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Managing the Complexities of Acute Graft-Versus-Host Disease: Current Challenges and Unmet Needs

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Managing the Complexities of Acute Graft-Versus-Host Disease: Current Challenges and Unmet Needs," is sponsored by CSL Behring. This program is intended for physicians.

Here's your host, Dr Charles Turck.

Dr Charles Turck:
This is ReachMD, and I'm Dr Charles Turck. Joining me to discuss optimizing acute graft-versus-host disease, or acute GVHD for short, management, are Dr Miguel-Angel Perales and Dr Anna Sureda. Dr Miguel-Angel Perales is the Chief of the Adult Bone Marrow Transplantation Service at Memorial Sloan Kettering Cancer Center in New York. Dr Perales, thanks for being here today.

Dr Miguel-Angel Perales:
Thank you for having me. Looking forward to an interactive discussion.

Dr Charles Turck:
And Dr Sureda is the Head of Clinical Hematology at the University of Barcelona in Spain. Dr Sureda, it's great to have you with us today as well.

Dr Anna Sureda:
Great to be here. Thank you very much for having me.

Dr Charles Turck:
We're excited that you're both here to discuss the current landscape of acute GVHD management. So, starting with you, Dr Perales, in your opinion, what are the challenges surrounding acute GVHD management?

Dr Miguel-Angel Perales:
In a nutshell, acute GVHD is complicated, and the patients are complex to manage. This is not a disease with a single problem like Crohn's disease. Here, patients have an underlying cancer, and then they undergo a transplant and develop a new immune system.[1] We're also dealing with a high risk of infections.[2] Patients are already on a lot of drugs to manage the transplant and other complications. Once these patients have acute GVHD, we're going to start steroids on top of the other medications to treat the acute GVHD, which further increases the risk of infections and organ complications.[3,4] With acute GVHD of the gut—one of the most challenging to manage in my opinion—a patient might have 3 or 4 liters of diarrhea, bloody stool, and abdominal pain in the most severe cases. These patients are suffering,[5] and they need close monitoring, supportive care, and a lot of drugs.[6] Patients may stay in the hospital for months. The longest hospitals they have encountered was over 12 months for the management of acute GVHD, and unfortunately, the patient eventually died.

There are biomarkers that have been studied that are supposed to help me manage these patients, such as predicting mortality and first-line treatment response in acute GVHD, and I can order these tests, but it's not clear to me that there is evidence to support their clinical use despite all the studies.[7]

Dr Anna Sureda:
There are quite a lot of factors that we don't know about the impact of acute GVHD. More research is needed to show biomarkers

contributing to improving outcome of our patients. In reality, we have identified the type of patients, transplant, and donors where there is an increased risk of developing acute GVHD, but when we look at the incidence of acute graft versus host disease, it's still really variable.[1,8] That is why it could be very important to have biomarkers to identify those patients that are at the higher risk of developing acute GVHD, or that are eventually, steroid refractory acute GVHD, and to assess treatment response and mortality risk. Nowadays, there are numerous studies evaluating potential biomarkers, but right now, they are really not very useful in clinical practice.[9]

Dr Miguel-Angel Perales:
And unfortunately, the treatment paradigm has not changed for a couple of decades. We're mainly using first-line steroids for acute GVHD. A paper that I like is Margie McMillan's paper, which shows that the complete response rate with first-line steroids is just under 50%, and sadly, 44% of high-risk patients died after 6 months.[10] Even with standard-risk patients, 22% died at 6 months.[10] I can't imagine any physician taking care of patients with acute GVHD is satisfied with these rates. Clearly, there is room for improvement. Besides, some of our guidelines are over a decade old or may not specify a treatment algorithm.[3,11] Anna, how are the guidelines in Europe?

