

Experts Discuss the Identification and Appropriate Treatment of GVHD



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During an *Around the Practice*® hosted by CancerNetwork®, experts in the hematology field gathered to discuss the onset of graft-vs-host disease (GVHD) after transplant. They focused on a patient who experienced GVHD during treatment, how to reduce symptoms of GVHD, and frontline treatment options. The panel was led by **Preet M. Chaudhary, MD, PhD**, a professor of medicine, Ronald H. Bloom Family Chair of Lymphoma Research, and chief of the Jane Anne Nohl Division of Hematology and Center for Blood Diseases in the Department of Medicine at the Keck School of Medicine of the University of Southern California (USC).

The panelists included **Eric Leon Tam, MD**, a blood and marrow transplant and hematology-oncology specialist at the USC Norris Comprehensive Cancer Center; **Lakshmi Savitala-Damerla, DMSc, MHA, PA-C**, a physician assistant from the USC Norris Comprehensive Cancer Center; and **Hector Cuevas**, a patient with leukemia and GVHD.

Initial Patient Diagnosis

CHAUDHARY: Hector, can you discuss your initial diagnosis?

CUEVAS: [I was diagnosed because] I had a ball in my groin. I had to go to the hospital for that because it was hurting, and that's when they told me [I had cancer]. I found out that I had several [tumors] in the back of my neck [and] on the bottom of my armpit, and that's when I found out about my leukemia.

CHAUDHARY: What were some of your initial concerns over the diagnosis?

CUEVAS: When you find out that you have cancer, the first thing that comes to mind is: I'm going to die. That was my biggest concern.

CHAUDHARY: What are the different types of allogeneic transplants that are typically used?

TAM: There are several different types of transplants. For allogeneic stem cell transplants using donors, we do a source either from the donor's peripheral blood or from the donor's bone marrow. We have match-related donors, who are people that are related to the recipient. We have match-unrelated donors, who come from the registry; these are individuals who have volunteered to donate bone marrow across the country. We can also do haploidentical and cord blood as well. At USC we don't do cord blood, but this is the blood that's taken from the umbilical cord of infants when they're born. We do [use] haploidentical. These are half-match individuals, so they could be a child or a parent of the patient.

CHAUDHARY: Which type of transplant has the highest incidence of GVHD?

TAM: Among the different types of transplants, typically the mismatch donors will [be associated with] the highest level of GVHD, [along with] the haploidentical donors. There are ways to try and minimize that now, but because of that mismatch, the immune [system] will react [more] and cause more problems further down the road, causing complications.

CHAUDHARY: Were any treatments given prior to the transplant? What type of transplant did you receive?

CUEVAS: I received chemotherapy and radiation. I had a bone marrow transplant.

CHAUDHARY: Would you say a little bit of GVHD is good but can be too much if it gets out of control?

TAM: Anecdotally, we do feel that way, because that at least tells us that the donor's immune system is active. It may not be attacking the right thing, and it doesn't guarantee that it's attacking the leukemia, but at least we know the immune system is responsive and active.

CHAUDHARY: How do patients typically present with chronic GVHD?

SAVITALA-DAMERLA: Typically, after a bone marrow transplant, we monitor our patients very closely, so they're coming in twice a week for the first 100 days. Each visit, we ask a series of questions, as we're monitoring for these symptoms starting from head to toe. For example, [we check] if they're having any headaches or dry eyes, mucositis symptoms with sores in their mouth, difficulty eating or drinking, or rashes. The most common way acute GVHD presents itself is on the skin; the [patients often] come with rashes and say their skin started itching, or that they're having this little rash, so that's how we identify acute GVHD.

As patients move through their transplant journey and they're further away from their transplant, some of these symptoms change and manifest in different ways. For example, as part of the screening, again we ask: Do you see any skin changes? Do you see any dimpling, do you feel tight? [This means that] if you're trying to reach for a glass in the cabinet or bending down to pick something up, does [your skin] feel tight? [That way] you know the skin is involved. Or they might say: I'm having difficulty walking up the stairs. I used to be able to do 3 or 4 flights of stairs, but now I can only do 1 or 2. Then you know the lungs are involved, or you do the blood work [and discover] the liver is involved. There are different ways of identifying acute vs

chronic [GVHD] depending on how far they are from the transplant.

