really only have ruxolitinib available as a second-line option. So if we look ahead at what's on the horizon, Dr. Ponce, can you tell us about emerging treatment options that are under investigation for this disease?

Dr. Ponce:
One of thetherapeutic options that are currently being under investigation is alpha-1 antitrypsin, also known as AAT. And it's a serine protease inhibitor that can modulate immune and inflammatory function, through alteration of cytokine profiles. What do we know about this? We know that low alpha-1 antitrypsin plasma levels in human donors was found to be associated with a higher rate of acute graft versus host disease. And recently, observation in prospective Phase 1-2 open lable study was performed to evaluate the use of alpha-1 antitrypsin as treatment on steroid-refractory acute graft versus host disease. [AAT]was evaluated in forty patients for the treatment of steroid-refractory acute graft versus host disease, and we found that the overall response rates by Day 28 – was 65%, and the complete response rate was 35%, which was a very encouraging result. Currently there are two clinical trials on their way to further evaluate alpha-1 antitrypsin for graft versus host disease. One of them, phase 2/3 study, with newly diagnosed lower GI acute graft versus host disease for high-risk patients, in combination with cortical steroids. And also, there is an early access trial for patients with steroid-refractory acute graft versus host disease. We have another drug, which is a combination of two murine monoclonal antibody again, CD3 and CD7, each of which is conjugated for recombinant ricin toxin HA. What do we know about this drug? It's two anti-T-cell

immunotoxins designed with a synergistic in vivo depletion and suppression of T-cells, allowing for a for rapid post-treatment reconstitution of the immune system. So one other major of limitation in the graft versus host disease has to do that we will exacerbate and the immune reconstitution of our patients, sothis fact of the drug is very critical, because, the reconstitution of the immune system is one of the aims after stem cell transplants. Then, and in Phase 1 and 2 trial, the six-month overall survival rate was 60%, including, 64% classified as high risk by biomarkers. And while the course of treatment was C3, C7, IG, and caused profound the transient of patient of T-cells and NK-cells. , Treatment-related adverse events in – were – included hypoalbuminemia, microangiopathy, and thrombocytopenia.

Dr. Doghramji:
Well thank you, Dr. Ponce, for breaking all that down for us. And now, let's tune in to get a deeper look at the molecular targets of these newer therapies.

Dr. Doghramji:
Now that we've learned a bit more about the mechanism of action of treatment options for steroid-refractory acute graft versus host disease, Dr. Cutler, do you have any thoughts on emerging therapies you'd like to share?

Dr. Cutler:
Sure, there are lots of other agents that are in development for the therapy of acute graft versus host disease. We're fortunate that it's now a renewed area of interest. I would first comment that prevention of acute graft versus host disease is really critical here, and as we develop more effective GVHD prevention strategies, hopefully we won't need these agents for advanced GVHD, but I will mention that agents that target T-cell trafficking, particularly to the GI tract, are being developed for acute GVHD. There is a non-depleting anti-CD6 antibody that's under development for the therapy of GVHD. Mesenchymal stem cells are returning as a possible therapeutic, and we continue to explore the role of extracorporeal phototherapy, or ECP, in the management of acute GVHD.

Dr. Doghramji:
Knowing what we do now about the current and future treatment landscape for acute graft versus host disease, let's switch gears a bit and focus on some best practices for its management. Dr. Ponce, can you outline the key components of a team-based approach to managing and monitoring patients with acute graft versus host disease?

Dr. Ponce:
Yes, of course. It's very critical to highlight the treatment of the patient with graft versus host disease is a the team effort. Multi-disciplinary input is critical at this point. So, more – our assessment and – and taking care of patients includes, um, our clinic nurse, inpatient or outpatient, and, uh, this person probably spent much of the time with the patient, so it's really important to have a good team. And, um, and then we assess the patient on different organs, so for the scan, we apply the Rule of Nine, so we are assessing their body surface area, and – and that way, it helps us to properly stage the patient in terms of what severity they have of graft versus host disease. We also have advanta – um, nurse practitioner or physician assistant, where we can discuss treatment options with patients and other team members. We also have the pharmacists. They provide insights about drug-drug interactions adverse events to be looking out for our patients. It's important to bring to the table other disciplines, so for example, having another oncologist on board can be very helpful. Same for endocrine, since patients do have issues with hyperglycemia and bone health. A dentist can be also very helpful. We also like to bring on board a nutritionist. Our patients tend to be malnourished, their appetite is decreased, they're having diarrhea. So it's important to keep the nutritional aspect onboard. It's important for our patients to have physical therapy or a routine. In the outpatient setting, we can provide info to the patient and infectious disease prophylaxis, particularly for patients who are on high doses of steroids. Some centers will do surveillance culture. Something to consider if your patient is in a prolonged use of corticosteroids and they have a line placed, for example. And then address GI symptoms – how to minimize that, or how to provide a better quality of life. It's important for patient overall care.

Dr. Doghramji:
Well, now we're almost out of time for today, so I just have one final question for you both. What are some key take-home messages for community providers? Dr. Ponce, let's hear from you first.

Dr. Ponce:
Alright, thank you. I think that it's important to remember that graft versus host disease is frequent. Even for patients who return back to the community after Day 100, it's common to see graft versus host disease developing. Many patients start having signs of graft versus host disease at the time of calcineurin inhibitor taper. So it's important to take into account the initial signs of symptoms. And the treatment remains corticosteroids, and, a drug approved for the treatment of steroid-refractory graft versus host disease is ruxolitinib. That is considered now the choice in case of failure of corticosteroids for response. It's important to remember that graft versus host disease does require a team effort, and multi-disciplinary care is critical to improve quality of life and also the outcome of our patient.

Dr. Doghramji:
And Dr. Cutler, I'll give you the final word.

Dr. Cutler:
Thanks. I would echo what Dr. Ponce said. I would encourage my community partners to consider referring the patients who are getting acute graft versus host disease back to the transplant center. While we are making nice strides and are beginning to have an algorithmic approach to acute GVHD, our progress really depends on clinical trials and learning new ways and better ways of treating acute GVHD. And so, to maximize our ability, new clinical trials, to help patients the most, and to hopefully improve outcomes, uh, hopefully referral back to the transplant center for management of that acute GVHD, is something that everyone will consider.

Dr. Doghramji:
Well with those key take-home messages in mind, I'd like to thank my guests, Drs. Doris Ponce and Corey Cutler, for speaking with me and our ReachMD audience about treating steroid-refractory acute graft versus host disease. It was great having you both on the program.

Dr. Cutler:
Thanks very much.

Dr. Ponce:
Thank you. Thank you very much. It's very motivating to be part of this, thank you.

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