Dr Anna Sureda:
So, the EBMT has recent guidelines that have been published over the last few years and that try to incorporate the way that we are performing allogenic stem cell transplant, new treatment strategies for acute GVHD, and new GVHD prophylaxis strategies.[12] But here, I want to mention that one of the first papers from the EBMT that was published in the late 90s, and basically that triggered the society to publish different kinds of guidelines, was a survey that was sent to all EBMT centers to try to understand how acute GVHD was treated in practice.[13,14] The survey results show that centers were using their own guidelines.[13] Today, we are trying to reinforce centers to follow EBMT guidelines, but in the end, we are still using our own internal guidelines, which are more in line with our own clinical setting. Although it's of interest to have guidelines published by the scientific societies, sometimes we have to use our own quote-unquote recipe. For example, not all patients will receive the same GVHD prophylaxis depending on the type of transplant.[8] So, we must consider the different background of each patient, which basically adds to the challenge of managing acute GVHD.

Regarding the treatment paradigm for acute GVHD, it's the same here, Miguel; we haven't changed the first-line treatment strategy for ages.[12] Most of our patients are being treated with IV high-dose corticosteroids. Around 50% of the patients won't respond and many of them will still develop significant toxicity from the use of these drugs.[10,15]

Dr Charles Turck:
Staying with you a moment longer, Dr Sureda, can you elaborate on why steroids as first-line treatment are not effective for treating the complexities of acute GVHD?

Dr Anna Sureda:
Sure. We have to take into consideration that steroids are not a targeted therapy. They have quite a lot of side effects that are not well tolerated by our patients, and that have a clear negative impact on the quality of life.[15,16] If a patient doesn't respond to our steroids, the patient is not getting any benefit from the drug. But, on the other side, the patient is getting a lot of side effects, and the side effect that is more worrisome for all of us are life-threatening infections.[17]

Even for patients who do respond to corticosteroids and that may get some benefit from the drug, they are still highly immunosuppressed,[18] and they still have a high risk of developing infections.

Additionally, this high level of immunosuppression can complicate the balance between what we call graft-versus-leukemia effect and acute GVHD.[19] For allogeneic hematopoietic stem cell transplantations to be curative, we are basically relying on the graft versus leukemia effect that comes through the T lymphocytes of the donor.[19-21] If we have a patient with a high risk of relapse after transplant, we really don't like to immunosuppress these patients too much to try to minimize the risk of disease relapse. However, once we have a patient with acute GVHD, we have to start steroids because we don’t have another choice for first-line treatment.

Dr Miguel-Angel Perales:
There aren’t many opportunities to optimize steroids. There is some debate over the appropriate steroid dose—1 milligram per kilogram or 2 milligrams per kilogram, and so forth—and some debate over how quickly we should taper steroids.[3] I have seen other clinicians use higher doses, but there is limited data to support it.[3] I think all you're going to get with high doses of steroids is more toxicity and complications from long-term steroid use—bone loss, diabetes, hypertension, Cushing syndrome—the list goes on and on.[22-24]

In cases of severe acute GVHD, even if there is an infection, we still need to use steroids to control the acute GVHD symptoms. I don't feel good about using steroids, but there is no other choice. Also, discontinuing all immune suppression might not even impact the

infection because the immune system needs time to reconstitute. And then the patient is going to die in the meantime.

Dr Charles Turck:
Dr Perales, if steroids for the first-line treatment of acute GVHD are rendering patients more vulnerable to complications like increased risk of relapse and infections, how do you manage the amount of immunosuppression in your patients in terms of these complications?

Dr Miguel-Angel Perales:
When we see patients, we do review the medication lists, but the first thing you try to do is control the acute GVHD. So, we're adding steroids. Once you control the acute GVHD, then you can look at what medications to take off to reduce immune suppression.

Relapse isn't the immediate concern when you're treating acute GVHD. Even if I have a patient with acute leukemia who has bad mutation, has residual disease going into transplant—so patient with a very high risk for relapse—and they've developed acute GVHD, I have to focus on treating the acute GVHD. In the end, it's because I don't have the luxury to consider different variables because I don't have other treatment options.

Dr Charles Turck:
Yeah, it seems like a very challenging spot to be in. So, Dr Sureda, can you comment on your approach to infections related to immunosuppression for your patients with acute GVHD?