TAM: Because the mechanisms for GVHD are very different for acute and chronic [disease], the manifestations are different. In acute [GVHD], typically it's the skin, the [gastrointestinal] tract, and the liver that are affected. In chronic GVHD, it's usually more cirrhosis and scarring, so you get scar tissue buildup, thickened skin, and fibrosis in the lungs—those types of symptoms.

Mitigating GVHD

CHAUDHARY: What different transplant preparation regimens and GVHD prophylaxis regimens do you use in your practice?

TAM: When we talk about allogeneic stem cell transplant conditioning, there are typically 3 categories. Nonmyeloablative is the lightest, in a sense, and we [also] have reduced intensity and myeloablative conditioning. The types of conditioning that we pick are combinations of chemotherapy with radiation and sometimes with some immunotherapy as well. Which regimen we pick depends on the patient and their current status: their age, their comorbidities, the disease status—whether they're in remission or not—and also the risk for GVHD and the type of donor they're using. All that comes into play. At our center, we have a very involved discussion about each patient to decide on which might be the best conditioning for them. Typically, it's radiation, chemotherapy, and immunotherapy.

The backbone of GVHD prophylaxis includes a class of medications called calcineurin inhibitors. This includes tacrolimus, cyclosporine, and also sometimes mTOR inhibitors with sirolimus (Rapamune). The principle behind [prophylaxis] is to inhibit the immune system enough so that the new donor cells [can] graft and grow. We release [the prophylaxis drugs] slowly over time so that you don't get a huge burst of immune system response recognizing the new host tissue, causing GVHD. The regimens for this

start right at the point of infusion of the new cells, and we carry that on for 3 or 6 months at the very minimum. The beauty about allogeneic stem cell transplants compared with solid organ transplants is that immunosuppression is not expected to be lifelong. The immune system is adaptive and can learn to adapt to the host, so, over a period of 6 months, we will test and see. If the patient is doing well, we'll try to reduce and eventually taper off and discontinue all medications, and we don't have to commit a patient to lifelong immunosuppression.

CHAUDHARY: Are there any new emerging treatments or strategies for GVHD prophylaxis?

TAM: New drugs are being approved by the FDA all the time. The one [approved] most recently [was abatacept (Orencia)], and current clinical trials continue to evolve around how best to reduce GVHD risk.¹ They're looking at different things, including immunosuppressive medications and also medications that decrease scarring, like chronic GVHD prophylaxis. Also, decreasing the level of immune system T cells sometimes helps decrease the risk of GVHD as well.

CHAUDHARY: After transplant, how do you usually monitor your patients? How often do you see them, and what do you test them for?

SAVITALA-DAMERLA: When they are newly transplanted, we keep a close eye on them, monitoring them frequently—twice a week—and then we slowly taper them off. [Monitoring goes down to] once a week, once every 2 weeks, then once a month as they're doing well and leveling off with their new immune system; [after that, we] just monitor them by asking questions. After a while, they understand the questions that we ask, so even before we go into the room, they have an idea and jump into the [discussion of] what is bothering them. In terms of diagnostic testing [for GVHD], there are no specific markers per se. For some [other medical conditions], there are biomarkers you can use. [Here, we have] some indirect markers, [but] no direct markers, so it's essentially

based on their cell counts, history, and physical examination. It's more of a clinical diagnosis than a diagnosis based on lab values.

CHAUDHARY: When did you begin to experience GVHD post transplant?

CUEVAS: It was almost a year after [my transplant that] I started feeling short of breath. I had a bit of a rash [too], but [my main symptom] was shortness of breath, and I would get tired.

CHAUDHARY: What resources do you use in your practice to educate patients about GVHD?