Dr Anna Sureda:
Similar to Miguel, if we have a patient with uncontrolled acute GVHD, we are not stopping to think, "OK, with additional immunosuppression we are going to increase the risk of infections." Although this might be true, the main focus right now is to get the acute GVHD under control. Uncontrolled acute GVHD, with or without concomitant infection, is one of the major causes of transplant-related mortality.[25] So, in spite of knowing that the risk of infection is going to increase, we still have to add corticosteroids.

Dr Charles Turck:
And, Dr Perales, what do you see as the biggest limitation critical to address to improve the management of acute GVHD?

Dr Miguel-Angel Perales:
I think we need more well-designed clinical trials. That is always going to be my answer. We have biomarkers to guide therapy, but I'm not convinced that they're ready to be used right now.[9] We need well-designed trials that prove which biomarkers are clinically useful to improve outcomes.

Dr Anna Sureda:
I fully agree. We need biomarkers to be included in prospective clinical trials that will allow later on to use them in our clinical practice. We also need prospective clinical trials to test potential new drugs, as well.

Dr Miguel-Angel Perales:
Yes, we'll need the companies willing to develop new drugs, too.

Dr Charles Turck:
Dr Perales, what types of drugs do you think need to be developed for acute GVHD?

Dr Miguel-Angel Perales:
I think we need these drugs everywhere: prevention, first line, and for steroid-refractory disease. Even with the best prevention, we're still going to see patients develop acute GVHD. So, we need better first-line treatment than steroids alone. And even with the best first-line treatment, we're not going to get 100% efficacy and response, so we need additional options for steroid refractory acute GVHD, too.

Dr Anna Sureda:
We need Phase 3, randomized, prospective clinical trials, and they are really very challenging to design. It's difficult to get a consensus on one standard of care for the control arm, and in the end, we will have to allow different standard of cares, and these complicates our ability to properly interpret the study results.

Dr Miguel-Angel Perales:
We have some debate over what the endpoints should be, too; right, Anna? Overall response, 28-day response, duration of response, etcetera. The FDA has been issuing guidance over what they want to see in acute GVHD study endpoints, and there are concerns that some of these changes may be difficult to achieve.[26]

Dr Anna Sureda:
Fully agree. Endpoints are not so easy to establish with regulatory agencies that they have their own specific preferences on the primary

and secondary endpoints. I think that prospective clinical trials are important to address the limitations we have with the management of acute GVHD, but there are still some hurdles that will need to be overcome in this specific setting.

Dr Charles Turck:
Now, before we close, given all these concerns and limitations with steroid use, Dr Perales and Dr Sureda, what do you wish for in a first-line treatment for acute GVHD looking forward?

Dr Anna Sureda:
My first wish would be the ability to identify beforehand which patients are at high risk for developing high-grade acute GVHD. My second wish would be to eliminate steroids as the first-line treatment strategy because we know that they are ineffective in a significant proportion of patients and that they are also toxic. Even though we have been using them for many years, it seems like we are downplaying the toxicity of corticosteroids. They are really toxic. But nevertheless, if we still have to work with the steroids, then my third wish would be to have better and more second-line treatment strategies than those that are currently available.

Dr Miguel-Angel Perales:
My real wish is not to see a patient develop acute GVHD to begin with. I would like to see treatments for high-risk patients that meaningfully impacts overall survival. For moderate patients, I wish for first-line therapies that decrease or eliminate the use of steroids while maintaining or improving current survival rates. If we had agents that worked as adjuncts and were not immunosuppressive, that would be ideal. It could translate into fewer infections and relapses.

Dr Charles Turck:
Those are great final comments for us to consider as we come to the end of today's program. And I want to thank my guests, Dr Miguel-Angel Perales and Dr Anna Sureda, for helping us better understand the complexities and unmet needs when it comes to managing acute GVHD. Dr Perales, Dr Sureda, it was great speaking with you both today.

Dr Miguel-Angel Perales:
Thank you. It's been a pleasure.

Dr Anna Sureda:
Thank you very much. A pleasure for me too.

Announcer:
This program was sponsored by CSL Behring. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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