SAVITALA-DAMERLA: Education starts from the beginning, from the moment the patient is deemed to be a transplant candidate. You start talking about what the transplant is and its most common complication: GVHD. During each visit in the pretransplant phase—from consult to finding the donor to [getting the] consent—we constantly talk about GVHD [and its] signs and symptoms. About 20% to 40% of our patients will have GVHD, whether it's acute or chronic. After they're done with the transplant, again, at every single visit [we] screen for these, and after a while the patients understand. Occasionally you will have a patient who [is unsure of what] you're talking about and the education restarts, so it's an ongoing education about what GVHD is and how to identify it [as early as possible].

TAM: We try to introduce [options] early. We have to [do so] when talking about transplants and the risks and complications. During the time when they've just been diagnosed with leukemia and they're going through chemotherapy, there's a whole kind of prospect for the transplant before them, and sometimes they do forget some of the details [they were told about GVHD]. [However], we constantly remind them, and once they're done with the transplant and they're being followed as an outpatient, that's when we're [sure to] start reminding them. Patients will ask us what they need to look out for, and we'll go through the typical symptoms

First-line Treatment Options

TAM: For chronic GVHD, the first line of treatment typically consists of high-dose steroids, and if the patient is off immunosuppression, like tacrolimus, we restart it. If they're still on it, then we need to consider increasing the dose for these patients. That's still the standard in the first line. In the second line, we have new therapies now, but the second line, and the sequencing of treatments, can often be a bit less standard; [it can be] physician and practice based.

CHAUDHARY: Does the original location of the GVHD affect your practice choice?

TAM: It does, particularly if it's steroid refractory. Steroids will work very well for most types of GVHD. At certain times, we can consider a [relatively] mild dose instead of a very large dose if the GVHD is not very severe, but steroids seem to work very well for most types of organs [and] organ systems. When [the disease is] steroid refractory, and the steroid is not doing as much, or the patient is not improving, as much as we'd like, then we need to consider the organ system affected. Certain therapies seem to work a bit better in certain organs. For example, extracorporeal photopheresis works a bit better for the skin and lungs in chronic GVHD. JAK inhibitors and ROCK inhibitors work a bit better for sclerosis as well. Ibrutinib [Imbruvica] is not often used anymore, but that seems to work very well on the skin [and] not so much in the other organ systems.

CHAUDHARY: What are the main adverse effects in patients receiving steroids?

TAM: Steroids are very heavy double-edged swords, especially for chronic GVHD symptoms; [patients] have to stay on steroids for a long period of time. The main concern we always have with high-dose steroids for a long period is an infection, so if they're not already on [it], we have to restart fungal prophylaxis, *Pneumocystis jirovecii* pneumonia prophylaxis, and things like that. Steroids can also wreak havoc on the body's metabolism and its homeostasis as well,

so weight gain, risk for infection, and whether they're diabetic [are factors that need to be considered]. It becomes a very holistic global approach for the patient once they're on steroids.

CHAUDHARY: What major lessons have you learned from treating patients with GVHD?

TAM: Chronic GVHD is a very clinical diagnosis. It's very tough to do, and you must always be on your toes because it can pop up [unexpectedly]. In Hector's case, it popped up a year after transplant when he was doing well and we thought he was in the clear. He was off all his medications, more or less. You should do some routine studies to check in on these patients. For example, for patients who receive high levels of radiation, you should do routine 1-year posttransplant PFTs [pulmonary function tests] to search for subclinical disease. It is something that always needs to be on the transplanters' radar, and whomever the patient is following up with afterward also needs to be aware of this. They might be admitted [to a hospital] for pneumonia—but [perhaps] it's not pneumonia. It could be chronic GVHD.

SAVITALA-DAMERLA: [We must] educate the patient on what to look out for; [we need to] monitor them and [pursue] preventative maintenance. For some of our patients who get [fractionated total body irradiation] as part of their conditioning regimen, we typically do PFTs at 6 months and 1 year. [It's also important to] let patients know that, once they're diagnosed with chronic GVHD, we are able to target and treat, but there's always a risk of it coming back. There is no permanent cure—[it's not a case of] giving one [treatment] and you're done. You always are on the lookout for chronic GVHD. ■

Reference

1. FDA approves abatacept for prophylaxis of acute graft versus host disease. FDA. December 15, 2021. Accessed March 15, 2023. <https://bit.ly/3mPlweZ>



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